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The Imidazole Group and Its Stacking Properties in Mixed Ligand Metal Ion Complexes

Helmut Sigel[a]; Roger Tribolet[a]; Osamu Yamauchi[b]
[a] Institute of Inorganic Chemistry, University of Basel, Basel, Switzerland [b] Department of Chemistry, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan

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The Imidazole Group and Its Stacking Properties in Mixed Ligand Metal Ion Complexes

HELMUT SIGEL and ROGER TRIBOLET
Institute of Inorganic Chemistry,
University of Basel,
Spitalstrasse 51,
CH-4056 Basel, Switzerland

OSAMU YAMAUCHI
Department of Chemistry,
Nagoya University,
Furo-cho, Chikusa-ku,
Nagoya, Japan 464

The imidazole group is an important metal ion binding site in biosystems. However, the fact that this group is also able to undergo stacking and hydrophobic interactions with other aromatic or aliphatic residues is less well known. In this Comment several examples are summarized for the solid state, as well as for solutions of low-molecular-weight mixed ligand complexes with an intramolecular ligand–ligand interaction involving the imidazole ring. Such an interaction occurs, e.g., in Cu(histidinate)(AA) complexes, where AA^- = tryptophanate, phenylalaninate or valinate, and the formation degree of the intramolecular adduct decreases in this order. In addition, evidence is presented for a purine-imidazole stack in M(adenosine 5′-triphosphate)(imidazole)$^{2-}$ complexes. It is thus becoming obvious that the imidazole group does not only bind metal ions but also has additional and rather significant structuring properties via the possibility to undergo stacking and to form hydrophobic adducts with other suitable residues.

Key Words: *hydrophobic interactions in metal ion complexes, stacking of imidazole group, intramolecular ligand–ligand interactions, stacking in metal ion complexes, ternary complex intramolecular interactions*

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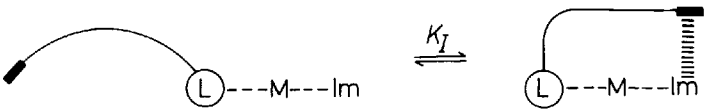
1. INTRODUCTION

The imidazole group is an important and versatile binding site for metal ions in biological systems[1-3] due to its presence in the side-chain of the amino acid histidine; in fact, this group often serves as an anchoring unit for metal ions in their binding to peptides and proteins.[3,4] It is therefore not surprising that the coordinating properties of this group are well known,[1,2,5] including not only binary but also relevant ternary or mixed ligand complexes.[6-8]

However, as an aromatic-ring system the imidazole residue of histidine is also able to participate in stacking interactions with other biologically occurring partners, e.g., with nucleotides and their derivatives.[9-12] There are also indications that imidazole-phenyl ring stacking may be of importance in electron transfer reactions in proteins.[13]

The reason why for metal ion complexes much less is known about the stacking properties of the imidazole moiety than about the phenyl[14-16] and indole[15-20] residues which are part of the side chains of phenylalanine and tryptophan, respectively, is evident: The phenyl and indole residues offer to metal ions no direct binding site in the aromatic-ring system, while in the case of imidazole a pyridine-like nitrogen is available. Metal ion coordination at this nitrogen often renders studies of the stacking properties rather difficult.[15] Hence, only scarce information on the intramolecular equilibrium (1) of mixed ligand complexes involving the formation of a ligand–ligand adduct between a suitable group of a ligand (L) and an imidazole residue (Im) of imidazole itself or another ligand carrying this group is presently available:



(1)

It is the aim of this Comment to summarize some examples and to emphasize the general importance of equilibrium (1), because there is little doubt that in biological systems imidazole interactions with other aromatic-ring residues or aliphatic groups are important.

If the "open" form in equilibrium (1) is designated as $M(L)(Im)_{op}$ and the species with the intramolecular adduct as $M(L)(Im)_{ad}$, the dimensionless equilibrium constant K_I is defined by Eq. (2):

$$K_I = [M(L)(Im)_{ad}]/[M(L)(Im)_{op}] \tag{2}$$

Values of K_I may be calculated from Eq. (3),[16,21-23]

$$K_I = \frac{K^{M(L)}_{M(L)(Im)}}{K^{M(L)}_{M(L)(Im)_{op}}} - 1 \tag{3a}$$

$$= \frac{10^{\Delta \log K}_{(M/L/Im)}}{10^{\Delta \log K}_{(M/L/Im)_{op}}} - 1 \tag{3b}$$

$$= 10^{\Delta\Delta \log K} - 1 \tag{3c}$$

which involves the following definitions:

$$M(L) + Im \rightleftharpoons M(L)(Im)_{op} \rightleftharpoons M(L)(Im)_{ad} \tag{4a}$$

$$K^{M(L)}_{M(L)(Im)} = K_{exp} = [M(L)(Im)]/([M(L)][Im]) \tag{4b}$$

$$= \frac{([M(L)(Im)_{op}] + [M(L)(Im)_{ad}])}{[M(L)][Im]} \tag{4c}$$

$$K^{M(L)}_{M(L)(Im)_{op}} = [M(L)(Im)_{op}]/([M(L)][Im]) \tag{5}$$

$$M + Im \rightleftharpoons M(Im) \qquad K^{M}_{M(Im)} = [M(Im)]/([M][Im]) \tag{6}$$

$$\Delta \log K_{(M/L/Im)} = \log K^{M(L)}_{M(L)(Im)} - \log K^{M}_{M(Im)}$$

$$= \log K^{(Im)}_{(Im)(L)} - \log K^{M}_{M(L)} \tag{7a}$$

$$M(L) + M(Im) \rightleftharpoons M(L)(Im) + M \tag{7b}$$

$$\Delta \log K_{(M/L/Im)_{op}} = \log K^{M(L)}_{M(L)(Im)_{op}} - \log K^{M}_{M(Im)}$$

$$= \log K^{(Im)}_{(Im)(L)_{op}} - \log K^{M}_{M(L)} \qquad (8)$$

$$\Delta\Delta \log K = \Delta \log K_{(M/L/Im)} - \Delta \log K_{(M/L/Im)_{op}} \qquad (9)$$

Clearly, knowledge of K_I (Eq. (3)) also allows us to calculate the percentage of the species with the intramolecular ligand–ligand adduct of equilibrium (1):

$$\%M(L)(Im)_{ad} = \frac{K_I}{1 + K_I} \cdot 100 \qquad (10)$$

It is evident that two main difficulties exist: (i) In a mixed ligand M(L)(Im) complex for which equilibrium (1) occurs there is no simple way to determine only $K^{M(L)}_{M(L)(Im)_{op}}$; the results of experiments are always values for $K^{M(L)}_{M(L)(Im)}$ ($= K_{exp}$; Eq. (4)). (ii) Any experimental error will be more crucial the more similar the two values are in Eq. (9); hence, whenever possible, well defined error limits should be obtained.

