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Ternary Complexes in Solution. Part 51*. Intramolecular Hydrophobic and Stacking Interactions in Mixed Ligand Complexes Containing Cu(II), 2,2′-Bipyridyl or 1,10-Phenanthroline, and a Simple Phosphate Monoester, D-Ribose 5′-Monophosphate or a Nucleoside 5′-Monophosphate (CMP, UMP, TMP, TuMP) with a Non-coordinating Base Residue

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Abstract

Stability constants of mixed ligand Cu(Arm)(R-MP) complexes (where Arm = 1,10-phenanthroline (Phen) or 2,2′-bipyridyl (Bpy) and R-MP^{2-} = phosphate monoester) have been determined by potentiometric pH titrations in aqueous solution at I = 0.1 M ($NaNO_3$) and 25 °C. The phosphate monoesters employed were 4-nitrophenyl phosphate ($NPhP^{2-}$), phenyl phosphate (PhP^{2-}), n-butyl phosphate (BuP^{2-}), D-ribose 5′-monophosphate ($RibMP^{2-}$) and the nucleotides: cytidine 5′-monophosphate (CMP^{2-}), uridine 5′-monophosphate (UMP^{2-}), thymidine 5′-monophosphate (TMP^{2-}) and tubercidin 5′-monophosphate ($TuMP^{2-}$ = 7-deazaadenosine 5′-monophosphate). The ternary Cu(Arm)(R-MP) complexes containing a phosphate monoester with an aliphatic or aromatic residue are significantly more stable than the corresponding Cu(Arm)(RibMP) complexes. This increased stability is attributed to intramolecular hydrophobic or stacking interactions between part of the residues R of R-MP^{2-} and the aromatic rings of Bpy or Phen. The stability of the Cu(Arm)(RibMP) complexes is used as a basis for a quantitative evaluation of the situation in the other Cu(Arm)(R-MP) complexes. The formation degree of the species with the intramolecular ligand–ligand adduct increases for the Cu(Arm)(R-MP) complexes in the series: $BuP^{2-} < PhP^{2-} \simeq NPhP^{2-}$; the formation degree for R-MP^{2-} ligands with a six-membered aromatic-ring system, i.e. PhP^{2-}, $NPhP^{2-}$, CMP^{2-}, UMP^{2-} and TMP^{2-}, is rather similar. The tendency of the nucleic base residues to form intramolecular stacks in the Cu(Arm)(R-MP) complexes follows the order: uracil ≲ cytosine ≲ thymine ≪ 7-deazaadenine; this series reflects approximately the hydrophobic properties of the base residues and the size of the aromatic-ring systems. The relevance of the results with regard to bio-systems is shortly indicated.

Introduction

The importance of noncovalent interactions for the shape of macromolecules, the selectivity in biological systems, etc. is now generally accepted [2, 3]. Especially prominent among noncovalent binding forces are hydrophobic and stacking interactions, which have also been considered in mixed ligand complexes [4–10]. For example, the tendency to form intramolecular hydrophobic or stacking adducts in mixed ligand complexes is quite well characterized for alkane-carboxylate [1] and arylalkanecarboxylate [11, 12] ligands; in these previous studies, ternary systems consisting of Cu^{2+} or Zn^{2+}, 2,2′-bipyridyl (Bpy) or 1,10-phenanthroline (Phen)* and a carboxylate ligand had been considered.

There are no comprehensive data available for corresponding mixed ligand complexes containing instead of a carboxylate a phosphate ligand. Due to the importance of phosphate groups as metal ion binding sites in biological systems we have now determined the extent of the intramolecular ligand–ligand interaction in mixed ligand complexes formed by

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*Abbreviations: AMP^{2-}, adenosine 5′-monophosphate; Arm, heteroaromatic N base, e.g. Bpy or Phen; Bpy, 2,2′-bipyridyl; BuP^{2-}, n-butyl phosphate; CMP^{2-}, cytidine 5′-monophosphate; M^{2+}, divalent metal ion; NMP^{2-}, nucleoside 5′-monophosphate; $NPhP^{2-}$, 4-nitrophenyl phosphate; NTP^{4-}, nucleoside 5′-triphosphate; Phen, 1,10-phenanthroline; PhP^{2-}, phenyl phosphate; $RibMP^{2-}$, D-ribose 5′-monophosphate; R-MP^{2-}, phosphate monoester (R may be any organic residue, e.g. phenyl or nucleosidyl); TMP^{2-}, thymidine 5′-monophosphate; $TuMP^{2-}$, tubercidin 5′-monophosphate (= 7-deaza-AMP^{2-}); UMP^{2-}, uridine 5′-monophosphate.

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Cu^{2+}, Bpy or Phen, and a phosphate monoester (R-MP^{2-}), i.e. 4-nitrophenyl phosphate ($NPhP^{2-}$), phenyl phosphate (PhP^{2-}) or n-butyl phosphate (BuP^{2-}).

The selectivity of enzymic reactions with nucleotides is determined to a large part by the nucleic base residues of the nucleotides [13]. These base residues are able to undergo hydrophobic and stacking interactions [4–6, 14–19]. In a comprehensive effort we are aiming to quantify these properties of the nucleic bases in mixed ligand complexes of nucleoside monophosphates. In the present study we are focusing on such nucleoside monophosphates (NMP^{2-}), which contain base residues that are not coordinating to the metal ion in binary M(NMP) complexes; this holds for the 5′-monophosphates of the cytidine (CMP^{2-}), uridine (UMP^{2-}), thymidine (TMP^{2-}) and tubercidin (= 7-deazaadenosine; $TuMP^{2-}$) residues (Fig. 1).

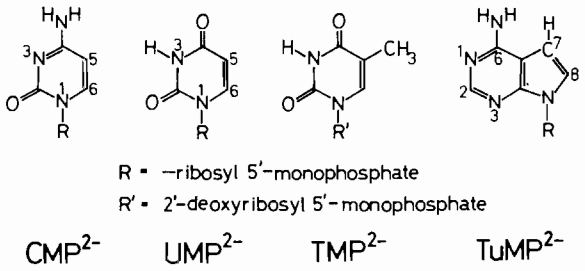


Fig. 1. Structures of the nucleoside 5′-monophosphates (NMP^{2-}) considered in this study.

The base moieties of UMP^{2-} and TMP^{2-} offer no binding site to a metal ion in the neutral pH range [20], i.e. as long as the H(N-3) unit is not ionized. CMP^{2-} and $TuMP^{2-}$ contain a potential binding site for metal ions, i.e. the pyridine-like N-3 and N-1, respectively. However, in M(CMP) [20] and M(TuMP) [21] these N sites are unable to undergo coordination (see also Section 2) for steric reasons: due to the dominating *anti* conformation these N sites are pointing away from the phosphate-coordinated metal ion.

