Ternary Complexes in Solution (Part 55[1]) with Phosphonates as Ligands. Various Intramolecular Equilibria in Mixed-ligand Complexes containing the Antiviral 9-(2-Phosphonomethoxyethyl)adenine, an Adenosine Monophosphate Analogue

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The stability constants of the mixed-ligand complexes formed between $Cu(arm)^{2+}$, where arm = 2,2'-bipyridyl (bipy) or 1,10-phenanthroline (phen), and the dianions of phosphonomethoxyethane (PME^{2-}) or 9-(2-phosphonomethoxyethyl)adenine ($PMEA^{2-}$) were determined by potentiometric pH titration in aqueous solution at 25 °C and I = 0.1 mol dm^{-3} ($NaNO_3$). The stability of the binary (arm)$(PMEA)^{2-}$ stacks was estimated and the experimental conditions for the titrations were carefully selected such that self-association of the adenine derivative PMEA and of its complexes was negligible, *i.e.* it was made certain that the properties of the monomeric Cu(arm)(PMEA) complexes were studied. The ternary Cu(arm)(PMEA) complexes are considerably more stable than the corresponding Cu(arm)$(R\text{-}PO_3)$ complexes, where $R\text{-}PO_3^{2-}$ represents a phosphonate (or a phosphate monoester) with a group R that is unable to participate in any kind of interaction within the complexes as, for example, methylphosphonate or ethylphosphonate. This increased stability is attributed to intramolecular stack formation in the Cu(arm)(PMEA) complexes and also to the formation of five-membered chelates involving the ether oxygen present in the $-O-CH_2-PO_3^{2-}$ residue of $PMEA^{2-}$. The latter interaction is separately quantified by studying the ternary Cu(arm)(PME) complexes which can form the five-membered chelates but where no intramolecular ligand–ligand stacking is possible. Application of these results allows a quantitative analysis of the intramolecular equilibria involving three structurally different Cu(arm)(PMEA) species, *e.g.* of the Cu(bipy)(PMEA) system about 3% exist with the metal ion solely co-ordinated to the phosphonate group, 10% as a five-membered chelate involving the $-O-CH_2-PO_3^{2-}$ residue of $PMEA^{2-}$, and 87% with an intramolecular stack between the adenine moiety of $PMEA^{2-}$ and the aromatic rings of bipy. In addition, the Cu(arm)(PMEA) complexes may be protonated leading to Cu(arm)(H·PMEA) species for which it is concluded that the proton is mainly located at the phosphonate group. However, of this species two isomers still coexist, one where $Cu(arm)^{2+}$ forms a stack with the adenine residue of $H(PMEA)^-$ and another one where $Cu(arm)^{2+}$ co-ordinates in an adenosine-type fashion to the nucleic base moiety of $H(PMEA)^-$; the percentages of the formation degree of these isomeric species have been estimated. Finally, the properties of adenosine 5'-monophosphate (AMP^{2-}) and of its $PMEA^{2-}$ analogue are compared in their ternary Cu(arm)(AMP) and Cu(arm)(PMEA) systems. The co-ordinating properties of the ether oxygen, which are crucial for the antiviral properties of PMEA, are discussed.

Nucleotides and their metal-ion complexes play a key role in all aspects of metabolism. Consequently, there have been great efforts to use derivatives of nucleobases, nucleosides and nucleotides as drugs, *e.g.* as antiviral agents.[2] One such compound is 9-(2-phosphonomethoxyethyl)adenine, its dianion we designate as $PMEA^{2-}$,† which may be considered as an analogue of adenosine 5'-monophosphate (5'-AMP^{2-}) as is evident from the chemical structures shown in Fig. 1.[3–5]

PMEA and some related compounds exhibit antiviral properties[6] and act against DNA viruses, *e.g.* herpes viruses, adenoviruses or poxviruses. In addition, they are also active against retroviruses, *i.e.* human immuno deficiency (HIV) and Moloney murine sarcoma viruses (MSV).[6,7] Another interesting observation is their cytostatic effect on L-1210 mouse leukemia cells.[6]

As the participation of nucleotides in metabolic processes depends on the presence of metal ions, we have recently studied the complexing properties of $PMEA^{2-}$ with the alkaline-earth ions and several divalent 3d ions, including Zn^{2+} and Cd^{2+}. It turned out[8] that in all M(PMEA) complexes an intramolecular equilibrium exists between a phosphonate–metal ion bound isomer and a species in which also the neighbouring ether oxygen (see Fig. 1) is involved forming a five-membered chelate.

† Abbreviations: A = adenine derivative; Ado = adenosine; 2'-AMP^{2-} = adenosine 2'-monophosphate; 3'-AMP^{2-} = adenosine 3'-monophosphate; 5'-AMP^{2-} = adenosine 5'-monophosphate; arm = heteroaromatic nitrogen base, *e.g.* bipy or phen; 5'-ATP^{4-} = adenosine 5'-triphosphate; bipy = 2,2'-bipyridyl; EtP^{2-} = ethylphosphonate; M^{2+} = Cu^{2+}, $Cu(bipy)^{2+}$ or $Cu(phen)^{2+}$, in a few instances (but this is then always clearly expressed so) this symbol is used also to represent a general divalent metal ion; MeP^{2-} = methylphosphonate; phen = 1,10-phenanthroline; PME^{2-} = dianion of phosphonomethoxyethane; $PMEA^{2-}$ = dianion of 9-(2-phosphonomethoxyethyl)adenine; Rib-MP^{2-} = D-ribose 5'-monophosphate; $R\text{-}PO_3^{2-}$ = general phosphonate and (in part also) general phosphate monoester ligand.

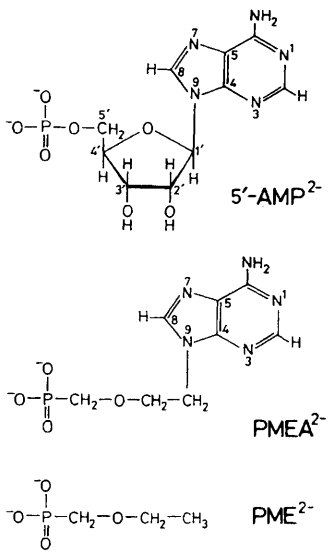
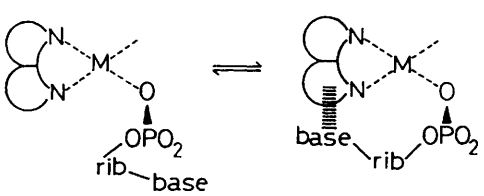


Fig. 1 Chemical structure of the dianion of 9-(2-phosphonomethoxyethyl)adenine ($PMEA^{2-}$) in comparison with the structures of adenosine 5'-monophosphate ($5'\text{-}AMP^{2-}$), which is shown in its dominating *anti* conformation,[3-5] and the dianion of phosphonomethoxyethane (PME^{2-})

Macrochelates as observed in M(5'-AMP) complexes,[9] where a metal ion may co-ordinate to the phosphate group and also to N-7 of the adenine residue, are not (or at least not to a significant extent) observed with M(PMEA) complexes, although under certain conditions a metal ion–adenine residue interaction, most probably with N-3, is possible.[8] To conclude, it is evident that the metal-ion co-ordinating properties[8] of $PMEA^{2-}$ and $5'\text{-}AMP^{2-}$ differ considerably.

Another aspect that warrants investigation is the tendency to undergo stacking; purine derivatives are well known for this property[10] and accordingly it is also expected for PMEA. Therefore we decided to study the mixed-ligand system consisting of Cu^{2+}, $PMEA^{2-}$ and a heteroaromatic amine (arm), *i.e.* 2,2'-bipyridyl (bipy) or 1,10-phenanthroline (phen), and to quantify the formation degree of the intramolecular stacks and to compare the results with the situation in the corresponding Cu(arm)(AMP) complexes. For these latter mentioned species the position of the intramolecular equilibrium (1) (rib = ribose) has already been determined.[11]



(1)

One major obstacle in the present attempt is the mentioned metal ion–ether oxygen interaction, *i.e.* the five-membered chelate ring formation in the binary M(PMEA) complexes,[8] because such an interaction has to a certain extent also to be expected in Cu(arm)(PMEA) complexes, and this of course will affect the formation of the intramolecular stacks. To overcome this problem we also studied phosphonomethoxyethane (as its anion PME^{2-}) (see Fig. 1), as this ligand should be able to undergo an ether oxygen–metal ion interaction in mixed-ligand complexes to the same extent as $PMEA^{2-}$, yet it cannot form any stacks; hence, the separation of these two different types of interaction should become possible.

