Study of Ternary Complexes of Copper(II) containing Tertiary Amines and Adenosine-5′-triphosphate in Dioxan–Water Media

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The proton–ligand formation constants of adenosine-5′-triphosphate (atp), the formation constants of the binary complexes [Cu(atp)], and the formation constants of the ternary complexes [CuA(atp)], where A = 2,2′-bipyridyl, 1,10-phenanthroline, 2-(2′-pyridyl)benzimidazole, or 2-(2′-pyridyl)imidazoline have been determined in dioxan–water (1 : 2 v/v and 1 : 1 v/v) solutions, and 0.2 mol dm^{-3} $NaClO_4$, at 30 °C. It is observed that the intramolecular hydrophobic stacking interaction between the tertiary amine and the basic part of atp is reduced in dioxan solution leading to negative Δ log *K* values in some cases.

The co-ordination chemistry of the nucleotide adenosine-5′-triphosphate (atp) is of interest because of its biochemical significance. This nucleotide is known to co-ordinate to a metal ion through the phosphate, because of the weak co-ordinating tendency of the nucleotide base and the ribose units.[1-5] In the case of Cu^{II}, the formation constant of its atp complex is high and may be due to additional binding with the nucleotide base.[6]

The study of ternary [CuAL] (L = atp) complexes has been carried out by Sigel *et al.*[7,8] where A = 2,2′-bipyridyl or 1,10-phenanthroline. In the ternary complex atp cannot be expected to act as a tridentate ligand because Cu^{II} does not prefer an axial co-ordination. Hence, co-ordination will occur only from the phosphate and $\Delta \log K = \log K^{MA}_{MAL} - \log K^{M}_{ML}$ is expected to be less positive than in the case of other bidentate O^-,O^- co-ordinating ligands. However, Δ log *K* has been found[7,8] to be more positive. In addition, in the case of [MAL] complexes where M = Zn^{II}, Mn^{II}, or Ca^{II},[8] with less significant or no $M \longrightarrow A$ π interaction, Δ log *K* is found to be positive. The extra stabilization in [MA(atp)] has been explained by Sigel *et al.*[7,8] by considering that in the ternary complex the nucleotide co-ordinates from the phosphate end only, but there is also an intramolecular stacking interaction between the bipyridyl molecule and the base moiety of the nucleotide. On the basis of electronic spectra, stacking has been explained to be due to a charge transfer interaction between the bipyridyl and the base moiety of the nucleotide.

Recently Orioli *et al.*[9] carried out an *X*-ray study of the above ternary complexes. They found two types of stacking interactions, intra- and inter-molecular. The intramolecular interaction has been shown to occur between the bipyridyl and nucleotide base as suggested by Sigel and is charge transfer in nature.

In order further to investigate the nature of the intramolecular charge-transfer interaction, in the present work, the formation constants of the [CuA(atp)] complexes, where A = 2,2′-bipyridyl (A^1), 1,10-phenanthroline (A^2), 2-(2′-pyridyl)benzimidazole (A^3), or 2-(2′-pyridyl)imidazoline (A^4) have been determined in 25% and 50% v/v dioxan–water medium and the values have been compared with those in aqueous solution.[7,8]

Experimental

All reagents used were of A.R. grade, except 2-(2′-pyridyl)-benzimidazole and 2-(2′-pyridyl)imidazoline which were prepared by a known method.[10]

A G.P. Electronics pH meter (no. 8021) with an accuracy of ±0.01 pH unit and a microburette with an accuracy of ±0.01 cm^3 were employed.

Table 1. Protonation constants and metal–ligand stability constants of the Cu^{II}–atp system in aqueous, 25% dioxan–water, and 50% dioxan–water media; I = 0.2 mol dm^{-3} ($NaClO_4$) at 30 °C

	K_1^H	K_2^H	$\log K^{CuA}_{CuAL}$
Aqueous	6.42 ± 0.01	4.06 ± 0.07	6.38 ± 0.09 [a] 6.03 ± 0.03 [b]
25% Dioxan–water (0.066 mol dioxan)	6.86 ± 0.05	3.98 ± 0.07	6.25 ± 0.03
50% Dioxan–water (0.1749 mol dioxan)	7.50 ± 0.01	4.98 ± 0.01	8.22 ± 0.20

[a] Ref. 7. [b] Ref. 8.

The proton–ligand and metal–ligand formation constants were determined in dioxan–water (1 : 2 v/v and 1 : 1 v/v) medium and I = 0.2 mol dm^{-3} ($NaClO_4$) at 30 °C.

The values of $\bar{n}_H$, K_1^H, K_2^H, $\bar{n}$, pL, log K_1, and log K_2 were calculated using normal Irving–Rossotti titrations.[11,12] The formation constants of the ternary complexes were determined by using a modified Irving–Rossotti titration technique[13] presuming complete formation of $[CuA]^{2+}$ prior to the formation of [CuAL]. In each individual measurement the pH values were corrected for 25% and 50% dioxan–water medium using a method suggested by Van Uitert and Haas.[14] At $\bar{n} = 0.5$, in the formation curve, $pL = \log K^{MA}_{MAL}$. More precise values were obtained by plotting pL at each point against $\log [(1 - \bar{n})/\bar{n}]$ and obtaining a straight line. At each point on the straight line $\log K^{MA}_{MAL} = pL - \log [(1 - \bar{n})/\bar{n}]$.