D-Ribose 5′-monophosphate ($RibMP^{2-}$) was also included into the present study, and comparisons of the results show that only the ternary complexes with this ligand, i.e. Cu(Arm)(RibMP), behave as expected [6, 22, 23] for mixed ligand Cu^{2+} complexes composed of a heteroaromatic N base (Arm) and an O donor ligand. All the other ternary Cu(Arm)(R-MP) complexes of the mentioned ligands considered in this study have an increased stability and this is indicative [10] for an intramolecular ligand–ligand interaction.

Experimental

Materials

2,2′-Bipyridyl and 1,10-phenanthroline monohydrate (both *pro analysi*) were obtained from Merck AG, Darmstadt, F.R.G. Tubercidin 5′-monophosphoric acid was purchased from Sigma Chemical Co., St. Louis, MO, U.S.A. [21]. All the other reagents were the same as used recently [20].

The preparation of the solutions and the determination of their exact concentrations were carried out as before [20].

Potentiometric pH Titrations

The experiments were performed and evaluated exactly as described in ref. 20, but the following two points warrant confirmation.

(1) The stability constants $K^{Cu(Ann)}_{Cu(Arm)(R\text{-}MP)}$ of the ternary Cu(Arm)(R-MP) complexes were determined for the simple phosphate monoesters, D-ribose 5′-monophosphate and the pyrimidine-nucleoside 5′-monophosphates under the previous conditions [20] for the binary Cu(R-MP) complexes, but the solutions contained now also Bpy or Phen. This means, the solutions were 0.3 mM in R-MP^{2-} and 1.67 or 3.33 mM in Cu^{2+} and Arm leading to [R-MP^{2-}]:[Cu^{2+}/Arm] ratios of 1:5.6 or 1:11 (I = 0.1 M, $NaNO_3$; 25 °C). In the pH range (depending on the R-MP between pH 4.0 and 5.8) used for the calculation of the stability constants of the ternary complexes, complex formation between Cu^{2+} and Bpy or Phen is already complete; this was evident from the identity of the titration curves obtained from a pair of solutions, one which only contained HNO_3 and the other with Cu^{2+}/Arm in addition. Of course, in the higher pH range such a pair of titrations begins to differ due to the formation of hydroxo complexes in the $Cu(Arm)^{2+}$ system; at the corresponding pH, collection of data for the calculations was stopped (see also ref. 20). Hence, in the calculations only complex formation between $Cu(Arm)^{2+}$ and R-MP^{2-} had to be considered, and as shown earlier [24], each of the systems could be treated as a binary one by considering the species H^+, H_2(R-MP) where appropriate, H(R-MP)$^-$, R-MP^{2-}, $Cu(Arm)^{2+}$ and Cu(Arm)(R-MP). Always at least four independent pairs of titrations were made.

(2) With TuMP the formation of Cu(Arm)(H·TuMP)$^+$ is also of importance. Therefore, the stability constants $K^{Cu(Arm)}_{Cu(Arm)(H\cdot TuMP)}$ and $K^{Cu(Arm)}_{Cu(Arm)(TuMP)}$ of the ternary complexes Cu(Arm)(H·TuMP)$^+$ and Cu(Arm)(TuMP) were determined under the conditions described above and in ref. 21, but the stability constants were computed for each pair of titrations with a curve-fitting procedure [25]; this became satisfactory by taking into account the species H^+, H_2(TuMP)$^{\pm}$, H(TuMP)$^-$, TuMP^{2-}, $Cu(Arm)^{2+}$, Cu(Arm)(H·TuMP)$^+$ and Cu(Arm)(TuMP).

Results and Discussion

1. Stability Constants of the Mixed Ligand Cu^{2+} Complexes Formed with Bpy or Phen and R-MP^{2-}

The experimental data of the potentiometric pH titrations may be completely described by considering the following equilibria:

$$H_2(NMP)^{\pm} \rightleftharpoons H(NMP)^- + H^+ \quad (1a)$$

where NMP^{2-} = CMP^{2-} or $TuMP^{2-}$

$$K^H_{H_2(NMP)} = [H(NMP)^-][H^+]/[H_2(NMP)^{\pm}] \quad (1b)$$

$$H(R\text{-}MP)^- \rightleftharpoons R\text{-}MP^{2-} + H^+ \quad (2a)$$

where $R\text{-}MP^{2-}$ = any phosphate monoester

$$K^H_{H(R\text{-}MP)} = [R\text{-}MP^{2-}][H^+]/[H(R\text{-}MP)^-] \quad (2b)$$

$$NMP^{2-} \rightleftharpoons (NMP - H)^{3-} + H^+ \quad (3a)$$

where NMP^{2-} = UMP^{2-} or TMP^{2-}

$$K^H_{NMP} = [(NMP - H)^{3-}][H^+]/[NMP^{2-}] \quad (3b)$$

$$Cu(Arm)^{2+} + R\text{-}MP^{2-} \rightleftharpoons Cu(Arm)(R\text{-}MP) \quad (4a)$$

$$K^{Cu(Arm)}_{Cu(Arm)(R\text{-}MP)} = [Cu(Arm)(R\text{-}MP)]/([Cu(Arm)^{2+}][R\text{-}MP^{2-}]) \quad (4b)$$

CMP and TuMP have a basic site at their nucleic base residue (see Fig. 1) and therefore the calculations have to be based on the species $H_2(NMP)^{\pm}$ (eqn. (1)); after release of the proton from the base moiety also eqn. (2) is applying for the species $H(NMP)^-$ as for all the other phosphate monoesters. Of course, the monoprotonated phosphate group of all R-MPs may accept a further proton and this will then lead, e.g. to $H_3(CMP)^+$ or to $H_2(UMP)$ species; the corresponding pK_a values are 0.4 ± 0.5 and 0.7 ± 0.3, respectively [20]. These results show that the first proton from the phosphoric acid residue is completely released at pH $\geqslant$ 3.5 and does therefore not affect complex formation between $Cu(Arm)^{2+}$ and $R\text{-}MP^{2-}$ (eqn. (4)), which occurs (depending on the $R\text{-}MP^{2-}$ considered) in the pH range 4.0 to 5.8. Similarly, equilibrium (3a), which is important for UMP^{2-} and TMP^{2-} due to the H(N-3) unit (Fig. 1), is gaining weight only at pH $\geqslant$ 7.5 and is therefore also not of importance for the formation of Cu(Arm)(R-MP) (eqn. (4)) in the mentioned pH range.