Experimental

The heteroaromatic amines, *i.e.* 2,2'-bipyridyl or 1,10-phenanthroline monohydrate (both *pro analysi*), were obtained from Merck AG, Darmstadt, Germany. All the other reagents were identical with those used previously.[8]

The equipment for the potentiometric pH titrations, the experimental as well as the evaluation procedures were all identical as described.[8] It should be noted that the calculated acidity constants are so-called practical, mixed or Brønsted constants.[12] The negative logarithms of these practical acidity constants given for aqueous solutions at $I = 0.1$ mol dm^{-3} ($NaNO_3$) and 25 °C may be converted into the corresponding concentration constants by subtracting 0.02 from the listed pK_a values.[12]

The stability constants, $K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)}$, $K^{Cu(arm)}_{Cu(arm)(PMEA)}$ and $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$, where $R\text{-}PO_3^{2-}$ = MeP^{2-}, EtP^{2-} or PME^{2-}, were determined under exactly the same conditions as described[8] for the corresponding Cu^{2+} complexes, but now a 1:1 ratio of arm:Cu^{2+} was employed. Under the experimental conditions the formation of the $Cu(arm)^{2+}$ complexes is practically complete in the pH range used for the evaluation as was evident from the titrations in the absence of PMEA and $R\text{-}PO_3$; this agrees with the well known high stability of the $Cu(bipy)^{2+}$ and $Cu(phen)^{2+}$ complexes.[13] The concentration of the phosphonate in the titration solutions was always 3×10^{-4} mol dm^{-3}, and the ratio phosphonate: (Cu^{2+}/arm) was 1:11 and 1:5.6 ($I = 0.1$ mol dm^{-3}, $NaNO_3$; 25 °C).

The results listed for the stability constants of the various ternary complexes in the tables are the averages of the evaluations of at least six, usually eight, independent pairs of titration curves. It may be emphasized that the calculated stability constants of the ternary complexes showed neither dependence on pH nor on the excess of Cu^{2+}/arm employed. For further details consult ref. 8.

Results and Discussion

An equilibrium such as (1) can only exist if there is also a mutual affinity between the considered aromatic ring systems in the absence of a bridging metal ion. Therefore, first the stability of $(arm)(PMEA)^{2-}$ stacks will be estimated (section 1); only a reasonable stability of such binary adducts justifies further studies in the corresponding mixed-ligand metal-ion systems. Indeed, the stability of the $(arm)(PMEA)^{2-}$ adducts is remarkable and the estimates are also employed later for further comparisons (see section 5 and Conclusions).

Another aspect that has to be considered is the correct choice of the experimental conditions, to guarantee that in the potentiometric pH titrations the monomeric species are studied, *i.e.* that self-association of the aromatic reactants is negligible. The corresponding considerations are outlined in section 2.

1 *Estimation of the Stability of Binary* $(arm)(PMEA)^{2-}$ *Stacking Adducts.*—It has previously been concluded[8] that the self-stacking tendencies of $PMEA^{2-}$ and of $5'\text{-}AMP^{2-}$ are expected to be similar in a first approximation. An equal similarity is expected for mixed stacks involving heteroaromatic amines (arm), such as 2,2'-bipyridyl (bipy) or 1,10-phenanthroline (phen). This assumption is supported by the stability constants[11,14,15] listed in Table 1 and which refer to equilibrium (2) where A represents an adenine derivative.

$$arm + A \rightleftharpoons (arm)(A) \qquad (2a)$$

$$K^{(arm)}_{(arm)(A)} = [(arm)(A)]/([arm][A]) \qquad (2b)$$

From entries 1–3 in Table 1 it is evident that the position of the phosphate group at the ribose ring in AMP^{2-} has no influence on the stability of the $(phen)(AMP)^{2-}$ stacks. As the heteroaromatic amine is an uncharged compound, the charge of the adenine derivative is expected also not to affect the stability

Table 1 Stability constants, $K^{(arm)}_{(arm)(A)}$ [equation (2)], of some binary stacked adducts formed between a heteroaromatic amine (arm), *i.e.* 2,2'-bipyridyl (bipy) or 1,10-phenanthroline (phen), and an adenine derivative (A). The constants were determined by ^{1}H NMR shift measurements in D_2O as solvent at 27 °C and I = 0.1 mol dm^{-3} ($NaNO_3$)

No.	(arm)(A)	$K^{(arm)}_{(arm)(A)}$ [a]	$K^{(arm)}_{(arm)(A)/cor}$ [b]	Ref.
1	(phen)(2'-AMP)$^{2-}$	27.5 ± 11.1	36	11
2	(phen)(3'-AMP)$^{2-}$	25.1 ± 7.8	33	11
3	(phen)(5'-AMP)$^{2-}$	29.7 ± 5.4	38	11
4	(phen)(Ado)	31.0 ± 9.5	42	15
5	(phen)(5'-ATP)$^{4-}$	26.8 ± 7.4	38	14
6	(bipy)(5'-ATP)$^{4-}$	13.6 ± 3.9	16	14
7	(phen)(PMEA)$^{2-}$		37 ± 9 [c]	
8	(bipy)(PMEA)$^{2-}$		16 ± 5 [c]	

[a] The error limits correspond to twice the standard deviation (2σ). [b] Stability constants corrected for the self-association of arm (*cf.* ref. 14). [c] These values and their error limits are estimates based on the other entries of the table.

of the stacking adducts, and this is confirmed by entries 3–5. Of course, replacement of phen by bipy leads, due to its smaller aromatic ring system, to a lower stability of the (bipy)(A) adducts compared with that of the (phen)(A) species (*cf.* entries 5 and 6 in Table 1).

With this information summarized in Table 1, which is of a rather systematic nature, it is possible to estimate the stabilities of the (phen)(PMEA)$^{2-}$ and (bipy)(PMEA)$^{2-}$ adducts; these values were not measured however as PMEA^{2-} is a scarce compound. The corresponding estimates are listed in entries 7 and 8 of Table 1. These estimated constants, which are based on ^{1}H NMR shift measurements of the other adenine derivatives given in Table 1, are certainly correct within the given error limits and they demonstrate that the (arm)(PMEA)$^{2-}$ stacks possess remarkable stability.

Regarding the present study it may be further emphasized that the properties of simple binary (arm)(A) adducts are drastically altered as soon as the two aromatic species forming a stack are linked together *via* the co-ordination of a metal ion. For example, the stabilities of the (phen)(2'-AMP)$^{2-}$, (phen)-(3'-AMP)$^{2-}$ and (phen)(5'-AMP)$^{2-}$ adducts are identical within experimental error (Table 1), yet the formation degrees of the intramolecular stacks formed in the corresponding Cu(phen)(AMP) complexes [see equilibrium (1)] are very different because now the position of the phosphate group at the ribose ring affects the overlap of the involved aromatic systems significantly.[11]

2 *Experimental Conditions for the Potentiometric* pH *Titrations in Aqueous Solution.*—From all the species considered in this study which contain aromatic rings phen is the one which shows the most pronounced tendency for self-stacking, with K^{self}_{phen} = 31.1 ± 3.4 dm^3 mol^{-1} in D_2O at 27 °C and I = 0.1 mol dm^{-3} ($NaNO_3$).[14] Hence, if one requires 97% (or more) of phen to be present in the monomeric form, in aqueous solution only concentrations of 5 × 10^{-4} mol dm^{-3} (or below) are allowed.[14] However, for Cu(phen)$^{2+}$ 10-fold larger concentrations may be employed, because one may assume that due to charge repulsion the self-association tendency of phen in the positively charged complex is reduced at least by a factor of one tenth, *i.e.* $K^{self}_{Cu(phen)}$ < 3 dm^3 mol^{-1}; indeed, for Zn(phen)$^{2+}$ $K^{self}_{Zn(phen)}$ equals 1.1 ± 0.2 dm^3 mol^{-1} as measured by ^{1}H NMR shift experiments in D_2O.[16]

Therefore, with [PMEA] = 3 × 10^{-4} mol dm^{-3} (*cf.* also ref. 8) and [Cu^{2+}–phen] = 3.33 × 10^{-3} mol dm^{-3} the concentrations in the present experiments (see also Experimental section) are such that the results obtained refer to monomeric species, *i.e.* self-association is certainly negligible for any of the reactants under our experimental conditions.

3 *Acidity Constants of* $H_3(PMEA)^+$ *and of Simple Diprotonated Phosphonates.*—From the chemical structure shown in Fig. 1 for PMEA^{2-} it is evident that this adenine derivative, just like 5'-AMP^{2-},[9] may accept three protons, two at the phosphonate residue and one at N-1 of the purine moiety.[8] Accordingly, the three deprotonation equilibria (3)–(5) have to be considered.

$$H_3(PMEA)^+ \rightleftharpoons H_2(PMEA)^{\pm} + H^+ \quad (3a)$$

$$K^H_{H_3(PMEA)} = [H^+][H_2(PMEA)^{\pm}]/[H_3(PMEA)^+] \quad (3b)$$

$$H_2(PMEA)^{\pm} \rightleftharpoons H(PMEA)^- + H^+ \quad (4a)$$

$$K^H_{H_2(PMEA)} = [H^+][H(PMEA)^-]/[H_2(PMEA)^{\pm}] \quad (4b)$$

$$H(PMEA)^- \rightleftharpoons PMEA^{2-} + H^+ \quad (5a)$$

$$K^H_{H(PMEA)} = [H^+][PMEA^{2-}]/[H(PMEA)^-] \quad (5b)$$

The release of the first proton [equilibrium (3)] occurs from the diprotonated phosphonate residue, and the acidity constant was recently estimated as $pK^H_{H_3(PMEA)} \approx 1.7$. In any case this pK_a is below 2.2 and does therefore not affect equilibria (4) and (5) or the formation of complexes (section 4).[8] The next proton is liberated from the H$^+$(N-1) site of the zwitterionic species with $pK^H_{H_2(PMEA)}$ = 4.16 ± 0.02 [equation (4)] and the final proton from the –P(O)$_2$(OH)$^-$ group [equation (5)] with $pK^H_{H(PMEA)}$ = 6.90 ± 0.01 as determined by potentiometric pH titrations in aqueous solutions (I = 0.1 mol dm^{-3}, $NaNO_3$; 25 °C).[8]