2. SOLID-STATE STRUCTURES OF Cu^{2+} COMPLEXES CONTAINING HISTAMINE AND AN AMINO ACID: INTRAMOLECULAR AROMATIC-RING STACKING

Despite previous conclusions that imidazole stacks can be formed in mixed ligand complexes in solution,[21,24] the final proof for such a ligand–ligand adduct was only recently achieved via X-ray diffraction studies[25]: The ternary complexes formed between Cu^{2+}, histamine (Ha), and *L*-phenylalaninate (Phe^-) or *L*-tyrosinate (Tyr^-) have been isolated, and the solid-state structures of [Cu(Ha)(Phe)(ClO_4)] and [Cu(Ha)(Tyr)(ClO_4)] were determined.[25] Views of these complexes are shown in Fig. 1 on the left- and right-hand sides, respectively. The partial overlap between the imidazole ring and the phenyl residue is nicely seen for both complexes. Some prominent features of the two structures are summarized below.

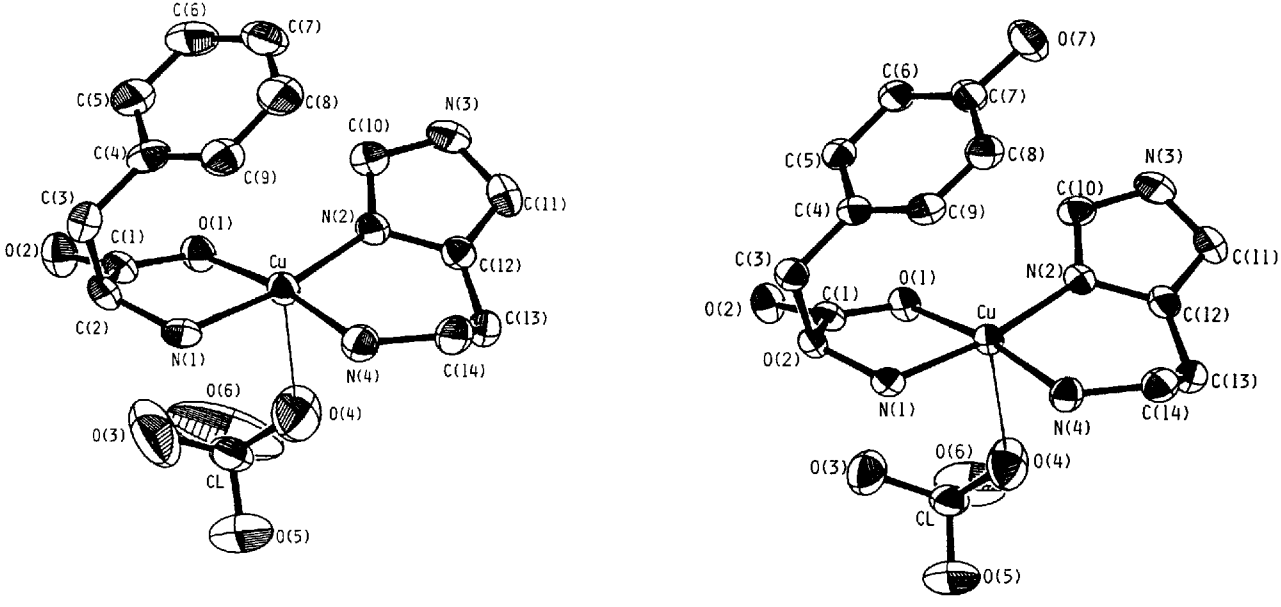


FIGURE 1 Structures of [Cu^{II}(histamine)(*L*-phenylalaninate)]ClO_4 (left) and [Cu^{II}(histamine)(*L*-tyrosinate)]ClO_4 (right) as obtained by an X-ray crystallographic analysis of the corresponding solids (Ref. 25).

Both complexes bear a remarkable structural similarity; the Cu^{2+} ion has a five-coordinate square-pyramidal geometry with the oxygen atom of a perchlorate ion occupying the remote axial position. The side chains of Phe^- and Tyr^- assume a bent conformation with the aromatic ring located above the Cu^{2+} coordination plane. The imidazole ring of Ha deviates from the coordination plane toward the aromatic side chain to be close to the phenyl residue.

The molecular structures (Fig. 1) reveal the stacking interaction between the imidazole and phenyl rings, and they substantiate the previous conclusions drawn for the ternary complexes in solution.[21,24] Certainly, the stacking interaction is somewhat limited by the angle (ca. 38°) and the only partial overlap between the two rings, but it is clearly there: the shortest distance, C(7)–C(10), is 3.49 Å for $Cu(Ha)(Phe)^+$ and 3.45 Å for $Cu(Ha)(Tyr)^+$, the separation between the centers of the mean planes being 4.15–4.20 Å. Interestingly, the bent conformation found in $Cu(Ha)(Phe)^+$ (Fig. 1; left) is probably a reflection of the stacking effect, because the side chain of Phe^- in $Cu(Phe)_2$ in the solid state[26] is stretched away from the coordination plane.

3. SOLUTION STUDIES OF A PYRROLE DERIVATIVE AS AN IMIDAZOLE-MODEL RESIDUE

As indicated before, to employ the imidazole group in studies with the aim to quantify its stacking properties in the presence of metal ions is difficult due to the coordinating properties of the also present pyridine-like nitrogen. An aromatic five-membered ring system of which similar stacking properties as those of the imidazole ring may, to a first approximation, be expected is the pyrrole group. Therefore, the stacking properties of 2-(1-pyrrole)acetate ($PyAc^-$) have recently been evaluated in 50% (v/v) dioxane–water solutions containing also Cu^{2+} or Zn^{2+} and 1,10-phenanthroline (Phen); the other 2-(aryl)acetate ligands shown in Fig. 2 have been included in the study[15] for reasons of comparison. The corresponding mixed ligand systems with formate ($HCOO^-$) or acetate (Ac^-) were used in the mentioned study as examples for complexes without an intramolecular ligand–ligand interaction; i.e., the stability of these complexes was the basis for the quantitative evaluations.

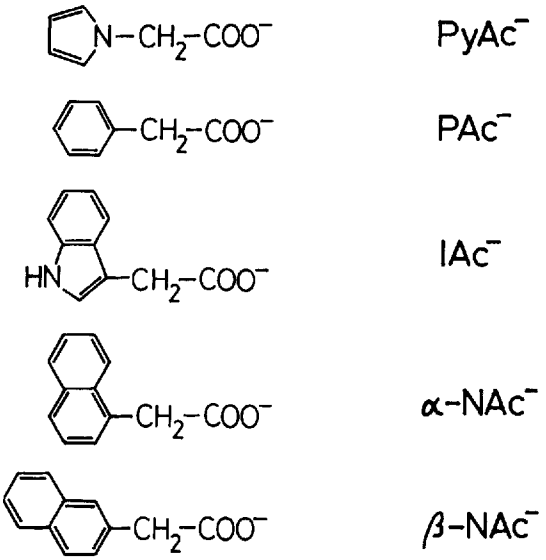


FIGURE 2 Structures of the 2-(aryl)acetate ligands ($ArAc^-$) considered in Section 3 of this Comment together with the abbreviations used in the text and in Tables I and II.