Hence, for most R-MP systems only equilibria (2) and (4) have to be considered in the evaluations, though for CMP also equilibrium (1) must be taken into account. The only real exception is the TuMP system: in this case a monoprotonated complex according to equilibrium (5) is formed in remarkable concentrations, and needs also to be considered

$$Cu(Arm)^{2+} + H(TuMP)^- \rightleftharpoons Cu(Arm)(H/TuMP)^+ \quad (5a)$$

$$K^{Cu(Arm)}_{Cu(Arm)(H/TuMP)} = [Cu(Arm)(H/TuMP)^+]/([Cu(Arm)^{2+}][H(TuMP)^-]) \quad (5b)$$

Hence, for the TuMP systems equilibria (1), (2), (4) and (5) must be taken into account. This observation corresponds to that made in binary systems [21], where $M(H/TuMP)^+$ complexes are formed.

The mentioned acidity constants of the ligands and the stability constants of the ternary Cu^{2+} complexes are listed in Table 1, together with the stability constants of the corresponding binary Cu(R-MP) complexes (eqn. (6)), needed for comparison.

$$Cu^{2+} + R\text{-}MP^{2-} \rightleftharpoons Cu(R\text{-}MP) \quad (6a)$$

$$K^{Cu}_{Cu(R\text{-}MP)} = [Cu(R\text{-}MP)]/([Cu^{2+}][R\text{-}MP^{2-}]) \quad (6b)$$

TABLE 1. Negative Logarithms of the Acidity Constants (eqns. (1)–(3)) of the Protonated Phosphate Ligands Considered in this Study and Logarithms of the Stability Constants for the Corresponding Binary Cu(R-MP) (eqn. (6)) and Ternary Cu(Arm)(R-MP) Complexes (eqn. (4)) as Determined by Potentiometric pH Titrations in Water at 25 °C and I = 0.1 M ($NaNO_3$)[a, b]

No.	Ligand	$pK^H_{H_2(NMP)}$	$pK^H_{H(R\text{-}MP)}$	pK^H_{NMP}	$\log K^{Cu}_{Cu(R\text{-}MP)}$	$\log K^{Cu(Bpy)}_{Cu(Bpy)(R\text{-}MP)}$	$\log K^{Cu(Phen)}_{Cu(Phen)(R\text{-}MP)}$
1	$NPhP^{2-}$		5.05 ± 0.01		2.33 ± 0.04	2.66 ± 0.02	2.71 ± 0.02
2	PhP^{2-}		5.85 ± 0.01		2.77 ± 0.01	3.11 ± 0.02	3.07 ± 0.02
3	BuP^{2-}		6.72 ± 0.02		3.12 ± 0.06	3.27 ± 0.06	3.23 ± 0.04
4	$RibMP^{2-}$		6.24 ± 0.01		2.96 ± 0.02	3.01 ± 0.01	3.00 ± 0.02
5	CMP^{2-}	4.33 ± 0.04	6.19 ± 0.02		2.84 ± 0.06	3.20 ± 0.05	3.30 ± 0.03
6	UMP^{2-}		6.15 ± 0.01	9.45 ± 0.02	2.77 ± 0.06	3.05 ± 0.02	3.14 ± 0.02
7	TMP^{2-}		6.36 ± 0.01	9.90 ± 0.03	2.87 ± 0.05	3.27 ± 0.02	3.35 ± 0.02
8	$TuMP^{2-}$	5.28 ± 0.02	6.32 ± 0.01		2.90 ± 0.08[c]	3.84 ± 0.04[c]	4.16 ± 0.03[c]

[a] The errors given are *three times* the standard error of the mean value or the sum of the probable systematic errors, whichever is larger. [b] The acidity constants and the stability constants of the binary Cu^{2+} complexes for the first seven entries are from ref. 20; the corresponding values for entry 8 are from ref. 21. [c] The stability constants for the complexes of the monoprotonated $H(TuMP)^-$ species are: $\log K^{Cu}_{Cu(H/TuMP)} = 1.75 \pm 0.15$ [21], $\log K^{Cu(Bpy)}_{Cu(Bpy)(H/TuMP)} = 2.37 \pm 0.03$, and $\log K^{Cu(Phen)}_{Cu(Phen)(H/TuMP)} = 2.65 \pm 0.02$ (cf., eqn. (5)).

The stability constant of the Cu(Phen)(CMP) complex has been determined before [26], but the agreement with the present result is poor, i.e. the former constant is 1.3 log units higher. The same observation has been made with the data for the corresponding binary Cu(CMP) and related complexes (see ref. 20). It appears that formerly [26] the formation of hydroxo complexes has been overlooked (see also ref. 27).

2. Evidence for the Formation of Intramolecular Ligand–Ligand Adducts and Quantification Procedure for the Stability of Ternary Complexes

For a series of structurally related ligands it is expected [28, 29] that plots of the complex-stability constants log K versus the ligand-acidity constants pK_a result in straight lines. Indeed, this is observed for the binary Cu(R-MP) complexes: Fig. 2 shows the plot for $\log K^{Cu}_{Cu(R\text{-}MP)}$ versus $pK^{H}_{H(R\text{-}MP)}$; the data for 4-nitrophenyl phosphate, phenyl phosphate, n-butyl phosphate, $RibMP^{2-}$, UMP^{2-} and TMP^{2-} of Table 1 furnish a straight reference line. The corresponding data for CMP^{2-} and $TuMP^{2-}$ give points which fall on this line, confirming that the stabilities of Cu(CMP) and Cu(TuMP) are solely governed by the basicity of the phosphate group; i.e. the base moieties have no influence on the stability of these two Cu(NMP) complexes as concluded already earlier [20, 21].

However, plotting $K^{Cu(Bpy)}_{Cu(Bpy)(R\text{-}MP)}$ versus $pK^{H}_{H(R\text{-}MP)}$ for the ternary Cu(Bpy)(R-MP) complexes of the same eight phosphate monoesters leads to the scattered dark points shown in Fig. 2; these points do not fit on a straight line, but all are falling *above* the reference line for the binary complexes indicating that the mixed ligand complexes are more stable. The same picture is obtained, if the corresponding data for the Cu(Phen)(R-MP) complexes are plotted. The fact, that for example the point for Cu(Bpy)(TuMP) in Fig. 2 is nearly one log unit above the reference line for the binary complexes is indicative of an additional interaction and this can only result from the formation of an intramolecular ligand–ligand adduct. Indeed, for ternary complexes with AMP [14a] and UMP [14b] formation of intramolecular ligand–ligand stacks has also been proven by X-ray single crystal analysis.