All the formation constants were subjected to refinement by using the computer program SCOGS.[15] The method was used in two ways: (i) by presuming the reaction to be of the type $[CuA]^{2+} + L^{2-} \rightleftharpoons [CuAL]$, as formation of $[CuA]^{2+}$ is complete in the lower pH range. The species considered to be present in the solution are H_2L, HL^-, L^{2-}, $[CuA]^{2+}$, and [CuAL]. As Cu^{2+} and A are equimolar and formation of $[CuA]^{2+}$ is complete, no free species A, HA^+, and H_2A^{2+} were considered (method 1); and (ii) by presuming the reaction to be simultaneous, $Cu^{2+} + A + L^{2-} \rightleftharpoons [CuAL]$, and considering all possible species to be present in the solution *i.e.*, H_2L, HL^-, L^{2-}, H_2A^{2+}, HA^+, A, [CuL], $[CuL_2]^{2-}$, $[CuA]^{2+}$, $[CuA_2]^{2+}$, and [CuAL] (method 2).

The formation constants of the ternary complexes $[CuA^3(atp)]$ and $[CuA^4(atp)]$ were determined only by method 1 in the computer program presuming complete formation of $[CuA]^{2+}$ because the values of $[CuA^3]$, $[CuA^3_2]$, $[CuA^4]$, and $[CuA^4_2]$ could not be determined.

The refined values of proton–ligand and metal–ligand formation constants and the mixed-ligand formation constants obtained by the graphical and computer methods are presented

Table 2. Stability constants of the ternary complexes [CuAL] (L = atp) and Δ log K in aqueous, 25% dioxan-water, and 50% dioxan-water media; I = 0.2 mol dm^{-3} ($NaClO_4$) at 30 °C

	[CuA^1(atp)]		[CuA^2(atp)]		[CuA^3(atp)]		[CuA^4(atp)]	
	log K^{CuA}_{CuAL}	Δ log K	log K^{CuA}_{CuAL}	Δ log K	log K^{CuA}_{CuAL}	Δ log K	log K^{CuA}_{CuAL}	Δ log K
Aqueous	6.91 ± 0.15 [a]	+0.58	6.08 ± 0.2 [b]	+0.05	—	—	—	—
25% Dioxan-water	6.10 ± 0.09 [c]	−0.15	6.15 ± 0.08 [c]	−0.10	6.77 ± 0.04 [c]	+0.57	5.15 ± 0.04 [c]	−1.10
(0.066 mol dioxan)	6.20 ± 0.08 [d]	—	6.22 ± 0.09 [d]	—	—	—	—	—
50% Dioxan water	8.32 ± 0.07 [c]	−0.24	7.93 ± 0.08 [c]	−0.29	8.47 ± 0.03 [c]	+0.25	6.99 ± 0.03 [c]	−1.23
(0.1749 mol dioxan)	8.39 ± 0.06 [d]		7.94 ± 0.07 [d]	—	—	—	—	—

[a] Ref. 7. [b] Ref. 8. [c] Method 1. [d] Method 2.

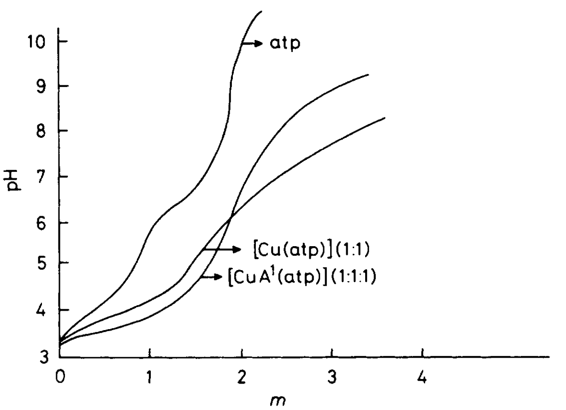

Figure 1. Titration curves for the ternary system [CuA^1(atp)] in aqueous medium (m = number of moles of base added per mole of total metal ion)

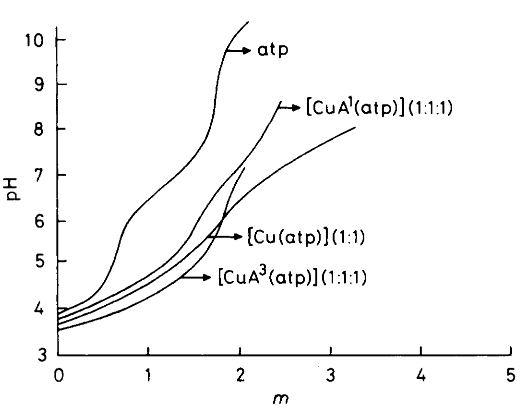

Figure 2. Titration curves for the ternary system [CuA(atp)] in 50% dioxan-water medium (m as for Figure 1)

in Tables 1 and 2. The values of the constants in aqueous medium are also quoted from the literature. Small deviations observed in the relative values of constants in dioxan–water medium and in aqueous medium may occur because the values have been determined under different experimental conditions.