The species PME^{2-} (Fig. 1) behaves as a common phosphonate (R-PO$_3^{2-}$) towards protons and therefore accepts in total only two protons; the corresponding deprotonation equilibria are (6) and (7). The acidity constant for the release of

$$H_2(R\text{-}PO_3) \rightleftharpoons H(R\text{-}PO_3)^- + H^+ \quad (6a)$$

$$K^H_{H_2(R\text{-}PO_3)} = [H^+][H(R\text{-}PO_3)^-]/[H_2(R\text{-}PO_3)] \quad (6b)$$

$$H(R\text{-}PO_3)^- \rightleftharpoons R\text{-}PO_3^{2-} + H^+ \quad (7a)$$

$$K^H_{H(R\text{-}PO_3)} = [H^+][R\text{-}PO_3^{2-}]/[H(R\text{-}PO_3)^-] \quad (7b)$$

the first proton from the –P(O)(OH)$_2$ group in H_2(PME) was estimated as $pK^H_{H_2(PME)} \approx 2.0$.[8] To be on the safe side, one may conclude that this pK_a is certainly below 2.5, *i.e.* it does not affect equilibrium (7) nor the formation of complexes (section 4). The release of the final proton, *i.e.* from –P(O)$_2$(OH)$^-$, was measured in aqueous solution by potentiometric pH titrations and $pK^H_{H(PME)}$ = 7.02 ± 0.01 (I = 0.1 mol dm^{-3}, $NaNO_3$; 25 °C).[8]

The above mentioned acidity constants were used in the calculations for the results presented in the following sections. Those for methylphosphonate and ethylphosphonate are listed in Table 4 and considered in section 7.

4 *Stabilities of the Ternary Complexes Formed between* Cu(arm)$^{2+}$ *and* PMEA^{2-} *or* PME^{2-}.—The experimental data from the potentiometric pH titrations may be completely described by considering equilibria (4), (5), (8) and (9), provided

$$M^{2+} + H(PMEA)^- \rightleftharpoons M(H\cdot PMEA)^+ \quad (8a)$$

$$K^M_{M(H\cdot PMEA)} = [M(H\cdot PMEA)^+]/([M^{2+}][H(PMEA)^-]) \quad (8b)$$

$$M^{2+} + PMEA^{2-} \rightleftharpoons M(PMEA) \quad (9a)$$

$$K^M_{M(PMEA)} = [M(PMEA)]/([M^{2+}][PMEA^{2-}]) \quad (9b)$$

the mathematical evaluation is not carried into the pH range where hydroxo complexes form. In expressions (8)–(11) M^{2+} represents Cu^{2+}, Cu(bipy)$^{2+}$ or Cu(phen)$^{2+}$.

Table 2 Logarithms of the stability constants of the ternary Cu(arm)(H·PMEA)$^+$ [equation (8)] and Cu(arm)(PMEA) complexes [equation (9)] as determined by potentiometric pH titrations, together with the negative logarithms of the acidity constants [equations (10) and (11)] of the Cu(arm)(H·PMEA)$^+$ species. The stability constants of the ternary Cu(arm)(PME) complexes were measured for comparison [equation (12)]. For the same reason the previous results [8] for the corresponding binary complexes are also listed. All constants refer to aqueous solutions at 25 °C and I = 0.1 mol dm^{-3} ($NaNO_3$)*

M^{2+}	$\log K^{M}_{M(H\cdot PMEA)}$	$\log K^{M}_{M(PMEA)}$	$pK^{H}_{M(H\cdot PMEA)}$	$\Delta \log K_{Cu}$
Cu^{2+}	1.48 ± 0.16	3.96 ± 0.04	4.42 ± 0.17	
$Cu(bipy)^{2+}$	1.77 ± 0.11	4.70 ± 0.02	3.97 ± 0.11	0.74 ± 0.04
$Cu(phen)^{2+}$	2.20 ± 0.09	4.97 ± 0.03	4.13 ± 0.10	1.01 ± 0.05
		$\log K^{M}_{M(PME)}$		$\Delta \log K_{Cu}$
Cu^{2+}		3.73 ± 0.03		
$Cu(bipy)^{2+}$		3.86 ± 0.03		0.13 ± 0.04
$Cu(phen)^{2+}$		3.90 ± 0.04		0.17 ± 0.05

* The values resulting for $\Delta \log K_{Cu}$ [equations (13), (14) and (20)] from the constants for the binary and ternary complexes are also listed. The errors given are three times the standard error of the mean value or the sum of the probable systematic errors, whichever is larger. The error limits of the derived data (columns 4 and 5) were calculated according to the error propagation after Gauss. Regarding the acidity constants of $H_2(PMEA)^{\pm}$ and $H(PME)^-$ see text in section 3.

The acidity constant for the connected equilibrium (10) may be calculated using equation (11).

$$M(H\cdot PMEA)^+ \rightleftharpoons M(PMEA) + H^+ \quad (10a)$$

$$K^{H}_{M(H\cdot PMEA)} = [M(PMEA)][H^+]/[M(H\cdot PMEA)^+] \quad (10b)$$

$$pK^{H}_{M(H\cdot PMEA)} = pK^{H}_{H(PMEA)} + \log K^{M}_{M(H\cdot PMEA)} - \log K^{M}_{M(PMEA)} \quad (11)$$

The constants for equilibria (8)–(10) are listed in the upper part of Table 2. Of course, the mathematical analysis of potentiometric pH titrations yields only the amount and distribution of species of a net charged type, *e.g.* of Cu(arm)(H·PMEA)$^+$, and additional information is required to evaluate the possibility of stacking and to locate the binding sites of the proton and the metal ion; these problems will be addressed in sections 5 and 6.

Similarly, the stability constants of the Cu(arm)(PMEA) complexes also warrant a more detailed analysis regarding the structure of these complexes in solution. To obtain the necessary information for such an evaluation we determined also the stability of the ternary complexes with PME^{2-} (see Fig. 1); with this ligand no intramolecular stacks can be formed in the Cu(arm)(PME) species. The potentiometric titration data request in this case consideration of equilibria (7) and (12), where R-PO_3^{2-} = PME^{2-} and M^{2+} = Cu^{2+}, $Cu(bipy)^{2+}$ or $Cu(phen)^{2+}$. The corresponding results are summarized in the lower part of Table 2.

$$M^{2+} + R\text{-}PO_3^{2-} \rightleftharpoons M(R\text{-}PO_3) \quad (12a)$$

$$K^{M}_{M(R\text{-}PO_3)} = [M(R\text{-}PO_3)]/([M^{2+}][R\text{-}PO_3^{2-}]) \quad (12b)$$

One way to quantify the stability of mixed-ligand complexes [17,18] is to consider equilibrium (13) and the corresponding equilibrium constant is calculated using equation (14).

$$Cu(arm)^{2+} + Cu(PMEA) \rightleftharpoons Cu(arm)(PMEA) + Cu^{2+} \quad (13a)$$

$$10^{\Delta \log K_{Cu}} = \frac{[Cu(arm)(PMEA)][Cu^{2+}]}{[Cu(arm)^{2+}][Cu(PMEA)]} \quad (13b)$$

$$\Delta \log K_{Cu} = \log K^{Cu(arm)}_{Cu(arm)(PMEA)} - \log K^{Cu}_{Cu(PMEA)} \quad (14)$$

Evidently the same considerations can be applied to the PME^{2-} systems. According to the general rule for complex stabilities, $K_1 > K_2$, one expects that equilibrium (13a) lies on the left with negative values for $\Delta \log K_{Cu}$ in agreement with statistical considerations.[17,19]

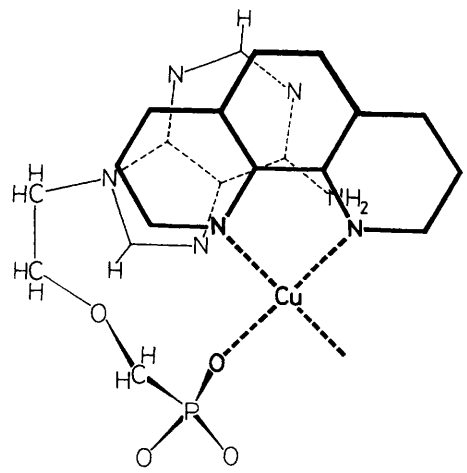


Fig. 2 Tentative and simplified structure of a species with an intramolecular stack for Cu(phen)(PMEA) in solution

Hence, all the ternary complexes of Table 2 (see column 5) are more stable than expected and equilibrium (13a) is clearly displaced to the right. In the case of the Cu(arm)(PME) complexes the metal ion is expected to co-ordinate not only to the phosphonate group but to a significant extent also to the neighbouring ether oxygen (see Fig. 1) as is already known for binary M(PME) complexes including Cu(PME);[8] this aspect will be evaluated in detail in section 8. However, the important point at this stage is that the values of $\Delta \log K_{Cu}$ for the Cu(arm)(PMEA) complexes are considerably larger than those for the Cu(arm)(PME) species (see column 5 in Table 2). This observation proves that in the Cu(arm)(PMEA) complexes a further intramolecular interaction must occur which is responsible for the further increase in stability and this can only be a stack formation, *e.g.* of the kind shown in Fig. 2. Therefore, further analysis of the measured equilibrium constants is warranted with the aim to separate the contribution of the Cu^{2+}–ether oxygen interaction from that of the intramolecular stack formation towards the observed increased complex stability (see sections 9 and 10).