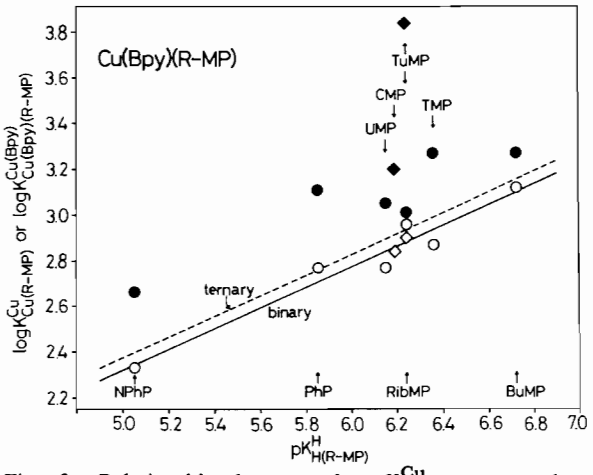


Fig. 2. Relationship between $\log K^{Cu}_{Cu(R\text{-}MP)}$ or $\log K^{Cu(Bpy)}_{Cu(Bpy)(R\text{-}MP)}$ and $pK^{H}_{H(R\text{-}MP)}$ for the binary Cu(R-MP) complexes (○, ◇) and the ternary Cu^{2+} complexes (●, ◆) formed with 2,2'-bipyridyl and $NPhP^{2-}$, PhP^{2-}, $RibMP^{2-}$, $BuMP^{2-}$, UMP^{2-}, TMP^{2-} (○, ●), CMP^{2-} or $TuMP^{2-}$ (◇, ◆). The (solid) least-squares line for the binary complexes is drawn through the six ○ data points: $y = (0.453 \pm 0.056)x + (0.055 \pm 0.340)$ ($\pm 1\sigma$) [20]; the (broken) reference line for the ternary complexes is shifted parallel to the binary least-squares line by $\Delta \log K_{(Cu/Bpy/RibMP)} = 0.05$ (Table 2). The plotted equilibrium constant values are from Table 1; regarding the TuMP systems see text in Section 3.

The increased stability of the ternary complexes as observed in Fig. 2 needs further quantification to allow more detailed conclusions. A common way to characterize the stability of mixed ligand complexes is via equilibrium (7) [5, 6]:

$$Cu(Arm)^{2+} + Cu(R\text{-}MP) \rightleftharpoons Cu(Arm)(R\text{-}MP) + Cu^{2+} \quad (7a)$$

$$10^{\Delta \log K_{Cu}} = \frac{[Cu(Arm)(R\text{-}MP)]\,[Cu^{2+}]}{[Cu(Arm)^{2+}]\,[Cu(R\text{-}MP)]} \quad (7b)$$

The corresponding equilibrium constant* may be calculated with eqn. (8):

$$\Delta \log K_{Cu} = \log K^{Cu(Arm)}_{Cu(Arm)(R\text{-}MP)} - \log K^{Cu}_{Cu(R\text{-}MP)} \quad (8a)$$

$$= \log K^{Cu(R\text{-}MP)}_{Cu(R\text{-}MP)(Arm)} - \log K^{Cu}_{Cu(Arm)} \quad (8b)$$

According to the general rule, $K_1 > K_2$, one expects that equilibrium (7a) is on its left side with negative values for $\Delta \log K_{Cu}$. This agrees with statistical considerations [5, 12]: for the coordination of a bidentate ligand followed by a monodentate ligand to the tetragonal or Jahn–Teller-distorted octahedral coordination sphere of Cu^{2+} $\Delta \log K_{Cu/statist} \simeq -0.5$ was estimated.

Hence, all ternary complexes of Table 1 and Fig. 2 are more stable than expected. However, in case of the ternary systems, Cu/Bpy/$RibMP^{2-}$ and Cu/Phen/$RibMP^{2-}$, the $\Delta \log K_{Cu}$ values are only slightly positive, i.e. $\Delta \log K_{Cu/Bpy/R\text{-}MP} = 0.05 \pm 0.02$ and $\Delta \log K_{Cu/Phen/R\text{-}MP} = 0.04 \pm 0.03$. This slight stability increase corresponds to the observations with carboxylate ligands in Cu/Bpy or Phen/$HCOO^-$ or CH_3COO^- systems [10–12, 30] and more important: such an increased stability is expected for mixed

*If further identification of $\Delta \log K_{Cu}$ for a certain equilibrium is needed, this is given by additional subscripts like $\Delta \log K_{Cu/Bpy/R\text{-}MP}$.

ligand complexes formed by a divalent 3d metal ion, a heteroaromatic N base and an O donor ligand [5, 6, 22–24]. Consequently, the Δ log K_{Cu} values for the Cu^{2+}/Bpy or Phen/$RibMP^{2-}$ systems are representative for the stability alterations resulting from aromatic N/O donor combinations in the coordination sphere of Cu^{2+}, and any *additional* stability increase as observed for the corresponding $R\text{-}MP^{2-}$ systems has to be attributed to *other* sources.

The obvious explanation (in agreement with X-ray structural analysis [14, 16]) for the increased Δ log K_{Cu} values, which vary for the $R\text{-}MP^{2-}$ systems 1–3 and 5–8 of Table 1 between 0.11 and 1.26 log units, is the formation of intramolecular ligand–ligand adducts within the ternary Cu^{2+} complexes. This conclusion agrees with the knowledge on the formation of binary hydrophobic (Arm)(iso-propyl derivative) adducts [31] or binary (Arm)(phenyl derivative) [11, 12, 32] and (Arm)(nucleotide) stacks [19, 33–35], as well as with previous ^1H NMR studies of these and of related ternary M(Arm)(alkanecarboxylate or phenylalkanecarboxylate)$^+$ [1, 10–12] and M(Arm)-(nucleotide) [19, 33, 34] complexes. Indeed, seven from the eight phosphate monoester ligands considered here (Table 1) are suitable for the formation of intramolecular hydrophobic or stacking adducts in ternary Cu(Arm)(R-MP) complexes; the single exception is ribose 5′-monophosphate which has no suitable aliphatic or aromatic group for a hydrophobic interaction and the corresponding Δ log K_{Cu} values discussed above agree herewith. A simplified structure for such a stacked species is shown in Fig. 3 for the ternary Cu^{2+} complex with 2,2′-bipyridyl and CMP^{2-}.