The acidity constants of the carboxylic acids of the mentioned carboxylate ligands (CA^-) together with the stability constants of their binary and ternary complexes are summarized in Table I. Plots of log $K^{M}_{M(CA)}$ and log $K^{M(Phen)}_{M(Phen)(CA)}$ versus $pK^{H}_{H(CA)}$ are shown in Fig. 3. It is evident that all points due to the binary $M(CA)^+$ complexes[15] of Cu^{2+} and Zn^{2+} fit within the error limits on straight lines as is expected.[23] The points due to the ternary M(Phen)-$(HCOO)^+$ and $M(Phen)(Ac)^+$ complexes result in straight lines (broken line in Fig. 3) which are parallel to those of the binary complexes. However, the ternary $M(Phen)(CA)^+$ complexes with an aromatic ring residue in the carboxylate ligand[15] are all significantly more stable than expected on the basis of the basicity of the carboxylate group. This stability increase is clear evidence that a further interaction within these ternary complexes must occur; i.e., that intramolecular stacks are formed. In addition, it is easy to connect the vertical distances between corresponding points (or lines) in Fig. 3 with the definitions given, e.g., for Δ log $K_{(M/L/Im)}$,

TABLE I

Negative logarithms of the acidity constants of several carboxylic acids, H(CA) (see also Fig. 2), and logarithms of the stability constants of the corresponding binary $M(CA)^+$ and ternary $M(Phen)(CA)^+$ complexes in 50% (v/v) dioxane–water at I = 0.1 M and 25°C, together with the resulting values for $\Delta \log K_{(M/Phen/CA)}$; the definitions of the constants are analogous to those given in Section 1[a]

No.	CA^- (Fig. 2)	$pK^H_{H(CA)}$	$\log K^{Cu}_{Cu(CA)}$	$\log K^{Cu(Phen)}_{Cu(Phen)(CA)}$	$\Delta \log K_{(Cu/Phen/CA)}$	$\log K^{Zn}_{Zn(CA)}$	$\log K^{Zn(Phen)}_{Zn(Phen)(CA)}$	$\Delta \log K_{(Zn/Phen/CA)}$
1	$HCOO^-$	4.73 ± 0.02	2.79 ± 0.02	2.82 ± 0.02	0.03 ± 0.03	1.96 ± 0.01	1.82 ± 0.02	−0.14 ± 0.02
2	Ac^-	5.97 ± 0.01	3.31 ± 0.02	3.35 ± 0.01	0.04 ± 0.02	2.31 ± 0.01	2.15 ± 0.01	−0.16 ± 0.01
3	$PyAc^-$	4.75 ± 0.01	2.73 ± 0.01	3.07 ± 0.01	0.34 ± 0.01	1.92 ± 0.01	1.85 ± 0.01	−0.07 ± 0.01
4	PAc^-	5.88 ± 0.01	3.22 ± 0.02	3.68 ± 0.04	0.46 ± 0.04	2.26 ± 0.02	2.29 ± 0.02	0.03 ± 0.03
5	IAc	6.38 ± 0.02	3.44 ± 0.05	4.13 ± 0.02	0.69 ± 0.05	2.48 ± 0.01	2.72 ± 0.01	0.24 ± 0.01
6	α-NAc^-	6.06 ± 0.02	3.23 ± 0.02	3.91 ± 0.01	0.68 ± 0.02	2.33 ± 0.01	2.62 ± 0.01	0.29 ± 0.01
7	β-NAc^-	5.92 ± 0.01	3.20 ± 0.02	3.90 ± 0.03	0.70 ± 0.04	2.31 ± 0.02	2.45 ± 0.01	0.14 ± 0.02

[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. The values of the error limits for $\Delta \log K_{(M/Phen/CA)}$ were calculated according to the error propagation after Gauss. I = 0.1 M was adjusted with $NaClO_4$ (entries 1, 2, 4, and 7), $NaNO_3$ (entry 3), or KNO_3 (entries 5 and 6). The data are collected from Tables I and V of Ref. 15.

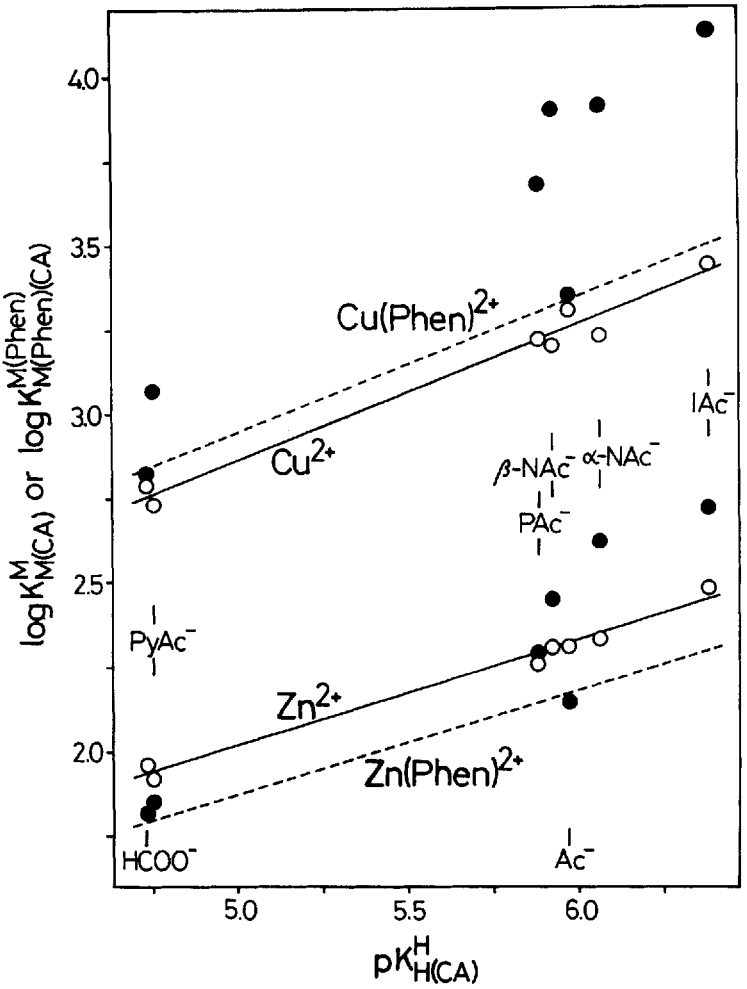


FIGURE 3 Relationship between log $K^{M}_{M(CA)}$ or log $K^{M(Phen)}_{M(Phen)(CA)}$ and $pK^{H}_{H(CA)}$ in 50% (v/v) dioxane–water for the binary complexes, $M(CA)^+$ (○), or the ternary complexes, $M(Phen)(CA)^+$ (●), with *simple* carboxylates, i.e., $HCOO^-$ and Ac^-, and the 2-(aryl)acetates (see Fig. 2). The plotted data (Ref. 15) are from Table I, and those of the binary complexes fit on straight lines (solid lines); the reference lines for the ternary complexes (broken lines) are drawn parallel to the solid lines but only through the points of $HCOO^-$ and Ac^- (see Section 3).