5 *Structural Considerations on the Monoprotonated* Cu(arm)(H·PMEA)$^+$ *Complexes.*—At which sites are the proton and the metal ion bound in the Cu(arm)(H·PMEA)$^+$ species? In $H_2(PMEA)^{\pm}$ one proton is at the adenine residue [$pK^{H}_{H_2(PMEA)}$ = 4.16] and the other at the phosphonate group [$pK^{H}_{H(PMEA)}$ =

6.90] (see section 3) and one of these two protons is replaced by $Cu(arm)^{2+}$; this replacement may occur in a direct or in an indirect manner as shown below. It is evident that replacement of either proton will lead, due to the two-fold positive charge of $Cu(arm)^{2+}$, to an increase in acidity for the other proton; hence, the pK_a values of the monoprotonated complexes should be compared with the above given two pK_a values of $H_2(PMEA)^{\pm}$.

For $Cu(H\cdot PMEA)^+$ $pK^{H}_{Cu(H\cdot PMEA)}$ equals 4.42 and therefore an increase in acidity is observed *only* if the proton is located at the phosphonate group and the metal ion at the adenine residue, a conclusion valid also for all the other binary $M(H\cdot PMEA)^+$ species (for further details see ref. 8). For $Cu(phen)(H\cdot PMEA)^+$ and $Cu(bipy)(H\cdot PMEA)^+$ one would arrive at a slight increase in acidity also with $pK^{H}_{H_2(PMEA)} = 4.16$, *i.e.* at ΔpK_a values of -0.03 (± 0.10) and -0.19 (± 0.11), respectively (*cf.* the value of 4.16 with the constants listed in the fourth column of Table 2). However, such an acidification is clearly too small; the expected difference is $\Delta pK_a \leqslant -0.5$[8,20] and hence, one has to conclude that also in the $Cu(phen)(H\cdot PMEA)^+$ and $Cu(bipy)(H\cdot PMEA)^+$ complexes the proton is predominantly located at the phosphonate group.

However, considering that in the $Cu(arm)(H\cdot PMEA)^+$ complexes the proton is at the phosphonate group these species may still exist in two different forms, *i.e.* one species in which $Cu(arm)^{2+}$ is directly co-ordinated to the adenine residue and which we designate as $Cu(arm)(H\cdot PMEA)^+_{ade}$ and a second one in which $H(PMEA)^-$ is stacked *via* its adenine moiety to the aromatic ring system of $Cu(arm)^{2+}$, designated as $Cu(arm)(H\cdot PMEA)^+_{st}$, and in which the metal ion does not directly bind to $H(PMEA)^-$; hence, one may rewrite equation (8b) in the form of equation (15).

$$K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)} = \frac{[Cu(arm)(H\cdot PMEA)^+_{ade}] + [Cu(arm)(H\cdot PMEA)^+_{st}]}{[Cu(arm)^{2+}][H(PMEA)^-]} \quad (15a)$$

$$= \frac{[Cu(arm)(H\cdot PMEA)^+_{ade}]}{[Cu(arm)^{2+}][H(PMEA)^-]} + \frac{[Cu(arm)(H\cdot PMEA)^+_{st}]}{[Cu(arm)^{2+}][H(PMEA)^-]} \quad (15b)$$

$$= K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)ade} + K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)st} \quad (15c)$$

Based on previous experience one may now make estimates for the equilibrium constants appearing in equation (15c), which may then be compared with the results of the experiments. (*i*) The stability constant $K^{Cu}_{Cu(H\cdot PMEA)} = 10^{1.48}$ (*cf.* Table 2) quantifies the interaction of Cu^{2+} with the adenine residue of $H(PMEA)^-$; experience shows that the stability constant for a Cu^{2+}–N donor interaction of this type decreases by about 0.2 log unit if the Cu^{2+} ion is already co-ordinated to bipy or phen.[21] Hence, we estimate for $K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)ade} \simeq 10^{(1.48-0.2)} = 10^{1.3}$. (*ii*) The stabilities of the stacking adducts formed between bipy or phen and an adenine residue of variously charged species are known (see Table 1); what needs to be estimated is the stability of stacks formed between the positively charged $Cu(bipy)^{2+}$ or $Cu(phen)^{2+}$ species and an adenine residue of the negatively charged $H(PMEA)^-$ species. It is this latter point which should stabilize the stacks by coulombic interactions ($+2/-1$) possibly involving also the formation of ion pairs.[22] Based on previous experience with distant charge effects[20,22] we conclude that there is a promoting effect of 0.4 log unit, which corresponds to a factor of 2.5. With the values $K^{(PMEA)}_{(bipy)(PMEA)} = 16$ and $K^{(PMEA)}_{(phen)(PMEA)} = 37$ of Table 1 we thus obtain $K^{Cu(bipy)}_{Cu(bipy)(H\cdot PMEA)st} = 10^{(1.2+0.4)} = 10^{1.6}$ and $K^{Cu(phen)}_{Cu(phen)(H\cdot PMEA)st} = 10^{(1.6+0.4)} = 10^{2.0}$.

The preceding estimates, together with equation (15c), lead now to the following results [equations (16) and (17)].

$$K^{Cu(bipy)}_{Cu(bipy)(H\cdot PMEA)} = K^{Cu(bipy)}_{Cu(bipy)(H\cdot PMEA)ade} + K^{Cu(bipy)}_{Cu(bipy)(H\cdot PMEA)st} \quad (16a)$$

$$= 10^{1.3} + 10^{1.6} \quad (16b)$$

$$= 20 + 40 = 60$$

$$\log K^{Cu(bipy)}_{Cu(bipy)(H\cdot PMEA)} = 1.8 \quad (16c)$$

$$K^{Cu(phen)}_{Cu(phen)(H\cdot PMEA)} = K^{Cu(phen)}_{Cu(phen)(H\cdot PMEA)ade} + K^{Cu(phen)}_{Cu(phen)(H\cdot PMEA)st} \quad (17a)$$

$$= 10^{1.3} + 10^{2.0} \quad (17b)$$

$$= 20 + 100 = 120$$

$$\log K^{Cu(phen)}_{Cu(phen)(H\cdot PMEA)} = 2.1 \quad (17c)$$

Comparison of the results given in equations (16c) and (17c) with the corresponding experimentally determined stability constants listed in the second column of Table 2 shows excellent agreement; naturally this further supports the developed ideas.

6 *Appreciation of Further Difficulties and Considerations on the Intramolecular Equilibrium between* $Cu(arm)^{2+}$*-adenine Co-ordinated and Stacked Species in* $Cu(arm)(H\cdot PMEA)^+$ *Systems.*—One has to emphasize that the species designated above as $Cu(arm)(H\cdot PMEA)^+_{ade}$ with $Cu(arm)^{2+}$ co-ordinated to the adenine residue and the proton at the phosphonate group of $H(PMEA)^-$ is most probably not a well defined species, but a mixture of (at least) two isomers. From adenosine it is well known[23] that it shows a dichotomy by distributing metal ions between the N-1 and N-7 sites; the same dichotomy must also be expected for $H(PMEA)^-$ as a ligand where the monoprotonated phosphate group is not directly involved in metal-ion binding.[8] It may be added that for $Cu(Ado)^{2+}$ evidence exists that N-7 is the preferred site for Cu^{2+} co-ordination.[23] Similarly, the stacked species $Cu(arm)(H\cdot PMEA)^+_{st}$ is most probably also a mixture of various isomers, but although one may expect that the aromatic ring systems are arranged in an approximately parallel and coplanar fashion with a distance of about 3.4 Å to each other,[24] the planar orientation of the ring systems may still vary.[16]

Despite these shortcomings one may consider the intramolecular equilibrium between $Cu(arm)^{2+}$-adenine co-ordinated and aromatic ring-stacked species [equation (18)]. Indeed,

$$Cu(arm)(H\cdot PMEA)^+_{ade} \rightleftharpoons Cu(arm)(H\cdot PMEA)^+_{st} \quad (18)$$

from equation (15) it is evident that the ratio R, or the dimensionless equilibrium constant K_I*, for equilibrium (18) may be calculated using equation (19).

$$R = K_I^* = \frac{[Cu(arm)(H\cdot PMEA)^+_{st}]}{[Cu(arm)(H\cdot PMEA)^+_{ade}]} \quad (19a)$$

$$= \frac{K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)st}}{K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)ade}} \quad (19b)$$

Application of equation (19b) with the equilibrium constants given in equations (16b) and (17b) leads to the results summarized in Table 3. Despite the large uncertainties, the results of Table 3 clearly prove the following. (*i*) Equilibrium (18) truly exists, *i.e.* both species occur in appreciable amounts. (*ii*) The stacked adduct occurs in a somewhat higher concentration in both $Cu(arm)(H\cdot PMEA)^+$ systems. (*iii*) As one might expect, the formation degree of $Cu(phen)(H\cdot PMEA)^+_{st}$ is higher than that of $Cu(bipy)(H\cdot PMEA)^+_{st}$.