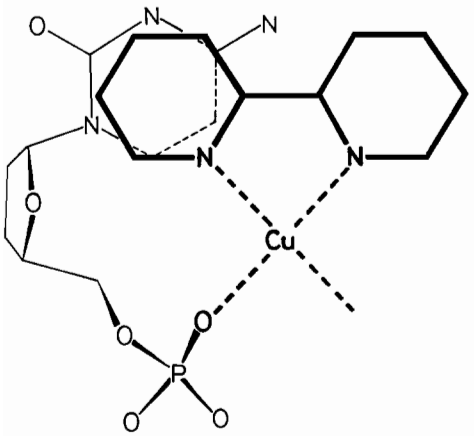


Fig. 3. Probable (schematic) structure of the 'closed' species, i.e. the isomer with an intramolecular stack, for Cu(Bpy)-(CMP) in solution.

3. Some Extra Comments on the TuMP Systems

The ligand $TuMP^{2-}$ is a special case because the difference between the two acidity constants, $pK^{H}_{H(TuMP)}$ (eqn. (2)) and $pK^{H}_{H_2(TuMP)}$ (eqn. (1)), equals only 1.04 log units and hence equilibria (1a) and (2a) are overlapping. Consequently, in correlations between complex stability and ligand acidity (see Section 2; Fig. 2) a microconstant [36], e.g. for $H(TuMP)^-$, should be employed which is corrected for any influence of a partially protonated base residue. The four microconstants and their interrelations with the two macro acidity constants for the overlapping deprotonation equilibria of $H_2(TuMP)^{\pm}$ have recently been given [21]; it was shown, for example, that $H(TuMP)^-$ exists in two isomeric forms: the species, $TuMP\cdot H^-$, with the proton at the phosphate group is dominating, it occurs to about 80%, while the base-protonated $H\cdot TuMP^-$ species has a formation degree of only about 20%.

It is evident that for the correlations of Fig. 2 the acidity constant for the $TuMP\cdot H^-$ isomer must be employed, because complex formation between Cu^{2+} and $TuMP^{2-}$ occurs with the phosphate group. Hence, in Fig. 2 the stability constants log K for the reaction between Cu^{2+} or $Cu(Arm)^{2+}$ and $TuMP^{2-}$ are plotted versus the micro acidity constant $pk^{TuMP}_{TuMP\cdot H} = 6.24$ ($= pK^{H}_{H(RibMP)} = 6.24 \pm 0.01$ [21]).

It should be added that the thermodynamic stability constants given in Table 1 were calculated with the macro acidity constants. This causes no problem for the values of log $K^{Cu}_{Cu(TuMP)}$ and log $K^{Cu(Arm)}_{Cu(Arm)(TuMP)}$ as in the corresponding equilibria the deprotonated $TuMP^{2-}$ species is involved. However, the stability constants, $K^{Cu}_{Cu(H/TuMP)}$ and $K^{Cu(Arm)}_{Cu(Arm)(H/TuMP)}$ (eqn. (5)), are based on the macro acidity constant, $K^{H}_{H_2(TuMP)}$, which refers to the release of a proton mainly from N-1. Consequently, for a comparison (referring to a phosphate-coordination) analogous to the one given in Fig. 2 the experimental values for the stability constants, log K, have to be 'corrected' by adding the difference between the micro and macro acidity constants, i.e. $pk^{H\cdot TuMP}_{H\cdot TuMP\cdot H} - pK^{H}_{H_2(TuMP)} = 6.05$ [21] $- 5.28$ (Table 1) $= 0.77$. The resulting basicity-adjusted experimental micro stability constants (based on the values of Table 1) for the complexes with the proton at N-1 are: log $k^{Cu}_{H\cdot TuMP\cdot Cu} = 2.52$ [21], log $k^{Cu(Bpy)}_{H\cdot TuMP\cdot Cu(Bpy)} = 3.14$ and log $k^{Cu(Phen)}_{H\cdot TuMP\cdot Cu(Phen)} = 3.42$. Considering that the error limits of these values are rather large, i.e approximately ± 0.3 to ± 0.4 log unit [21], these data fit well into the picture of Fig. 2.

There is one further aspect which should be pointed out: the experimental data of the potentiometric pH titrations for the TuMP systems are completely described by equilibria (1), (2), (4) and (5) (see Section 1), if the evaluation is not carried into the pH range where formation of hydroxo complexes occurs. In the light of the above discussion it should be emphasized that the use of macroconstants is enough for a thermodynamic description of the formation of metal ion complexes [36]. Clearly, the analysis of potentiometric pH titrations only yields

the amount and distribution of species of a net charge type, e.g. of Cu(Bpy)(H/TuMP)$^+$, and additional information is required to locate the binding sites of the proton and the metal ion. Such information is obtained from the following considerations:

The results summarized in Table 1 for eqns. (1), (2) and (4) to (6) may be linked with the following equilibrium (9):

$$M(H/TuMP)^+ \rightleftharpoons M(TuMP) + H^+ \quad (9a)$$

where M = Cu^{2+}, $Cu(Bpy)^{2+}$ or $Cu(Phen)^{2+}$

$$K^H_{M(H/TuMP)} = [H^+][M(TuMP)]/[M(H/TuMP)^+] \quad (9b)$$

The corresponding acidity constant may be calculated with eqn. (10):

$$pK^H_{M(H/TuMP)} = pK^H_{H(TuMP)} + \log K^M_{M(H/TuMP)} - \log K^M_{M(TuMP)} \quad (10)$$

The results are:

$$pK^H_{Cu(H/TuMP)} = (6.32 \pm 0.01) + (1.75 \pm 0.15) - (2.90 \pm 0.08)$$
$$= 5.17 \pm 0.17$$

$$pK^H_{Cu(Bpy)(H/TuMP)} = (6.32 \pm 0.01) + (2.37 \pm 0.03) - (3.84 \pm 0.04)$$
$$= 4.85 \pm 0.05$$

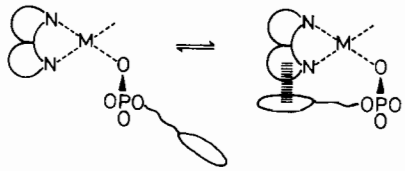
$$pK^H_{Cu(Phen)(H/TuMP)} = (6.32 \pm 0.01) + (2.65 \pm 0.02) - (4.16 \pm 0.03)$$
$$= 4.81 \pm 0.04$$

These acidity constants of the complexes may be compared with the ligand-acidity constant $pK^H_{H_2(TuMP)} = 5.28$ (Table 1), or even better with $pk^{TuMP\cdot H}_{H\cdot TuMP\cdot H} = 5.36$ [21]. The proton in Cu(H/TuMP)$^+$ is released with a slightly lower pK_a than the proton from N-1 in $(H\cdot TuMP\cdot H)^-$ ($\Delta\ pK_a \sim 0.2$). This indicates that in Cu(H/TuMP)$^+$ the metal ion is largely coordinated to the phosphate group and the proton to N-1, because the distance between the phosphate group and N-1 in the *anti* conformation [37] is large (about 10 Å) [38] and therefore the acidification of a proton at N-1 by a metal ion coordinated at the phosphate group is expected to be low. In agreement herewith is the acidification in Cu(Bpy)-(H/TuMP)$^+$ ($\Delta\ pK_a \sim 0.5$) and Cu(Phen)(H/TuMP)$^+$ ($\Delta\ pK_a \sim 0.6$) more significant, because these ternary complexes exist mainly in a 'folded' form (see Fig. 3 and Section 4) and therefore the metal ion is now much closer to the H^+(N-1) site. Hence, these protonated Cu^{2+} complexes should best be formulated as $(H\cdot TuMP\cdot Cu)^+$, $(H\cdot TuMP\cdot Cu(Bpy))^+$ and $(H\cdot TuMP\cdot Cu(Phen))^+$, in agreement with recent conclusions [21] for other M(H/TuMP)$^+$ species.