Δ log $K_{(M/L/Im)_{op}}$ and $\Delta\Delta$ log K in Eqs. (7), (8), and (9). Regarding Eq. (9), it is helpful to realize that the constant $10^{\Delta\Delta \log K}$ quantifies for the present systems the position of equilibrium (11), which is formulated below with the ligand acetate (Ac^-) and 1-pyrroleacetate ($PyAc^-$) as an example:

$$M(PyAc)^+ + M(Phen)(Ac)^+ \rightleftharpoons M(Phen)(PyAc)^+ + M(Ac)^+ \qquad (11)$$

It is evident that the coordination spheres of the metal ions on both sides of this equilibrium are identical; consequently, the value for $\Delta\Delta$ log K (Eq. (9)) is a true reflection of the extent of the intramolecular stack formation in $M(Phen)(PyAc)^+$ between the pyrrole residue and the Phen-ring system. Indeed, this type of stack formation has been proven to occur for several of the ligands shown in Fig. 2 by ^1H NMR (upfield) shift measurements,[14,15,27,28] as well as by UV spectrophotometry (charge-transfer bands).[15,27]

The quantitative evaluations regarding stack formation (Eq. (1)) of the M^{2+}/Phen/$ArCA^-$ systems and the corresponding equilibrium constants given in Table I via Eqs. (7), (8), (9), and (3c) are summarized in Table II. Several comparisons are possible, a few of which are given below: Replacement of 2-phenylacetate (PAc^-) in $M(Phen)(PAc)^+$ by 2-(1-pyrrole)acetate ($PyAc^-$) reduces Δ log $K_{M/Phen/CA}$ or $\Delta\Delta$ log K of the Cu^{2+} and Zn^{2+} complexes in 50% aqueous dioxane by 0.12 and 0.10 log unit (entries 3a/4a and 3b/4b in Table II); i.e., the geometry of the coordination sphere of the metal ion has, in this case, no significant influence on the extent of the decrease in stacking, and this suggests that the decrease is governed by the reduction of the size of the aromatic ring. However, of $Zn(Phen)(PyAc)^+$ and $Cu(Phen)(PyAc)^+$, still about 17 and 50%, respectively, exist in the stacked form.

A similar comparison shows that replacement of PAc^- in $M(Phen)(PAc)^+$ by 2-(3-indole)acetate (IAc^-) increases Δ log $K_{M/Phen/CA}$ or $\Delta\Delta$ log K of the Cu^{2+} and Zn^{2+} complexes by 0.23 and 0.21 log unit (entries 4a/5a and 4b/5b in Table II). Again, the kind of metal ion has no significant influence; the extent of stack

TABLE II

Extent of intramolecular aromatic-ring stack formation (Eq. (1)) in ternary Cu^{2+} or Zn^{2+} complexes containing 1,10-phenanthroline (Phen) and a 2-(aryl)acetate ($ArAc^-$; Fig. 2): Intramolecular and dimensionless equilibrium constant K_I (Eq. (2)) and percentage of the stacked species $M(Phen)(ArAc)^+_{ad}$ (Eq. (10)) in 50% (v/v) dioxane–water at I = 0.1 M (see Table I) and 25°C. The definitions of the constants are analogous to those given in Section 1[a]

No.[a]	Complex	$\Delta \log K_{(M/Phen/CA)}$[b]		$\Delta\Delta \log K$	K_I	% $M(Phen)(ArAc)^+_{ad}$
1a	$Cu(Phen)(HCOO)^+$	0.03 ± 0.03	0.04 ± 0.02[c]			
2a	$Cu(Phen)(Ac)^+$	0.04 ± 0.02				
3a	$Cu(Phen)(PyAc)^+$	0.34 ± 0.01		0.30 ± 0.02	1.00 ± 0.11	50 ± 3
4a	$Cu(Phen)(PAc)^+$	0.46 ± 0.04		0.42 ± 0.05	1.63 ± 0.29	62 ± 4
5a	$Cu(Phen)(IAc)^+$	0.69 ± 0.05		0.65 ± 0.06	3.47 ± 0.58	78 ± 3
6a	$Cu(Phen)(\alpha\text{-}NAc)^+$	0.68 ± 0.02		0.64 ± 0.03	3.37 ± 0.29	77 ± 2
7a	$Cu(Phen)(\beta\text{-}NAc)^+$	0.70 ± 0.04		0.66 ± 0.04	3.57 ± 0.42	78 ± 2
1b	$Zn(Phen)(HCOO)^+$	−0.14 ± 0.02	−0.15 ± 0.01[c]			
2b	$Zn(Phen)(Ac)^+$	−0.16 ± 0.01				
3b	$Zn(Phen)(PyAc)^+$	−0.07 ± 0.01		0.08 ± 0.02	0.20 ± 0.05	17 ± 4
4b	$Zn(Phen)(PAc)^+$	0.03 ± 0.03		0.18 ± 0.03	0.51 ± 0.11	34 ± 5
5b	$Zn(Phen)(IAc)^+$	0.24 ± 0.01		0.39 ± 0.02	1.45 ± 0.11	59 ± 2
6b	$Zn(Phen)(\alpha\text{-}NAc)^+$	0.29 ± 0.01		0.44 ± 0.02	1.75 ± 0.12	64 ± 2
7b	$Zn(Phen)(\beta\text{-}NAc)^+$	0.14 ± 0.02		0.29 ± 0.03	0.95 ± 0.12	49 ± 3

[a]The data are collected from Tables III and IV of Ref. 15. To facilitate comparisons the above entry numbers are the same as those used for the corresponding systems in Table I; the letters "a" and "b" refer to the Cu^{2+} and Zn^{2+} complexes, respectively.

[b]These values correspond to those of Table I in Section 3; the error ranges are again *three times* the standard error (see footnote "a" in Table I).

[c]This value corresponds to $\Delta \log K_{(M/Phen/CA)_{op}}$ (analogous to Equation (8)).

formation is clearly governed by the size of the aromatic-ring system. Hence, taking the above results together (Table II), one may conclude that the tendency to form intramolecular stacks in ternary complexes decreases for the following amino acid residues in the series, indole > phenyl > imidazole, with the position of the imidazole group being based on the results obtained with the pyrrole derivative.

The indole residue and the naphthyl group are of very similar size. In agreement herewith the extent of stack formation in Cu(Phen)(IAc)$^+$, Cu(Phen)(α-NAc)$^+$, and Cu(Phen)(β-NAc)$^+$ is, within the error limits, identical (Table II; entries 5a to 7a). The same is true for the similarly structured IAc^- and α-NAc^- ligands in Zn(Phen)(CA)$^+$, but the somewhat different steric orientation of the naphthyl group towards the carboxylate group leads to a reduced stack formation in Zn(Phen)(β-NAc)$^+$ (cf. entries 5b to 7b). This result indicates that the geometry of the coordination sphere of the metal ion may also have an effect: Within the equatorial Cu^{2+} sphere the α- and β-naphthyl residues may interact with the Phen ring to the same extent, while in the tetrahedral or octahedral Zn^{2+} sphere, the same extent of overlap with the Phen system is not achieved. Clearly, differences in the geometry of the metal ion coordination sphere are reflected in intramolecular ligand–ligand interactions only, if a ligand is not flexible and adaptable enough to the steric restrictions imposed by the metal ion coordination sphere.[15,28] However, in general one has to conclude that metal–ion bridging between two suitable moieties promotes their interaction.[14–16,19–22]