7 *Stabilities of Ternary* $Cu(arm)(R\text{-}PO_3)$ *Complexes with a Pure Phosphate–*Cu^{2+} *Co-ordination and Correlation between*

Table 3 Estimates for the stacked *versus* Cu(arm)$^{2+}$-adenine co-ordinated ratios for Cu(arm)(H·PMEA)$^{+}$ complexes and percentages of the stacked Cu(arm)(H·PMEA)$^{+}_{st}$ and Cu(arm)$^{2+}$-adenine bound Cu(arm)(H·PMEA)$^{+}_{ade}$ species (see section 6)

Cu(arm)$^{2+}$	log $K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)_{st}}$ [a]	log $K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)_{ade}}$ [a]	$R = \frac{[Cu(arm)(H\cdot PMEA)^{+}_{st}]}{[Cu(arm)(H\cdot PMEA)^{+}_{ade}]}$ [b]	% Cu(arm)(H·PMEA)$^{+}_{st}$	% Cu(arm)(H·PMEA)$^{+}_{ade}$
Cu(bipy)$^{2+}$	1.6 ± 0.2	1.3 ± 0.2	2.0 (1.3/3.2)[c]	67 (57/76)[c]	33 (43, 24)[c]
Cu(phen)$^{2+}$	2.0 ± 0.2	1.3 ± 0.2	5.0 (3.2/7.9)[c]	83 (76/89)[c]	17 (24, 11)[c]

[a] These equilibrium constants follow from equations (16a), (16b) and (17a), (17b). The error limits are estimated. [b] See equation (19a). [c] To provide a feeling for the error limits, the first value in parentheses is calculated with the lower limit of log $K^{Cu(arm)}_{Cu(arm)(H\cdot PMEA)_{st}}$ and the second with the corresponding upper limit.

Complex Stability and Phosphonate Group Basicity.—To be able to quantify the observed increased stabilities of the ternary Cu(arm)(PME) and Cu(arm)(PMEA) complexes (see last paragraph in section 4) it is necessary to know the exact contribution of the Cu^{2+}–phosphonate binding to the overall stability of these ternary complexes. As in an isomeric complex system the stability of only one of these isomers cannot be measured directly [25] it is necessary to determine such a stability in an indirect way. This is best achieved by constructing baseline plots for the dependency of complex stability (log K) on ligand basicity (pK_a); for a family of structurally closely related ligands plots for log K *versus* pK_a result in a straight line.[25,26] It is evident that, once such a plot has been constructed, for any known pK_a value the stability of the corresponding complex can be calculated.

For ternary Cu(arm)(R-PO_3) complexes with pure Cu^{2+}–phosphonate binding the correlation for the values of log $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$ [see equation (12b)] may be obtained, in principle, in the way described previously for phosphate monoester systems.[27] For the binary Cu(R-PO_3) complexes the relation between complex stability and phosphate group basicity has been well defined in the pH range 5–7;[28] very recently it was shown in addition that on the same plots of log $K^{Cu}_{Cu(R\text{-}PO_3)}$ *versus* $pK^{H}_{H(R\text{-}PO_3)}$ the data points for phosphonate systems also fitted [8] and in this way the pH range was extended up to 8. This least-squares regression line valid for pH 5–8 was calculated from in total eight data points; the corresponding straight-line equation is given in the first row of Table 5 (see later).

Unfortunately, a corresponding line cannot be easily constructed for mixed-ligand systems because with several of the ligands used in the binary systems, in the ternary Cu(arm)-(R-PO_3) complexes an intramolecular ligand–ligand interaction exists;[27] for example, phenyl phosphate is perfectly suited to the construction of a baseline for binary Cu(R-PO_3) complexes but not for one due to ternary Cu(arm)(R-PO_3) complexes because formation of an intramolecular stack between the phenyl residue and the aromatic ring systems of bipy or phen alters the stability of these complexes.[27] However, it was shown previously for D-ribose 5′-monophosphate (RibMP^{2-}) that in its ternary Cu(arm)(RibMP) complexes no intramolecular ligand–ligand interaction occurs;[27] therefore with this ligand the effect of arm relative to the stability of the binary complex can be quantified according to equation (20) which corresponds to the definitions given in equations (13) and (14) for PMEA^{2-}

$$\Delta \log K_{Cu} = \log K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)} - \log K^{Cu}_{Cu(R\text{-}PO_3)} \quad (20)$$

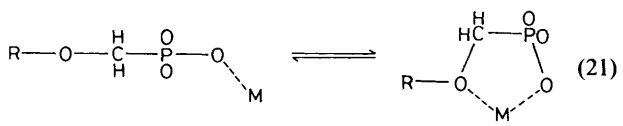
It may be added here that to identify $\Delta \log K_{Cu}$ for further equilibria additional subscripts will be given where necessary, *e.g.* $\Delta \log K_{Cu/bipy/R\text{-}PO_3}$.

The results corresponding to equation (20) for Cu^{2+}/arm/RibMP systems are listed in the first row of Table 4. The slightly positive values of $\Delta \log K_{Cu/bipy/RibMP}$ and $\Delta \log K_{Cu/phen/RibMP}$ correspond to general experience, *i.e.* such an increased stability is expected for mixed-ligand complexes formed by a divalent 3d metal ion, a heteroaromatic N base and an O donor ligand.[17,18,29]

To see if phosphonate ligands not only behave like phosphate monoester ligands in binary complexes [8] but also in ternary complexes, we have studied the systems with methylphosphonate (MeP^{2-}, $CH_3PO_3^{2-}$) and ethylphosphonate (EtP^{2-}, $CH_3CH_2PO_3^{2-}$); the corresponding results are summarized in Table 4. For methylphosphonate and ethylphosphonate no intramolecular ligand–ligand interaction is expected in the Cu(arm)(R-PO_3) complexes; indeed the stability differences Δ log $K_{Cu/arm/R\text{-}PO_3}$ for these two ligands correspond within the error limits to those observed for $\Delta \log K_{Cu/arm/RibMP}$ proving that phosphonates and phosphate monoesters behave alike.

There are now in principle three data points (*cf.* Table 4) available for the construction of log $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$ *versus* $pK^{H}_{H(R\text{-}PO_3)}$ plots; however, straight lines based on only three data pairs cannot be expected to be very reliable. Therefore we preferred to make use of the justified assumption [19,27,30] that the slopes m of the regression lines for binary and their corresponding ternary systems are identical, and that only the intercepts b are different. The arithmetic mean of the three values for $\Delta \log K_{Cu/bipy/R\text{-}PO_3}$ given in Table 4 is 0.024 ± 0.012 (1σ); hence, the intercept b for the Cu(bipy)(R-PO_3) correlation line equals 0.009 (= −0.015 + 0.024) and the error limit (s.d.) increases from 0.019 for the binary system to 0.022 for the ternary system. These results are listed in the second row of Table 5. Similarly, the arithmetic mean for $\Delta \log K_{Cu/phen/R\text{-}PO_3}$ (Table 4), which equals 0.033 ± 0.009 (1σ), leads to the results given in the third row of Table 5, which define the straight-line equation valid for the dependency between log $K^{Cu(phen)}_{Cu(phen)(R\text{-}PO_3)}$ and $pK^{H}_{H(R\text{-}PO_3)}$ for ternary Cu(phen)(R-PO_3) complexes in the pH range 5–8. It is satisfying to note that the results of Table 5 agree within the error limits with the previous ones [27] valid only for phosphate monoester complexes and the pH range 5–7. Hence, with these straight-line equations and the pK_a value of any phosphonate (or phosphate) group the corresponding affinity constants with the Cu(arm)$^{2+}$ species can be calculated; use of this procedure is now made in sections 8 and 10.

8 *Proof for an Increased Stability of the* Cu(arm)(PME) *Complexes and Structure of these Species in Solution.*—For M(PME) complexes the participation of the ether oxygen (see Fig. 1) in complex formation is well established [8] and as surmised already in section 4 this property must also be expected for the ternary Cu(arm)(PME) complexes; hence, equilibrium (21) has to be considered. To facilitate writing, M represents in equilibrium (21) and also in equations (22)–(27) Cu^{2+}, Cu(bipy)$^{2+}$ or Cu(phen)$^{2+}$.