Finally, it should be emphasized that for the considerations in Section 4 regarding the formation degree of the folded or stacked form of Cu(Arm)(H/TuMP)$^+$ or Cu(Arm)(TuMP) the location of the proton or the use of micro acidity constants as discussed above is of no significance because these effects cancel in calculations based on eqn. (8).

4. Calculation Procedures for the Formation Degree of Intramolecular Ligand–Ligand Adducts

The occurrence of a ternary complex in a folded form corresponding to the one indicated in Fig. 3 does not mean that all Cu(Arm)(R-MP) species exist in this form. Hence, an intramolecular equilibrium between an 'open' and a 'closed' form as indicated in equilibrium (11a) must be considered:



(11a)

If these two isomers are designated as M(Arm)(R-MP)$_{op}$ and M(Arm)(R-MP)$_{cl}$, the dimensionless constant of this equilibrium is defined by eqn. (11b) [31]:

$$K_I = [M(Arm)(R\text{-}MP)_{cl}]/[M(Arm)(R\text{-}MP)_{op}] \quad (11b)$$

Equilibrium (4a) may therefore be rewritten:

$$M(Arm)^{2+} + R\text{-}MP^{2-} \rightleftharpoons M(Arm)(R\text{-}MP)_{op} \rightleftharpoons M(Arm)(R\text{-}MP)_{cl} \quad (12a)$$

The corresponding observed equilibrium constant, which equals that of eqn. (4b), is then defined by eqn. (12b):

$$K^{M(Arm)}_{M(Arm)(R\text{-}MP)} = \frac{([M(Arm)(R\text{-}MP)_{op}] + [M(Arm)(R\text{-}MP)_{cl}])}{[M(Arm)^{2+}][R\text{-}MP^{2-}]} \quad (12b)$$

$$= K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}} + K_I \cdot K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}} \quad (12c)$$

$$= K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}}(1 + K_I) \quad (12d)$$

In these expressions the stability of the open complex is defined as given in eqn. (13):

$$K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}} = [M(Arm)(R\text{-}MP)_{op}]/([M(Arm)^{2+}][R\text{-}MP]) \quad (13)$$

The term $(1 + K_I)$ of eqn. (12d) is often addressed [29] as stability enhancement factor. Clearly, values for K_I may now be calculated from eqn. (14)

$$K_I = \frac{K^{M(Arm)}_{M(Arm)(R\text{-}MP)}}{K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}}} - 1 \quad (14)$$

but also from eqn. (15) involving $\Delta \log K_M$ (eqns. (7) and (8)) [31]:

$$K_I = \frac{10^{\Delta \log K_{(M/Arm/R\text{-}MP)}}}{10^{\Delta \log K_{(M/Arm/R\text{-}MP)_{op}}}} - 1 \quad (15)$$

Both equations are applicable provided the stability of the open complex in equilibrium (11a) can be quantified.

Regarding values for $K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}}$ of eqn. (14) the following procedure is possible. For the binary Cu(R-MP) complexes the relation between complex stability and phosphate-group basicity is well defined from the plots of log $K^{Cu}_{Cu(R\text{-}MP)}$ versus $pK^{H}_{H(R\text{-}MP)}$ (Fig. 2):

$$\log K^{Cu}_{Cu(R\text{-}MP)} = (0.453 \pm 0.056) \times pK^{H}_{H(R\text{-}MP)} + (0.055 \pm 0.340)$$

This least-squares regression line has been calculated [20] from six data points having a standard deviation (SD) from the least-squares line of ±0.026 (1σ). A corresponding line cannot be calculated for the mixed ligand systems because here complex stability also depends on the extent of the intramolecular ligand–ligand interaction (see Section 2 and Fig. 2). However, a single point for a mixed ligand system is available: in Cu(Arm)(RibMP) no intramolecular ligand–ligand interaction occurs (Section 2); therefore with $\Delta \log K_{Cu} = \log K^{Cu(Arm)}_{Cu(Arm)(RibMP)} - \log K^{Cu}_{Cu(RibMP)}$ and the justified assumption [1, 11, 12] that the slopes of the regression lines for binary and their corresponding ternary systems are identical, reference lines for the ternary systems can be calculated. With $\Delta \log K_{(Cu/Bpy/RibMP)} = (3.010 \pm 0.003) - (2.962 \pm 0.005) = 0.048 \pm 0.006$ (1σ) and $\Delta \log K_{(Cu/Phen/RibMP)} = (2.997 \pm 0.006) - (2.962 \pm 0.005) = 0.035 \pm 0.008$ (1σ) one obtains the following equations for the reference lines of the ternary Cu(Arm)(R-MP) systems containing Bpy or Phen without any ligand–ligand interaction; the first of these equations is used in Fig. 2 (broken line):

$$\log K^{Cu(Bpy)}_{Cu(Bpy)(R\text{-}MP)} = 0.453 \times pK^{H}_{H(R\text{-}MP)} + 0.103$$

$$\log K^{Cu(Phen)}_{Cu(Phen)(R\text{-}MP)} = 0.453 \times pK^{H}_{H(R\text{-}MP)} + 0.090$$

The error limits of log stability constants calculated with given $pK^{H}_{H(R\text{-}MP)}$ values and these equations are ±0.027 (1σ) log units for the Bpy systems and also for the Phen systems. Now values for $K^{Cu(Arm)}_{Cu(Arm)(R\text{-}MP)_{op}}$ for any of the phosphate monoester systems may be calculated, and hence, eqn. (14) can now be applied for the calculation of K_I. Users of the two mentioned straight-line equations are recommended to apply them for phosphate ligands with pK_a values between 5 and 7, and to consider as error limits of the calculated stability constant, log $K^{Cu(Arm)}_{Cu(Arm)(R\text{-}MP)}$, two or three times the given standard deviation.