There is one further point which warrants emphasis: The results discussed in this section (Tables I and II) are based on experiments carried out in 50% (v/v) dioxane–water as solvent. Therefore, it is important to note that, e.g., for the M(Phen)(PAc)$^+$ complex[14] the formation of the intramolecular ligand–ligand adduct is *favored* by the addition of some dioxane (or ethanol) to an aqueous solution of the complex; indeed, several of such examples are now known.[14,28–30] This observation is contrary to the experience with simple unbridged stacks or hydrophobic adducts, which are strongly destabilized by the addition of an organic solvent (like dioxane or ethanol) to an aqueous solution. Such a destabilization of the ligand–ligand adduct in these mixed ligand complexes occurs only

at high concentrations of the organic solvent (usually more than 70%). Considering that there is now good evidence that in the active-site cavity of an enzyme or protein the "equivalent solution" or "effective" dielectric constant is lower than in water,[31,32] the indicated promoted interaction is most probably of importance in biological systems.[16,33]

4. EXTENT OF INTRAMOLECULAR LIGAND–LIGAND INTERACTIONS IN TERNARY AMINO ACID COMPLEXES CONTAINING HISTIDINATE

Intramolecular ligand–ligand interactions between suitable side chains of amino acids are known for binary[29,30,34] and ternary[21,35,36] complexes. Part of this knowledge was obtained[21,34] by evaluating stability data available in the literature. The previous evaluations[21] carried out for mixed ligand complexes containing histidinate (His^-) and a second amino acid anion (AA^-),[37,38] i.e., of Cu(His)(AA) complexes, are listed in Table III. Due to the knowledge accumulated in the ten years since Ref. 21 was written, more detailed interpretations of these data are now possible.

The values given in Table III for $\Delta \log K_{(Cu/His/AA)_{op}}$ (Eq. (8)) are based on amino acid anions which behave toward Cu^{2+} in solution (at least largely) as bidentate ligands.[5,21] The values for $\Delta \log K_{(Cu/His/AA)}$ (Eq. (7)) where AA^- is an amino acetate with a side chain suitable for an interaction with the imidazole group (see Fig. 4) are in several instances rather large; in fact, for the Cu^{2+}/*D*-His^-/*L*-Trp^- system even a *positive* value for $\Delta \log K_{(Cu/D\text{-}His/L\text{-}Trp)}$ is observed (entry 5 in Table III). As in the $\Delta \log K_{(M/L/Im)}$ consideration (Eq. (7))[39] an *increase* in the stability of a ternary complex cannot originate from steric restrictions (which may, however, lead to stereoselectivity); a *cooperative* effect between the two different amino acid anions bound to the same metal ion must be responsible for the stability enhancement.

There are two such cooperative effects possible: (i) An *indirect* effect resulting from the π-accepting imidazole group of His^-, which leads to a preferred coordination of O donors in 3d metal ion complexes.[3,6–8,39] However, in the $\Delta\Delta \log K$ evaluation (Eq. (9)) this effect cancels, as is easily seen in equilibrium (12),

TABLE III

Intramolecular hydrophobic and aromatic-ring stacking interactions in ternary Cu(His)(AA) amino acid complexes (Fig. 4): Estimates for the intramolecular dimensionless equilibrium constant K_I of the mixed amino acid complexes (Fig. 5) and for the percentage of the corresponding complexes with the intramolecular ligand–ligand adduct, $Cu(His)(AA)_{ad}$. The data refer to aqueous solutions at I = 0.1 M (KNO_3) and 25°C[a]

No.	Cu(His)(AA) (Fig. 4)[b]	$\Delta \log K_{(Cu/His/AA)}$ (analogous to Eq. (7))	$\Delta \log K_{(Cu/His/AA)_{op}}$ (analogous to Eq. (8))	$\Delta\Delta \log K$ (see Eqs. (9),(12))	K_I (analogous to Eqs. (1)–(3))	% $Cu(His)(AA)_{ad}$ (cf. Eq. (10))
1	Cu(*D*- or *L*-His)(*L*-Ser)	−0.77	−0.68[c]			
2	Cu(*D*- or *L*-His)(*L*-Thr)	−0.59				
3	Cu(*D*- or *L*-His)(*L*-Met)	−0.69				
4	Cu(*L*-His)(*L*-Trp)	−0.12	−0.68	0.56	2.6	72
5	Cu(*D*-His)(*L*-Trp)	+0.34	−0.68	1.02	9.5	90
6	Cu(*L*-His)(*L*-Phe)	−0.54	−0.68	0.14	0.38	28
7	Cu(*D*-His)(*L*-Phe)	−0.34	−0.68	0.34	1.2	55
8	Cu(*L*-His)(*L*-Val)	−0.55	−0.68	0.13[d]	0.35[d]	26[d]
9	Cu(*D*-His)(*L*-Val)	−0.61	−0.68	0.07[d]	0.17[d]	15[d]
10	Cu(*L*-His)(*L*-Leu)	−0.69	−0.68	~ −0.01[c]	~0[c]	~0(≤20)[c]
11	Cu(*D*-His)(*L*-Leu)	−0.72	−0.68	~ −0.04[c]	~0[c]	~0(≤20)[c]
12	Cu(*L*-His)(Gly)	−0.86	−0.93			
13	Cu(*L*-His)(*L*-Ala)	−1.00				
14	Cu(*L*-His)(*L*-Ser)	−0.88				
15	Cu(*L*-His)(*L*-Thr)	−0.98				
16	Cu(*L*-His)(*L*-Val)	−0.81	−0.93	0.12	0.32	24

[a]The data are abstracted from Table VII of Ref. 21. The stability constants on which $\Delta \log K_{(Cu/His/AA)}$ is based are from Refs. 37 (entries 1–11) and 38 (entries 12–16).

[b]Additional abbreviations not defined in Fig. 4 are: Ala^-, alaninate; Gly^-, glycinate; Met^-, methioninate; Ser^-, serinate; Thr^-, threoninate.

[c]This value is certainly a fair basis for the comparisons, as Ser^-, Thr^- and Met^- behave toward Cu^{2+} in solution as bidentate ligands[5]; see also Ref. 21.

[d]Assuming an error limit for $\Delta\Delta \log K$ of ±0.05 log unit (see, e.g., Table II), then the differences between the *D*- and *L*-His complexes are not significant (see also the text in Section 4).

[e]There is no significant difference between the *L*- and *D*-His complexes; assuming an error limit of ±0.05 for $\Delta\Delta \log K = -0.01$ and −0.04 one obtains for the "upper limits" of $Cu(His)(Leu)_{ad}$ 9% and 2%, respectively; based on a larger error limit, i.e., $\Delta\Delta \log K \leq 0.1$, one may conclude that most probably % $Cu(His)(Leu)_{ad} \leq 20\%$.