Results and Discussion

It is known that organic solvents affect log K^H values of the ligand. With increasing solvent dielectric constant, log K^H of the ligand decreases and it becomes more acidic. With decreasing dielectric constant of the solvent, log K^H increases and the ligand becomes more basic.

However, the solvent may itself be protonated and also increase the proton accepting property of water by breaking the hydrogen bond. The latter two effects decrease the log K^H value of the ligand and work against the former dielectric effect. The values of the protonation constants of the ligands in turn increase or decrease the value of the M–L formation constant.

However, Steger and Corsini [16] have measured the protonation constants and the stability constants of metal complexes of some 5-substituted derivatives of oxine (quinolin-8-ol) in 40, 60, and 75% dioxan. They observed that log K^H and log K^M_{ML} increased linearly with increasing mole fraction of dioxan. Van Uitert *et al.* [17] showed that the values of log K_{ML} for several acetylacetonates were linear functions of the mole fraction of dioxan in the solvent.

Hence it can be presumed that the only factor affecting the formation constants in dioxan solvent is the dielectric constant of the medium and that protonation of the solvent is not significant. Hence in the computer programs protonation of the solvent has been neglected.

As expected, atp shows a higher basicity in dioxan medium and hence the formation constant of [Cu(atp)] is also higher in 25% and 50% dioxan than in aqueous medium. The order of the formation constants of the ternary complexes in 25% and 50% dioxan water medium is as follows: [CuA^3(atp)] > [CuA^1(atp)] = [CuA^2(atp)] > [CuA^4(atp)]. This can be explained by considering the extent of Cu $\longrightarrow$ A π interaction.[18-20] In the case of the $[CuA^1]^{2+}$ and $[CuA^2]^{2+}$ complexes, Cu $\longrightarrow$ A π interactions are of equal extent. However in $[CuA^3]^{2+}$, the co-ordination is from one pyridine N and one benzimidazole ring N and hence the Cu $\longrightarrow$ A π interaction is greater. This results in an increase in the formation constants of the ternary complexes. In case of $[CuA^4]^{2+}$ co-ordination is from one pyridine N and one imidazoline ring N. In this case, π interaction is possible only with the pyridine ring, as the imidazoline ring is saturated and has no delocalized π-electron cloud. Consequently, it is less π-interacting than bipyridyl and hence [CuA^4(atp)] is less stable than other ternary complexes.

In the cases of O^-,O^- co-ordinating ligands, it has been observed earlier [21] that the formation constants of both binary and ternary complexes in 50% dioxan solvent are higher than in aqueous medium. Hence, Δ log K is found to be positive and of the same magnitude in aqueous and 50% (v/v) dioxan-water solution.

As stated earlier, [CuA(atp)] shows a positive $\Delta \log K$ value in aqueous solution.[7,8] However, in the present study it is observed (Table 2) that $\Delta \log K$ become less positive with increasing dioxan percentage in the solvent. In 25% and 50% dioxan–water medium, $\Delta \log K$ is negative in [CuA(atp)] complexes, where A = A^1, A^2, or A^4. It is positive only when A = A^3.

Destabilization of the ternary complexes in dioxan–water medium is also evident from the titration curves of [CuA^1(atp)] in aqueous and 50% dioxan–water medium, Figures 1 and 2. In Figure 1 (*i.e.* in aqueous medium) the Cu^{2+} + atp curve is above that of $Cu^{2+} + A^1$ + atp, showing the greater stability of the ternary complex and leads to positive $\Delta \log K$. However, in 50% dioxan–water medium (Figure 2) the Cu^{2+} + atp curve is below that of [CuA^1(atp)] but above that of [CuA^3(atp)]. This shows that in [CuA^1(atp)] there is less stabilization leading to a negative $\Delta \log K$, whereas [CuA^3(atp)] is more stable giving a positive $\Delta \log K$. The position of the curves can only be considered up to pH 5, because after pH 5 [Cu(atp)] undergoes hydroxo-complex formation and falls below the [CuA^1(atp)] curve in every case.

This shows that the solvent molecules play an important role in the destabilization of the ternary complex. It can be expected that in case of [CuA(atp)] the intramolecular stacking interaction between the tertiary amines and adenosine base of atp may be partly hydrophobic [22] in nature. This interaction is greater in aqueous medium, but in dioxan medium the solvent molecules probably interfere with the intramolecular stacking interaction between the bipyridyl and the adenosine ring and thus, the ternary complex is destabilized. This leads to negative $\Delta \log K$ values. In the case of [CuA^3(atp)], however, even in 50% dioxan–water medium, $\Delta \log K$ is found to be positive. This may be because π delocalization occurs over a larger area in A^3 and hence the stacking interaction holds even in 50% dioxan–water medium and results in a positive $\Delta \log K$ value.

Thus, the study indicates that the stacking interaction is probably solvent dependent and points to the fact that in biological systems the stacking interaction will depend on the nature of the medium in which the interaction is being considered.

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