To be able to apply eqn. (15) for the calculation of the dimensionless equilibrium constant K_I, values for $\Delta \log K_{(Cu/Arm/R\text{-}MP)_{op}}$ must be obtained. As in the ternary Cu(Arm)(RibMP) complexes no ligand–ligand interaction is occurring (Section 2) the log stability difference for the open form (eqn. (11a)) is well represented by the values for the Cu(Arm)-(RibMP) systems, i.e. by eqn. (16):

$$\Delta \log K_{(Cu/Arm/R\text{-}MP)_{op}} = \Delta \log K_{(Cu/Arm/RibMP)} \quad (16)$$

By employing eqn. (16) the following definition is possible (eqn. (17)):

$$\Delta\Delta \log K = \Delta \log K_{(Cu/Arm/R\text{-}MP)} - \Delta \log K_{(Cu/Arm/RibMP)} \quad (17)$$

It is probably helpful to realize that the constant $10^{\Delta\Delta \log K}$ is the ratio of two equilibrium constants (see eqns. (15) and (17)); consequently $10^{\Delta\Delta \log K}$ must itself also be an equilibrium constant. Indeed, $10^{\Delta\Delta \log K}$ quantifies the position of equilibrium (18), where $R\text{-}MP^{2-}$ is a phosphate monoester with a ligand residue suitable for a ligand–ligand interaction; i.e. $R\text{-}MP^{2-}$ is one of the ligands given in Table 1 under entries 1–3 or 5–8.

$$Cu(R\text{-}MP) + Cu(Arm)(RibMP) \rightleftharpoons Cu(Arm)(R\text{-}MP) + Cu(RibMP) \quad (18)$$

It is evident that the coordination spheres of the Cu^{2+} ions on both sides of this equilibrium are identical; consequently, the value for $\Delta\Delta \log K$ (eqn. (17)) is a true reflection of the extent of the intramolecular hydrophobic or stacking interaction in the Cu(Arm)-(R-MP) complexes. Furthermore, with eqn. (17) one may rewrite eqn. (15) and obtain then eqn (19):

$$K_I = 10^{\Delta\Delta \log K} - 1 \quad (19)$$

Whenever possible, it is advisable to apply for the calculation of K_I eqns. (15) or (19) because experience shows [31] that by the use of the $\Delta \log K_M$ formulation (eqn. (8)) systematic errors cancel to a large part. However, in those cases where in the binary R-MP complex the metal ion is not only coordinated to the phosphate group, but also interacting with the base residue, as for example in Cu(AMP) [21], the $\Delta \log K_M$ formulation cannot be applied; here equation (14) must be employed and $K^{M(Arm)}_{M(Arm)(R\text{-}MP)_{op}}$ has to be determined via the straight-line equations [39]. A careful comparison of the vertical distances between corresponding data points in Fig. 2 reveals the connection between the two evaluation methods, i.e. eqns. (14) and (15) (or (19)).

5. Extent of the Formation of Intramolecular Hydrophobic and Stacking Adducts in Cu(Arm)(R-MP) Complexes

All ligands considered in this study form their binary Cu(R-MP) complexes only via a coordination of the metal ion to the phosphate group; hence, eqn. (19) may be applied for the determination of the position of equilibrium (11a). Obviously, any experimental error will be the more significant in the application of eqns. (15) and (19), the smaller the difference in eqn. (17) is, because $10^{\Delta\Delta \log K}$ is the crucial parameter of eqn. (19). Therefore, a careful calculation of the error propagation has to accompany any evaluation of stability constants for the formation of intramolecular ligand–ligand adducts.

It may be wise to emphasize again that $10^{\Delta\Delta \log K}$ quantifies the position of equilibrium (18), and to add that for those cases with $\Delta\Delta \log K > 0$, i.e. $10^{\Delta\Delta \log K} > 1$, equilibrium (18) is shifted towards its right side. Clearly, from $10^{\Delta\Delta \log K} > 1$ follows also $K_I > 0$ (eqn. (19)), i.e. species with an intramolecular ligand–ligand interaction are existing. Knowledge of K_I finally allows to calculate the percentage of the folded or closed species of equilibrium (11a) with eqn. (20):

$$\%\text{Cu(Arm)(R-MP)}_{cl} = \frac{K_I}{1 + K_I} \times 100 \qquad (20)$$

The results of the calculations based on eqns. (8) and (16) to (20) are summarized in Table 2. These data provide worthwhile information on intramolecular ligand–ligand interactions and thus allow also interesting comparisons; some of these will be discussed below, others may be made by the readers.

Entries 1 to 3 of Table 2 show that the intramolecular ligand–ligand interaction in Cu(Arm)(R-MP) increases for the $R\text{-}MP^{2-}$ series: n-butyl phosphate < phenyl phosphate ≃ 4-nitrophenyl phosphate. This is understandable because between the butyl residue of BuP^{2-} and the aromatic-ring systems of Bpy or Phen only a simple hydrophobic interaction can occur, whereas the phenyl ring of PhP^{2-} or $NPhP^{2-}$ allows formation of an aromatic-ring stack with Bpy or Phen. The percentages calculated for Cu(Arm)(R-MP)$_{cl}$ of these phosphate monoester systems are in excellent accordance with related carboxylate ligands: for example, 48 ± 9% were determined [11] for Cu(Phen)(2-phenylacetate)$_{cl}^{+}$ and 45 ± 5% for Cu(Phen)(phenyl phosphate)$_{cl}$ (entry 2b in Table 2); in both ligands, i.e. 2-phenylacetate and phenyl phosphate, the number of atoms between the coordinating O atom and the phenyl residue is identical. A similar comparison is possible between the values for Cu(Phen)(propionate)$_{cl}^{+}$ (9 ± 14%) [30], Cu(Phen)-(2-methylpropionate)$_{cl}^{+}$ (13 ± 11%) [1], Cu(Phen)-(3-methylbutyrate)$_{cl}^{+}$ (19 ± 9%) [1], and Cu(Phen)(n-

TABLE 2. Extent of the Intramolecular Ligand–Ligand Interaction (see for example Fig. 3) in Ternary Cu(Arm)(R-MP) Complexes with 2,2'-Bipyridyl or 1,10-Phenanthroline and a Phosphate Ligand ($R\text{-}MP^{2-}$): Intramolecular and Dimensionless Equilibrium Constant K_I (eqns. (11) and (19)) and Percentage (eqn. (20)) of the Closed Cu(Arm)(R-MP)$_{cl}$ Species with the Hydrophobic or Stacking Interaction in Water at 25 °C and I = 0.1 M ($NaNO_3$)[a]