AMINO ACIDS

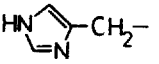
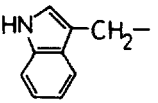
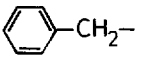
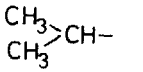
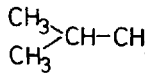
$R-CH(NH_3^+)COO^-$	AA	R^-
Histidine	His	
Tryptophan	Trp	
Phenylalanine	Phe	
Valine	Val	
Leucine	Leu	

FIGURE 4 Structures of the amino acids (AA) considered in Section 4 of this Comment together with the abbreviations used in the text and in Table III.

which is quantified by $10^{\Delta\Delta \log K}$ and which is formulated below as an example with His^-, Trp^- (having an interacting side chain) and Ala^- (without an interacting side chain):

$$Cu(Trp)^+ + Cu(His)(Ala) \rightleftharpoons Cu(His)(Trp) + Cu(Ala)^+ \quad (12)$$

It is obvious that the Cu^{2+} coordination spheres are identical on both sides of equilibrium (12). The other possibility (ii) is a *direct* intramolecular ligand–ligand interaction, which occurs in the above example (Eq. (12)) in Cu(His)(Trp) between the imidazole group of His^- and the indole residue of Trp^-; it is this intramolecular stack formation which is responsible for the position of equilibrium (12), because a corresponding stack can obviously not be formed in Cu(His)(Ala). Hence, the $\Delta\Delta$ log K evaluation with Eqs. (9) and (3c) only considers the intramolecular adduct formation and leads thus to the dimensionless equilibrium constant K_I (Eq. (2)) of equilibrium (1). In other words, we may conclude that the

increased stability of the systems corresponding to entries 4 through 9 and 16 in Table III are due to intramolecular hydrophobic or aromatic-ring stacking interactions involving the imidazole group.

This conclusion is further supported[35] by (i) the circular dichroism spectral magnitude anomalies of the complexes, and by (ii) evaluations of the constants due to equilibrium (13)[35,36] which is similar to equilibrium (12) but maintains the ligand field effects nearly constant in all the species involved:

$$\text{Cu(His)(Ala)} + \text{Cu(En)(AA)}^{+} \rightleftharpoons \text{Cu(His)(AA)} + \text{Cu(En)(Ala)}^{+} \quad (13)$$

In Eq. (13) En refers to ethylenediamine (= 1,2-diaminoethane) and AA^- to Phe^-, Tyr^- or Trp^-. The log K values (>0) for this equilibrium decrease for Cu(*D*-His)(*L*-AA) complexes in the series: $Trp^- > Tyr^- > Phe^-$ (= *L*-AA^-); this order coincides with the result obtained with equilibrium (12) in Ref. 21 and *vide infra*.

It is evident, as indicated already in Sections 1 and 3, that by using the $\Delta \log K_{(M/His/AA)}$ values (analogous to Eq. (7)) of complexes in which no interaction is likely or possible (= $\Delta \log K_{(M/His/AA)_{op}}$), the values of the intramolecular equilibrium constants, K_I (analogous to Eqs. (1) and (2)), and the percentages of the isomers with a ligand–ligand adduct (Eq. (10)), may be calculated (Table III). In this connection it should be noted that the K_I values calculated from the equilibrium data determined by different authors[37,38] are in excellent agreement (cf. entries 8 and 16 in Table III). A further advantage of using the $\Delta\Delta$ log K procedure is that systematic errors cancel, which are present, for example, in the constants of Eqs. (4), (5), and (6).

A view of the results of Table III shows that the extent of intramolecular adduct formation in the Cu(His)(AA) complexes depends on the chirality of the amino acids involved. This is a reflection of the fact that the amino acid anions may bind to the equatorial part of the Cu^{2+} coordination sphere in a *cis* (Fig. 5) and in a *trans* arrangement. If the structures of the complexes in aqueous solution are similar to those found in the solid ternary Cu(*L*-histidinate)(*L*-threoninate) (cf. Ref. 40) and Cu(*L*-histidinate)(*L*-asparaginate) complexes,[41] i.e., with the α-amino groups

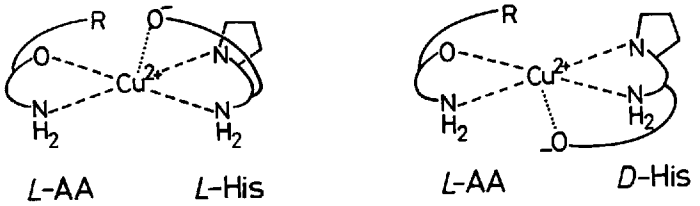


FIGURE 5 Possible structures of ternary Cu^{2+} complexes containing histidinate and another amino acid anion (*cis* arrangement) (Refs. 37, 40, and 41) with a side-chain group R able to interact with the imidazole residue of histidine (see Fig. 4 and Section 4). The apical coordination of the carboxylate group of histidinate is possibly not complete in solution.

cis, then the (at a distorted apical position) weakly coordinated carboxylate group of His^- and the side chain of the other amino acid anion are on the same side in the complex of the amino acids with the same chirality (Fig. 5; left side). In contrast, in the *cis* form of the Cu(*D*-His)(*L*-AA) complexes the two side chains are on opposite sides of the equatorial coordination plane of Cu^{2+} (Fig. 5; right side): consequently, the side-chain group R will not be affected in its intramolecular interaction with the imidazole ring by the carboxylate group and a weakly, apically coordinated and relatively far distant water molecule will have only a minor effect; indeed, there are many examples known where Cu^{2+} remains five-coordinate[17,18,41–45] and then no steric inhibition at all would occur in the Cu(*D*-His)(*L*-AA) complexes. In addition, in the penta-coordinated structures[18,41,43,46] Cu^{2+} is usually somewhat displaced from the base plane containing the stronger bonds toward the more weakly bound top atom of the pyramid, and, of course, this would facilitate the ligand–ligand interaction even more. Hence, one would expect that the intramolecular ligand–ligand interaction is more pronounced in the Cu(*D*-His)(*L*-AA) complexes than in the *L*,*L*-species, and indeed this expectation is very clearly confirmed for the complexes formed with *L*-tryptophanate and *L*-phenylalaninate; in the case of *L*-valinate and *L*-leucinate the differences between the isomers are within the expected error limits preventing any conclusion (see Table III).

There are two ways to rationalize further the lower formation degree of the intramolecular ligand–ligand adduct in the Cu(*L*-His)(*L*-AA) complexes where $L\text{-AA}^- = Trp^-$ or Phe^-: (i)

The adduct formation is simply somewhat inhibited by the presence of the carboxylate group (see Fig. 5). (ii) The *cis* form of Cu(*L*-His)(*L*-AA) isomerizes partly into the form with the two α-amino groups *trans* and then the side chains are again on opposite sides, allowing an easier R/imidazole interaction. Such an isomerization via the glycinate-like coordinated amino acid anion appears as rather likely because the energy barrier for the *cis/trans* isomerization is already low in the solid state[47,48] and therefore most probably even lower in solution[49]; however, this isomerization would still occur on account of the intramolecular ligand–ligand interaction. It is evident that both points or a combination of them explain the experimental results for the Cu(*L*-His)(*L*-AA) complexes. Maybe it should, in this connection, also be emphasized that the "closed" form of equilibrium (1) may well be a mixture of species with somewhat different structures; of course, in such cases[14,16,28] K_I quantifies the overall formation degree of these species.