(21)

The position of the concentration-independent equilibrium (21) between an 'open' isomer, $M(PME)_{op}$, and a 'closed' species, $M(PME)_{cl}$, is defined by the intramolecular and hence dimensionless equilibrium constant K_I [equation (22)]. Of

$$K_I = [M(PME)_{cl}]/[M(PME)_{op}] \quad (22)$$

Table 4 Negative logarithms of the acidity constants [equation (7)] of $H(RibMP)^-$, $H(MeP)^-$ and $H(EtP)^-$, logarithms of the stability constants of the corresponding binary Cu(R-PO_3) [equation (12)] and ternary Cu(arm)(R-PO_3) complexes [equation (12)] and resulting values for Δ log $K_{Cu/arm/R\text{-}PO_3}$ [equation (20)]. All constants refer to aqueous solutions at 25 °C and I = 0.1 mol dm^{-3} ($NaNO_3$)*

$R\text{-}PO_3^{2-}$	$pK^{H}_{H(R\text{-}PO_3)}$	log $K^{Cu}_{Cu(R\text{-}PO_3)}$	log $K^{Cu(bipy)}_{Cu(bipy)(R\text{-}PO_3)}$	Δ log $K_{Cu/bipy/R\text{-}PO_3}$	log $K^{Cu(phen)}_{Cu(phen)(R\text{-}PO_3)}$	Δ log $K_{Cu/phen/R\text{-}PO_3}$
$RibMP^{2-}$	6.24 ± 0.01	2.962 ± 0.005	3.010 ± 0.003	0.048 ± 0.006	2.997 ± 0.006	0.035 ± 0.008
MeP^{2-}	7.53 ± 0.01	3.492 ± 0.017	3.506 ± 0.013	0.014 ± 0.021	3.539 ± 0.023	0.047 ± 0.029
EtP^{2-}	7.77 ± 0.01	3.610 ± 0.013	3.620 ± 0.013	0.010 ± 0.018	3.626 ± 0.017	0.016 ± 0.021

* The errors given with the values in the second column are three times the standard error of the mean value (3 σ) or the sum of the probable systematic errors, whichever is larger. The error limits in the other five columns to the right correspond only to a single standard deviation (1 σ) as these values are needed for the calculations for the base-line correlations as described in section 7 (see also Table 5); the error limits for the values given with Δ log K_{Cu} were calculated according to the error propagation after Gauss. However, it is recommended that for all general comparisons the values in columns 3–7 should be rounded to two digits after the point and also three times the standard deviation (3σ) should be employed. The constants listed in the first row are from ref. 27; the values for $pK^{H}_{H(R\text{-}PO_3)}$ and log $K^{Cu}_{Cu(R\text{-}PO_3)}$ with $R\text{-}PO_3^{2-}$ = MeP^{2-} and EtP^{2-} are from ref. 8, while those of the corresponding mixed-ligand systems have been measured now.

Table 5 Base-line correlations between the co-ordination of Cu^{2+} or $Cu(arm)^{2+}$ to phosphonates or phosphate monoesters ($R\text{-}PO_3^{2-}$) and the basicity of the corresponding ligating groups. The correlations refer to aqueous solutions at 25 °C and I = 0.1 mol dm^{-3} ($NaNO_3$)*

M^{2+}	m	b	s.d.
Cu^{2+}	0.465 ± 0.025	−0.015 ± 0.164	0.019
$Cu(bipy)^{2+}$	0.465	0.009	0.022
$Cu(phen)^{2+}$	0.465	0.018	0.021

* The slope (m) and the intercept (b) for the straight base-line plot of log $K^{Cu}_{Cu(R\text{-}PO_3)}$ *versus* $pK^{H}_{H(R\text{-}PO_3)}$ are calculated[8] from the equilibrium constants of six simple phosphate monoesters (4-nitrophenyl phosphate, phenyl phosphate, *n*-butyl phosphate, D-ribose 5′-monophosphate, uridine 5′-monophosphate and thymidine 5′-monophosphate; ref. 28) and two also simple phosphonates (methylphosphonate and ethylphosphonate; ref. 8); the error limits given with m and b correspond to one standard deviation (1σ), and the correlation coefficient was determined as R = 0.991.[8] For the entries in the second and third rows the same values of the slope and intercept are used, but the intercept (b) is now in each case adjusted to the corresponding mixed-ligand system by adding the value for Δ log $K_{Cu/arm/R\text{-}PO_3}$ as described in section 7. In the straight-line equation, $y = m{\cdot}x + b$, x represents the pK_a value of any phosphate monoester or phosphonate and y the calculated log $K^{Cu}_{Cu(R\text{-}PO_3)}$ or log $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$ value of the corresponding Cu(R-PO_3) or Cu(arm)(R-PO_3) complex. The first value in the last column to the right is the standard deviation (s.d.) resulting from the differences between the experimental and calculated values for the eight mentioned ligand systems;[8] in the two values below, the error of Δ log $K_{Cu/arm/R\text{-}PO_3}$ is also taken into account. These s.d. values multiplied by two or three are considered as reasonable error limits for any stability constant calculation in the pK_a range 5–8.

course, the experimentally measured stability constant for a M(PME) complex is defined by equation (12b), yet due to equilibrium (21) this expression may be rewritten as given in equation (23), which then may be further developed[8,9,25] to equations (24) and (25).

$$K^{M}_{M(PME)} = \frac{[M(PME)_{op}] + [M(PME)_{cl}]}{[M^{2+}][PME^{2-}]} \quad (23)$$

$$= K^{M}_{M(PME)_{op}} + K_I{\cdot}K^{M}_{M(PME)_{op}} = K^{M}_{M(PME)_{op}}(1 + K_I) \quad (24)$$

$$K_I = \frac{K^{M}_{M(PME)}}{K^{M}_{M(PME)_{op}}} - 1 = 10^{\log \Delta} - 1 \quad (25)$$

The stability constant, $K^{M}_{M(PME)_{op}}$, of the open isomer is not directly accessible by experiments, yet it may be calculated with the known $pK^{H}_{H(PME)}$ value (section 3) and the equations of the correlation lines listed in Table 5. Hence, the stability-constant difference of equation (26) can be calculated, which then also

$$\log \Delta_{PME} = \log K^{M}_{M(PME)} - \log K^{M}_{M(PME)_{op}} \quad (26)$$

defines the second term in equation (25) above. Clearly, knowledge of the dimensionless equilibrium constant K_I [equations (22) and (25)] allows us then to calculate, according to equation (27), the percentage of the closed form, $M(PME)_{cl}$, occurring in equilibrium (21).

$$\%\ M(PME)_{cl} = 100 \cdot K_I/(1 + K_I) \quad (27)$$

The results of the corresponding calculations are summarized in the upper part of Table 6. Comparison of the data in columns 2–4 proves that the Cu(arm)(PME) species are indeed more stable than expected on the basis of the basicity of the PME phosphonate group. Consequently *via* equations (25) and (27) the intramolecular equilibrium constant K_I and the percentages for the closed species, $Cu(arm)(PME)_{cl}$, can be calculated. It is evident that the formation degree of the five-membered chelate involving the ether oxygen (last column in Table 6) is at least as pronounced in the mixed ligand Cu(arm)(PME) complexes as in the parent Cu(PME) complex.

9 *Evaluation of the Increased Stability of the* Cu(arm)(PMEA) *Complexes and Conclusions Regarding the Structures of these Species.*—It is well known that any kind of chelate formation[8,9,25] or intramolecular ligand–ligand interaction[19,25,27,30,31] must be reflected in an increased complex stability. Hence, positive values are expected for the stability difference, log Δ, as defined in equation (28), where M^{2+} =

$$\log \Delta_{PMEA} = \log K^{M}_{M(PMEA)} - \log K^{M}_{M(PMEA)_{op}} \quad (28)$$

Cu^{2+}, $Cu(bipy)^{2+}$ or $Cu(phen)^{2+}$. This definition is analogous to equation (26) given for the PME systems and accordingly $K^{M}_{M(PMEA)_{op}}$ represents the stability constant of the open isomer, *i.e.* the metal ion is only co-ordinated to the phosphonate group and no other interaction occurs in this species.