No.	Complex	$\Delta \log K_{(Cu/Arm/R\text{-}MP)}$[b]	$\Delta \log K_{op}$	$\Delta\Delta \log K$[c]	K_I	Cu(Arm)(R-MP)$_{cl}$ (%)
1a	Cu(Bpy)(NPhP)	0.33 ± 0.04	0.05 ± 0.02	0.28 ± 0.05	0.91 ± 0.22	48 ± 6
b	Cu(Phen)(NPhP)	0.38 ± 0.04	0.04 ± 0.03	0.34 ± 0.05	1.19 ± 0.27	54 ± 6
2a	Cu(Bpy)(PhP)	0.34 ± 0.02	0.05 ± 0.02	0.29 ± 0.03	0.95 ± 0.14	49 ± 4
b	Cu(Phen)(PhP)	0.30 ± 0.02	0.04 ± 0.03	0.26 ± 0.04	0.82 ± 0.15	45 ± 5
3a	Cu(Bpy)(BuP)	0.15 ± 0.08	0.05 ± 0.02	0.10 ± 0.09	0.26 ± 0.25	21 ± 16
b	Cu(Phen)(BuP)	0.11 ± 0.07	0.04 ± 0.03	0.07 ± 0.08	0.17 ± 0.21	15 ± 15
4a	Cu(Bpy)(RibMP)	0.05 ± 0.02[d]				
b	Cu(Phen)(RibMP)	0.04 ± 0.03[d]				
5a	Cu(Bpy)(CMP)	0.36 ± 0.08	0.05 ± 0.02	0.31 ± 0.08	1.04 ± 0.38	51 ± 9
b	Cu(Phen)(CMP)	0.46 ± 0.07	0.04 ± 0.03	0.42 ± 0.07	1.63 ± 0.44	62 ± 6
6a	Cu(Bpy)(UMP)	0.28 ± 0.06	0.05 ± 0.02	0.23 ± 0.07	0.70 ± 0.26	41 ± 9
b	Cu(Phen)(UMP)	0.37 ± 0.06	0.04 ± 0.03	0.33 ± 0.07	1.14 ± 0.34	53 ± 7
7a	Cu(Bpy)(TMP)	0.40 ± 0.05	0.05 ± 0.02	0.35 ± 0.06	1.24 ± 0.30	55 ± 6
b	Cu(Phen)(TMP)	0.48 ± 0.05	0.04 ± 0.03	0.44 ± 0.06	1.75 ± 0.39	64 ± 5
8a	Cu(Bpy)(TuMP)	0.94 ± 0.09	0.05 ± 0.02	0.89 ± 0.09	6.76 ± 1.65	87 ± 3
b	Cu(Phen)(TuMP)	1.26 ± 0.09	0.04 ± 0.03	1.22 ± 0.09	15.6 ± 3.4	94 ± 1
8*a[e]	Cu(Bpy)(H/TuMP)$^{+}$	0.62 ± 0.15	0.05 ± 0.02	0.57 ± 0.15	2.72 ± 1.32	73 ± 10
b[e]	Cu(Phen)(H/TuMP)$^{+}$	0.90 ± 0.15	0.04 ± 0.03	0.86 ± 0.15	6.24 ± 2.57	86 ± 5

[a]The error limits are based on those of Table 1; they were calculated according to the error propagation after Gauss. [b]These values were calculated according to eqn. (8) with the constants of Table 1. [c]Calculated with eqn. (17). [d]These values correspond to $^{*}\Delta \log K_{(Cu/Arm/R\text{-}MP)_{op}}$; see text and eqn. (16). [e]See footnote 'c' in Table 1.

butyl phosphate)$_{cl}$ (15 ± 15%; 3b in Table 2); of course, with larger aliphatic residues the stability of intramolecular hydrophobic adducts increases further: e.g. Cu(Phen)(6-methylheptanoate)$_{cl}^{+}$ (34 ± 9%) [1].

For entries 1 to 3 of Table 2 there is no difference in the formation degree of the closed form between the Cu(Bpy)(R-MP) and the Cu(Phen)(R-MP) complexes. This is not surprising as the alkyl and aryl residues of R-MP^{2-} are small and the distance between these residues and the metal ion-coordinating group is short, and therefore *only one* of the pyridine-like rings of Bpy or Phen is accessible for the interacting residue. This is different for the Cu(Arm)(NMP) entries 5 through 8*: here the distances between the coordinating and adduct-forming groups are larger, increasing the flexibility and allowing access to the middle ring of Phen. Consequently, there is the trend for more closed species with Cu(Phen)(NMP) than with Cu(Bpy)-(NMP); quite obvious is this trend (Table 2) with the large double-ring base residue in the ternary complexes formed with TuMP^{2-} (cf. Figs. 1 and 3). That the formation degree of the intramolecular stack in Cu(Arm)(TuMP) is somewhat larger than in Cu(Arm)-(H/TuMP)$^{+}$ is the result of the repulsion between the positively charged $^{+}$H(N-1) site in the latter complex and Cu^{2+} (see also Section 3).

Though not always beyond the error limits, the following trend for the stacking properties of the base moieties is indicated from the Cu(Arm)(R-MP) results in Table 2 (entries 5 to 8); uracil $\lesssim$ cytosine $\lesssim$ thymine $\ll$ 7-deazaadenine. This trend agrees with the observations made in studies of the self-association of the corresponding nucleosides and nucleotides [15, 40], and it probably parallels the hydrophobic properties of the base residues. It is also in agreement with the stability of the binary adducts (Bpy)-(UTP)$^{4-}$ ($K \approx 1$ M^{-1}) [41], (Bpy)(ATP)$^{4-}$ ($K \simeq 16$ M^{-1}) [35], and (Phen)(ATP)$^{4-}$ ($K \simeq 38$ M^{-1}) [35] as measured in D_2O by ^{1}H NMR. A comparison of an earlier collection of data for related systems (Table 6 in ref. 19) with the present results indicates further that the extent of stacking in Cu(Bpy)(TuMP) and Cu(Bpy)(AMP) is comparable. In addition, it appears that the formation degree of the intramolecular stack increases from Cu(Bpy)(NMP) to Cu(Bpy)-(NTP)$^{2-}$.

To conclude, the described results demonstrate once again [1, 10–12, 17, 35, 42] that a metal ion-bridge between two suitable groups able to form hydrophobic or stacking adducts considerably promotes the formation of these adducts. More important, it is evident that from relatively simple models information may be gained about the properties of nucleotides and their base moieties regarding the strength of their interactions with neighboring molecules, and even insight into the factors which influence this strength (like distance, length and kind of connecting 'bridges', size of the groups, etc.) is thus becoming available.

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