Finally, the results listed in Table III show that the stability of the intramolecular ligand–ligand adduct formed between the imidazole group and the side-chain residue of the other AA^- in the Cu(His)(AA) complexes decreases within the series, indole (Trp^-) > phenyl (Phe^-) > *iso*-propyl (Val^-) ≳ 2-methyl-propyl (Leu^-). This observation is in accordance with the results discussed in Section 3, and also with those obtained[29,30] for binary $Cu(AA)_2$ complexes. It shows that the size of the aromatic groups is important and that aromatic-ring stacks are (usually) somewhat more stable than hydrophobic adducts with aliphatic residues. In addition, it is important to understand[23,50] that a value of 0.3 log unit for ΔΔ log K (see, e.g., Tables II and III) means that in equilibrium (1) half of the complexes exist with a ligand–ligand adduct and that this corresponds to a free energy change (ΔG°) of −1.7 kJ/mol at 25°C; when in equilibrium (1) only 10% of the intramolecular adduct is formed for ΔΔ log K = 0.05 and ΔG° = −0.3 kJ/mol, whereas a 90% formation degree of the adduct corresponds to ΔΔ log K = 1 and ΔG° = −5.7 kJ/mol. Hence, the energy difference involved between the formation of the isomers in equilibrium (1) may be very low but the formation degree of a certain species already remarkably high; such a situation appears to be ideal to facilitate, e.g., enzymic selectivity.

5. EVIDENCE FOR PURINE-IMIDAZOLE STACKS IN MIXED LIGAND NUCLEOTIDE-IMIDAZOLE COMPLEXES

A careful analysis[51] of stability data[8] for ternary complexes consisting of a metal ion, e.g., Zn^{2+} or Cd^{2+}, imidazole (Im), and adenosine 5′-triphosphate (ATP^{4-}) or uridine 5′-triphosphate (cf. Fig. 6) showed that the N-7 base-backbinding of the metal ion occurring in $M(ATP)^{2-}$ complexes[52] is released upon formation of ternary $M(ATP)(Im)^{2-}$ complexes.[51] This result was confirmed[51] by ^1H NMR shift measurements in D_2O under conditions where the known[53] self-association of $M(ATP)^{2-}$ complexes is relatively low; in these experiments the shifts of H-2, H-8, and H-1′ of $Zn(ATP)^{2-}$ and $Cd(ATP)^{2-}$ were monitored in dependence on the concentration of added imidazole. The corresponding ^1H NMR shift values are plotted in the upper parts of Figs. 7 and 8; the lower parts of these figures show the distribution of the complexes present under the experimental conditions in the mixed ligand systems.

The chemical shift of H-2 moves downfield with increasing concentrations of imidazole (Figs. 7 and 8). This is in line with the expected reduced self-association tendency of the ternary Zn^{2+} or Cd^{2+}/ATP/imidazole systems compared with the corresponding binary M^{2+}/ATP systems (see left side in Figs. 7 and 8 where

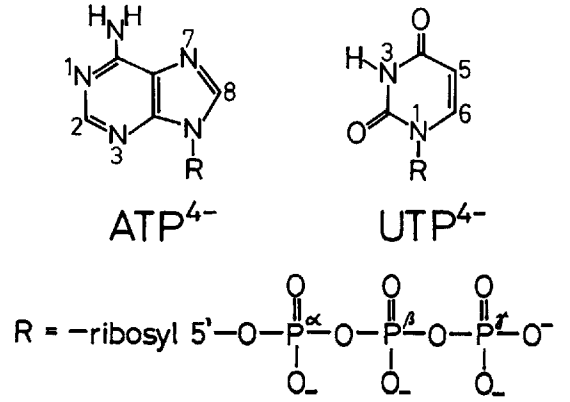


FIGURE 6 Structures of adenosine 5′-triphosphate (ATP^{4-}) and uridine 5′-triphosphate (UTP^{4-}) considered in Section 5 of this Comment.

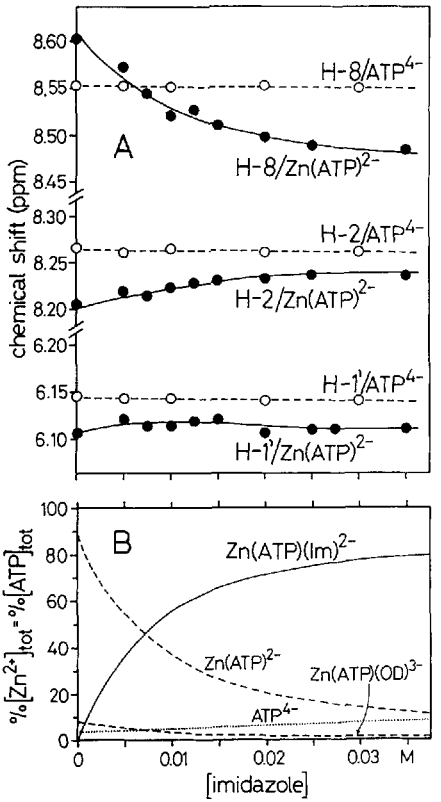


FIGURE 7 Comparison of (A) the chemical shifts of $Zn(ATP)^{2-}$ under the influence of increasing concentrations of imidazole with (B) the resulting increasing concentration of the ternary $Zn(ATP)(Im)^{2-}$ complex in D_2O at pD 8.4. (A) Dependence of the chemical shifts of H-2, H-8, and H-1′ of $Zn(ATP)^{2-}$ (●; $[Zn^{2+}]_{tot} = [ATP]_{tot} = 5 \times 10^{-3}$ M; the formation degree of $Zn(ATP)^{2-}$ is close to 90%, see below in (B)) on increasing concentrations of imidazole in D_2O at pD 8.4 (I = 0.1, $NaNO_3$; 27°C). The three nearly horizontal, broken lines represent the chemical shifts of H-2, H-8, and H-1′ of uncomplexed ATP (5×10^{-3} M) also at pD 8.4 and under the influence of increasing concentrations of imidazole (○). The spectra were measured on a Bruker FT-90 instrument at 90.025 MHz, relative to internal $(CH_3)_4N^+$, and converted to values relative to sodium 3-(trimethylsilyl)propane-sulfonate by adding 3.188 ppm. (B) Effect of increasing concentrations of imidazole (pD 9.2; I = 0.1; 25°C) on the concentration of the species present in a D_2O solution of Zn^{2+} and ATP (each 5×10^{-3} M). These results were computed with the constants given in Ref. 51, and they are given as the percentage of the total Zn^{2+} present (= total ATP). Reproduced by permission of the American Chemical Society from Ref. 51.