Values for $K^{M}_{M(PMEA)_{op}}$ can be calculated in the way described for PME complexes in section 8; the corresponding results are listed in the lower part of Table 6. The stability differences log Δ_{PMEA} derived according to equation (28) are given in the fourth column; all these values are *positive* in agreement with the above mentioned expectation thus confirming that in these PMEA complexes additional intramolecular interactions occur giving rise to a stability higher than expected on the basis of the basicity of the PMEA phosphonate group. However, most important is the fact that the log Δ_{PMEA} values are significantly larger than those for log Δ_{PME} as a comparison between the corresponding values in the upper and lower parts of Table 6

Table 6 Quantification of the stability increase *via* log Δ [equations (26) and (28)] for the Cu(arm)(PME) and Cu(arm)(PMEA) complexes, and extent of the intramolecular chelate formation [equation (27)] in the Cu(arm)(PME) species at 25 °C and I = 0.1 mol dm^{-3} ($NaNO_3$). The results for the corresponding binary complexes are given for comparison

M^{2+}	$\log K^{M}_{M(PME)}$ [a]	$\log K^{M}_{M(PME)_{op}}$ [b]	$\log \Delta_{PME}$ [c]	K_I [c,d]	% $M(PME)_{cl}$ [c,e]
Cu^{2+}	3.73 ± 0.03	3.25 ± 0.06	0.48 ± 0.07	2.02 ± 0.47	67 ± 5
$Cu(bipy)^{2+}$	3.86 ± 0.03	3.27 ± 0.07	0.59 ± 0.08	2.89 ± 0.68	74 ± 5
$Cu(phen)^{2+}$	3.90 ± 0.04	3.28 + 0.06	0.62 ± 0.07	3.17 ± 0.69	76 ± 4
	$\log K^{M}_{M(PMEA)}$ [a]	$\log K^{M}_{M(PMEA)_{op}}$ [b]	$\log \Delta_{PMEA}$ [c]		
Cu^{2+}	3.96 ± 0.04	3.19 ± 0.06	0.77 ± 0.07		
$Cu(bipy)^{2+}$	4.70 ± 0.02	3.22 ± 0.07	1.48 ± 0.07		
$Cu(phen)^{2+}$	4.97 ± 0.03	3.23 ± 0.06	1.74 ± 0.07		

[a] These values are from Table 2. [b] These constants were calculated with the pK_a values 7.02 and 6.90 for $H(PME)^-$ and $H(PMEA)^-$, respectively (section 3), and the straight-line equations of Table 5; the corresponding error limits are three times the s.d. values of Table 5. [c] The error limits for log Δ, K_I and % $M(PME)_{cl}$ were calculated according to the error propagation after Gauss. [d] See equations (22) and (25). [e] See equilibrium (21).

demonstrates. The higher stability of the binary Cu(PMEA) complex compared with Cu(PME) has been attributed to an interaction with the adenine residue;[8] hence, for Cu(PMEA) there exists not only the two isomers depicted in equilibrium (21) but there is a third species which involves the nucleic base moiety (Fig. 1). The corresponding equilibria for the Cu(PMEA) system have been discussed in detail[8] and are not considered further here.

Of interest at this stage is the considerable further stability increase of the ternary Cu(arm)(PMEA) complexes if compared with the corresponding Cu(arm)(PME) species as is borne out by the values listed for log Δ_{PMEA} and log Δ_{PME} in Table 6. This additional stability enhancement is more clearly seen in Fig. 3 where plots of log $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$ *versus* $pK^{H}_{H(R\text{-}PO_3)}$ are shown. The broken line refers to the co-ordination of $R\text{-}PO_3^{2-}$ to $Cu(bipy)^{2+}$ and the solid line to the corresponding reaction with $Cu(phen)^{2+}$; it should be noted that here $R\text{-}PO_3^{2-}$ represents phosphonates with a group R unable to undergo any kind of interaction within the complexes. Clearly, the most remarkable observation is that the points due to Cu(arm)(PME) and Cu(arm)(PMEA) are significantly above the correlation lines; in addition, those for Cu(bipy)(PMEA) and Cu(phen)(PMEA) are even about 1 log unit above the points of the corresponding Cu(arm)(PME) complexes definitely proving that in the Cu(arm)(PMEA) species further interactions must occur, *i.e.* that intramolecular stacks of the type shown in Fig. 2 are formed.

The vertical distances in Fig. 3 between the points due to Cu(arm)(PMEA) and Cu(arm)(PME) and the baselines are evidently a measure for the extent of the intramolecular interactions occurring in these complexes and the mentioned distances correspond to the log Δ values as defined in equations (26) and (28). Of course, the increased stability of the Cu(arm)(PME) species is due to the formation of the five-membered chelates shown in equilibrium (21) and as evaluated in section 8 (see also the upper part of Table 6). Comparison of the chemical structures of $PMEA^{2-}$ and PME^{2-} in Fig. 1 reveals that both ligands are equally well suited to the formation of the mentioned five-membered chelates while stack formation is possible only with $PMEA^{2-}$. Hence, for Cu(arm)(PMEA) the existence of (at least) three different isomers has to be considered in solution.

The formation of the five-membered chelates involving the ether oxygen of PME^{2-} or $PMEA^{2-}$ occurs certainly within the equatorial part of the co-ordination sphere of Cu^{2+} because with the apical positions only weak interactions are possible[32,33] and the stability increase as expressed by log Δ_{PME} with *ca.* 0.5–0.6 is substantial indeed (*cf.* Table 6); the corresponding chelated PMEA isomer is now designated as $Cu(arm)(PMEA)_{cl/O}$. Application of space-filling molecular models reveals that the adenine residue of a $PMEA^{2-}$ ligand equatorially chelated to Cu^{2+} *via* the phosphonate group and

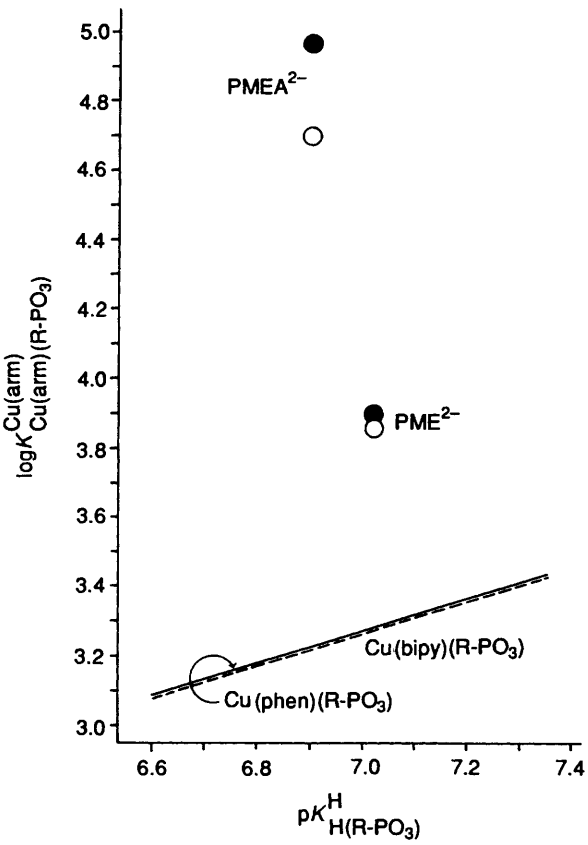


Fig. 3 Evidence for an enhanced stability of the Cu(arm)(PME) and Cu(arm)(PMEA) complexes based on the relationship between log $K^{Cu(arm)}_{Cu(arm)(R\text{-}PO_3)}$ and $pK^{H}_{H(R\text{-}PO_3)}$ for the ternary Cu(bipy)(PME) and Cu(bipy)(PMEA) (○), as well as for the Cu(phen)(PME) and Cu(phen)(PMEA) (●) complexes in aqueous solution at I = 0.1 mol dm^{-3} ($NaNO_3$) and 25 °C. The plotted data are from Table 2 and section 3. The two reference lines represent the log K *versus* pK_a relationship for Cu(arm)($R\text{-}PO_3$) complexes; it should be emphasized that $R\text{-}PO_3^{2-}$ here symbolizes phosphonates (or phosphate monoesters) with an R group unable to undergo any kind of hydrophobic, stacking or other type of interaction; the broken line holds for arm = bipy and the solid line for arm = phen. Both straight lines are calculated with the information given in Table 5 and they represent the situation for ternary complexes without an intramolecular ligand–ligand interaction

the ether oxygen cannot stack well with the aromatic rings of the also equatorially co-ordinated arm; a substantial and strain-free overlap of the aromatic ring systems is possible only if the ether oxygen is not equatorially co-ordinated to Cu^{2+}. This latter

situation is depicted in Fig. 2. However, from the molecular models it is also evident that an *apical* ether oxygen co-ordination and simultaneous stack formation would be compatible with each other in the Cu(arm)(PMEA) species. Hence, there are various intramolecularly stacked Cu(arm)(PMEA) species possible, including those with somewhat different orientations of the aromatic rings towards each other. As there is at present no way to distinguish these various isomers and conformers from each other we treat all the stacked species together and designate them as Cu(arm)(PMEA)$_{st}$. The sum of the above reasonings then gives rise to the equilibrium scheme (29), where the pure phosphonate co-ordinated isomer is designated as Cu(arm)(PMEA)$_{op}$. It is evident that the upper branch of this equilibrium scheme reflects equilibrium (21) while the lower branch is analogous to equilibrium (1).

$$\begin{array}{l} \qquad\qquad\qquad\qquad\qquad\qquad\quad \text{Cu(arm)(PMEA)}_{cl/O} \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \diagup\!\!\diagup \; K_{l/O} \\ \text{Cu(arm)}^{2+} + \text{PMEA}^{2-} \overset{K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}}}{\rightleftharpoons} \text{Cu(arm)(PMEA)}_{op} \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \diagdown\!\!\diagdown \; K_{l/st} \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \text{Cu(arm)(PMEA)}_{st} \end{array} \quad (29)$$

10 *Quantitative Evaluation of the Intramolecular Equilibria involving Three Different* Cu(arm)(PMEA) *Species.*—Based on the equilibrium scheme (29) the corresponding equilibrium constants can be defined as in equations (30)–(32). With these

$$K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}} = [Cu(arm)(PMEA)_{op}]/([Cu(arm)^{2+}][PMEA^{2-}]) \quad (30)$$

$$K_{l/O} = [Cu(arm)(PMEA)_{cl/O}]/[Cu(arm)(PMEA)_{op}] \quad (31)$$

$$K_{l/st} = [Cu(arm)(PMEA)_{st}]/[Cu(arm)(PMEA)_{op}] \quad (32)$$

definitions the experimentally accessible equilibrium constant (9b) can be reformulated as equation (33).

$$K^{Cu(arm)}_{Cu(arm)(PMEA)} = \frac{[Cu(arm)(PMEA)]}{[Cu(arm)^{2+}][PMEA^{2-}]}$$

$$= \{[Cu(arm)(PMEA)_{op}] + [Cu(arm)(PMEA)_{cl/O}] + [Cu(arm)(PMEA)_{st}]\}/\{[Cu(arm)^{2+}][PMEA^{2-}]\} \quad (33a)$$

$$= K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}} + K_{l/O} \cdot K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}} + K_{l/st} \cdot K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}} \quad (33b)$$

$$= K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}}(1 + K_{l/O} + K_{l/st}) \quad (33c)$$

By analogy with equations (22) and (25) one arrives easily at equation (34) (*cf.* also ref. 8), where Cu(arm)(PMEA)$_{int/tot}$ refers to the sum of all the species present with an intramolecular interaction.

$$K_l = K_{l/tot} = \frac{K^{Cu(arm)}_{Cu(arm)(PMEA)}}{K^{Cu(arm)}_{Cu(arm)(PMEA)_{op}}} - 1 = 10^{\log\Delta} - 1 \quad (34a)$$

$$= \frac{[Cu(arm)(PMEA)_{int/tot}]}{[Cu(arm)(PMEA)_{op}]}$$

$$= \frac{[Cu(arm)(PMEA)_{cl/O}] + [Cu(arm)(PMEA)_{st}]}{[Cu(arm)(PMEA)_{op}]} \quad (34b)$$

$$= K_{l/O} + K_{l/st} \quad (34c)$$

Clearly, in those cases where the stacked species, *i.e.* Cu(arm)(PMEA)$_{st}$, are not formed, the above equations reduce to the two-isomer problem [equilibrium (21)] treated in equations (22)–(26), and the results of which are listed in Table 6 for the Cu(arm)(PME) systems as discussed in section 8.

It is evident that K_l ($= K_{l/tot}$) can be calculated according to equation (34a) because the values for log Δ_{PMEA} as defined in equation (28) are known and listed in the lower part of Table 6. These K_l values are given in the third column of Table 7 and, of course, they now allow us to calculate the concentrations of the open isomers, Cu(arm)(PMEA)$_{op}$. To be able to calculate the formation degree of the species that form the five-membered chelate with the ether oxygen, *i.e.* Cu(arm)(PMEA)$_{cl/O}$ [equation (31)], the justified assumption is made that the species Cu(arm)(PME)$_{cl}$ (section 8) and Cu(arm)(PMEA)$_{cl/O}$ have the same stability, *i.e.* that the equilibrium constant $K_{l/O}$ for Cu(arm)(PMEA)$_{cl/O}$ equals the corresponding value for Cu(arm)(PME)$_{cl}$ [see equilibrium (21) and Fig. 1]. Knowing K_l and $K_{l/O}$ one can now calculate $K_{l/st}$ from equation (34c) and hence the formation degree of the Cu(arm)(PMEA)$_{st}$ species; of course, the difference between 100 and the sum of the percentages for Cu(arm)(PMEA)$_{op}$ and Cu(arm)(PMEA)$_{cl/O}$ will also result in % Cu(arm)(PMEA)$_{st}$ and hence in $K_{l/st}$. The results of these calculations are listed in Table 7; they will be discussed below.

Conclusions

Considering the equilibrium scheme (29) and the corresponding results summarized in Table 7 various aspects are immediately evident. (*i*) All three structurally different species of Cu(arm)(PMEA) are formed in appreciable amounts. (*ii*) The stacked species (Fig. 2) are clearly the dominating ones reaching a formation degree of about 90%. (*iii*) Consequently, the formation degree of the five-membered chelates involving the ether oxygen is suppressed to about 10% (and below) compared with the approximately 75% present in the Cu(arm)(PME) systems (*cf.* Table 6).

A further aspect that deserves emphasising is the fact that the values for $K_{l/st}$ of Cu(bipy)(PMEA) and Cu(phen)(PMEA) differ by a factor of about two, *i.e.* 26.31 (± 4.92) *versus* 50.78 (± 8.89) (Table 7). It is evident that this is the result of the smaller aromatic ring system of 2,2'-bipyridyl compared to that of 1,10-phenanthroline and indeed the same factor of about two was already observed for the metal ion unbridged stacks discussed in connection with Table 1. Moreover, for Cu(bipy)(5'-AMP) and Cu(phen)(5'-AMP) the K_l values for stack formation differ also by a factor of about two, *i.e.* 4.37 (± 1.02) *versus* 8.77 (± 1.81).[11] Hence, it appears that this is a general phenomenon for the interaction between bipy or phen and an adenine residue. The actual formation degrees of the intramolecular stacks in Cu(bipy)(5'-AMP) and Cu(phen)(5'-AMP) are 81 (± 4) and 90 (± 2)%, respectively,[11] and in fact, these are values rather similar to those observed now for Cu(bipy)(PMEA) and Cu(phen)(PMEA) (see Table 7).

It is evident that 9-(2-phosphonomethoxyethyl)adenine (as its anion $PMEA^{2-}$) is a fascinating compound which resembles in many respects adenosine 5'-monophosphate (5'-AMP^{2-}). In fact, it appears that the similarity is quite pronounced as long as the ether oxygen of $PMEA^{2-}$ is not participating (or at least not in a dominating way) in

Table 7 Intramolecular equilibrium constants for the formation of the three differently structured Cu(arm)(PMEA) species shown in the equilibrium scheme (29), together with the percentages in which these species occur in aqueous solution at 25 °C and $I = 0.1$ mol dm^{-3} ($NaNO_3$)[a]

arm	log Δ_{PMEA}	$K_I = K_{I/tot}$	% Cu(arm)(PMEA)$_{int/tot}$	% Cu(arm)(PMEA)$_{op}$	$K_{I/O}$	$K_{I/st}$	% Cu(arm)(PMEA)$_{cl/O}$[b]	% Cu(arm)(PMEA)$_{st}$[c]
bipy	1.48 ± 0.07	29.20 ± 4.87	96.99 ± 0.53	3.31 ± 0.53	2.89 ± 0.68	26.31 ± 4.92	10 ± 3	87 ± 3 (21)
phen	1.74 ± 0.07	53.95 ± 8.86	98.18 ± 0.29	1.82 ± 0.29	3.17 ± 0.69	50.78 ± 8.89	6 ± 2	92 ± 2 (22)

[a] The values listed in the second column are from the fourth column in the lower part of Table 6. The values for $K_I = K_{I/tot}$ follow now from equation (34a) and % Cu(arm)(PMEA)$_{int/tot}$ is calculated analogously to equation (27). The values given in the fifth column for % Cu(arm)(PMEA)$_{op}$ follow from 100 − % Cu(arm)(PMEA)$_{int/tot}$. The constants for $K_{I/O}$ in the above column 6 are from column 5 in the upper part of Table 6 (for the corresponding justification see text in section 10); with equation (34c) and the now known values for K_I and $K_{I/O}$ that for $K_{I/st}$ may be calculated (column 7). All error limits in this table correspond to three times the standard deviation (3σ); they were calculated according to the error propagation after Gauss. [b] These values were calculated *via* equation (31) with $K_{I/O}$ and % Cu(arm)(PMEA)$_{op}$. [c] The values for % Cu(arm)(PMEA)$_{st}$ follow from the difference % Cu(arm)(PMEA)$_{int/tot}$ − % Cu(arm)(PMEA)$_{cl/O}$ [*cf.* equation (34b)]; % Cu(arm)(PMEA)$_{st}$ may also be calculated *via* equation (32) with $K_{I/st}$ and % Cu(arm)(PMEA)$_{op}$. The results are the same for both calculation methods (aside from possible differences in the last digit due to differences in rounding) yet the error limits (which are given in parentheses) are understandably larger for the second method.

interactions. Consequently, the mixed-ligand complexes Cu(arm)(5'-AMP) and Cu(arm)(PMEA), in which stacking is dominating, appear as quite alike, while the binary M(5'-AMP) and M(PMEA) complexes differ in their structures considerably[8,9] due to the participation of the ether oxygen[8] in the complex forming properties of $PMEA^{2-}$. However, with metal ions like Zn^{2+}, which prefer an octahedral, square-pyramidal or tetrahedral co-ordination sphere,[1a,34–36] in mixed-ligand complexes of the type described it would sterically be possible to have ether oxygen co-ordination and stack formation at the same time (see also the discussion in section 9). It is therefore remarkable that the ether oxygen is important for the biological activity of PMEA, *e.g.* for its antiviral action;[6,7] deletion of this oxygen or substitution by other groups leads to a loss or at least a considerable reduction of the biological activity.

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