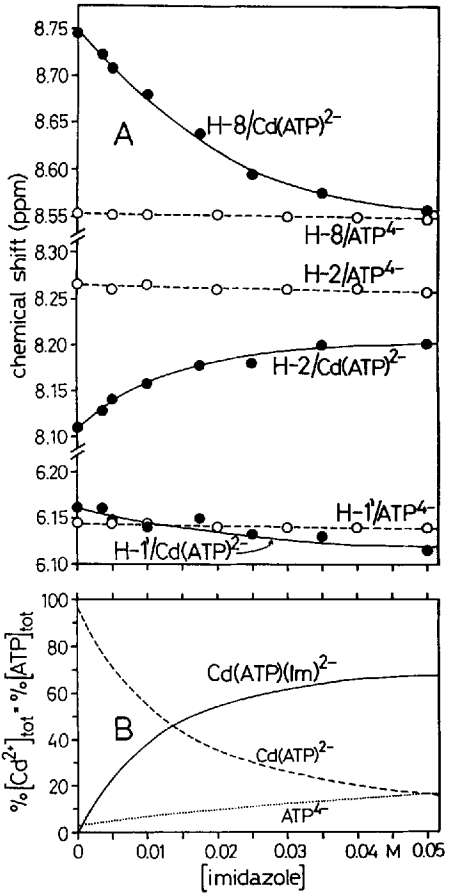


FIGURE 8 Comparison of (A) the chemical shifts of $Cd(ATP)^{2-}$ under the influence of increasing concentrations of imidazole with (B) the resulting increasing concentration of the ternary $Cd(ATP)(Im)^{2-}$ complex in D_2O at pD 8.4. (A) Dependence of the chemical shifts of H-2, H-8, and H-1′ of $Cd(ATP)^{2-}$ (●; $[Cd^{2+}]_{tot} = [ATP]_{tot} = 5 \times 10^{-3}$ M; the formation degree of $Cd(ATP)^{2-}$ is about 96%, see below in (B)) on increasing concentrations of imidazole in D_2O at pD 8.4 (I = 0.1, $NaNO_3$; 27°C). The three nearly horizontal, broken lines represent the chemical shifts of H-2, H-8, and H-1′ of uncomplexed ATP (5×10^{-3} M) also at pD 8.4 and under the influence of increasing concentrations of imidazole (○) (see also legend to Fig. 7). (B) Effect of increasing concentrations of imidazole (pD 8.4; I = 0.1; 25°C) on the concentration of the species present in a D_2O solution of Cd^{2+} and ATP (each 5×10^{-3} M). These results ($[Cd(ATP)(OD)^{3-}] < 0.5\%$) were computed with the constants given in Ref. 51, and they are given as the percentage of the total Cd^{2+} present (= total ATP). Reproduced by permission of the American Chemical Society from Ref. 51.

[Im] = 0).[51] Under the initial conditions of these experiments, about 15% of the total $M(ATP)^{2-}$ are self-associated.

The downfield shift observed for H-8 of the binary $M(ATP)^{2-}$ complexes, if compared with free ATP^{4-}, is less pronounced with Zn^{2+} than with Cd^{2+} (left side in Figs. 7 and 8 where [Im] = 0); this observation agrees with the lower formation degree of the macrochelated (i.e., N-7 backbound) $M(ATP)^{2-}$ isomer in the Zn^{2+} system.[52,53] Addition of imidazole to $M(ATP)^{2-}$ induces a significant upfield shift for H-8 in both systems, showing that N-7 is released in $M(ATP)^{2-}$ upon formation of $Zn(ATP)(Im)^{2-}$ (Fig. 7A) and $Cd(ATP)(Im)^{2-}$ (Fig. 8A). However, it was concluded before[51] from a comparison of the extent of the aforementioned upfield shifts for H-8 with the formation degrees of the ternary complexes as shown in the lower parts of Figs. 7 and 8 that these upfield shifts must have a further source: "This is especially evident from the $Zn(ATP)^{2-}$/Im system (Figure 7A), where the upfield shift of H-8 proceeds significantly beyond the shift position of H-8 in uncomplexed ATP^{4-}. This additional upfield shift suggests that coordination of imidazole to $M(ATP)^{2-}$ obviously has also a shielding effect on H-8; most probably in $M(ATP)(Im)^{2-}$ also some intramolecular stacking between the coordinated imidazole and the purine system of ATP occurs."

That the imidazole ring is able to participate in stacking interactions has already been shown in Sections 2 to 4, and there is also an earlier suggestion,[11] based on thermodynamic parameters, that in $Zn(ATP)(histamine)^{2-}$ stacking may occur. In addition, it is well known[14,19,20,54] that bridging by a metal ion facilitates stacking between otherwise only weakly interacting aromatic-ring systems. In fact, the upfield shifts observed for H-2, H-8 and H-1′ of ATP^{4-} (5×10^{-3} M), upon addition of a 10-fold excess of imidazole, are minute, i.e., on the order of 0.01 ppm (Fig. 8), indicating that the stability of the binary, unbridged stack is very low.

We have now attempted to make a semi-quantitative evaluation of the ^1H NMR shift data of Figs. 7 and 8 and to provide in this way conclusive evidence that intramolecular stacking in $M(ATP)(Im)^{2-}$ complexes is occurring. This means, we calculated for each experimental point of Figs. 7 and 8 the effect occurring

due to the release of N-7 from the coordination sphere of M^{2+} upon coordination of imidazole to $M(ATP)^{2-}$ and we also took into account the extent of the upfield shifts due to the self-association of the still present binary $M(ATP)^{2-}$ complexes. The concentration of the species in the systems is known (lower parts of Figs. 7 and 8) and the necessary background information regarding the chemical shifts for these calculations is available in Refs. 51 and 53. In this way we obtained for each imidazole concentration the corresponding corrected chemical shift, which is now "free" of the effect due to the release of N-7 and the self-association of $M(ATP)^{2-}$, i.e., we obtain the "pure" effect of imidazole upon its coordination to $M(ATP)^{2-}$. These corrected chemical shifts are plotted for H-8, H-2, and H-1′ in dependence on the imidazole concentration in Fig. 9. The curve-fits through the points of Fig. 9 were calculated with the known[8] stability constants $K^{M(ATP)}_{M(ATP)(Im)}$, of the $Zn(ATP)(Im)^{2-}$ and $Cd(ATP)(Im)^{2-}$ complexes; the agreement is obviously satisfactory.

Figure 9 shows that for all three considered protons *upfield* shifts are obtained upon formation of $Zn(ATP)(Im)^{2-}$ and $Cd(ATP)(Im)^{2-}$. This is clear evidence that purine-imidazole stacks are formed in these ternary complexes; the upfield shifts $\Delta\delta$ ($= \delta_0 - \delta_\infty$) are for $Zn(ATP)(Im)^{2-}$ 0.12 ± 0.02 (2σ), 0.07 ± 0.01, and 0.05 ± 0.01 ppm for H-8, H-2, and H-1′, respectively, and for $Cd(ATP)(Im)^{2-}$ 0.09 ± 0.03 (2σ), 0.09 ± 0.01, and 0.06 ± 0.02 ppm for H-8, H-2, and H-1′, respectively. The fact that the upfield shifts appear to be somewhat more pronounced for H-8 seems to indicate that the stacking interaction occurs preferably between imidazole and the imidazole part (and not the pyrimidine part) of the purine ring, though of course stacked species with different structures may well be present.

A quantitative evaluation of the position of equilibrium (1) is not possible with the available information; i.e., the extent of the upfield shift for a complete purine-imidazole stack in $M(ATP)(Im)^{2-}$ is not known. However, this upfield shift is expected to be on the order of 0.15 to 0.5 ppm.[14,55] Hence, by using the above-mentioned upfield shifts $\Delta\delta$, we may estimate that between about 15 to 50% of $Zn(ATP)(Im)^{2-}$ and $Cd(ATP)(Im)^{2-}$ exist with an intramolecular stack (Eq. (1)).

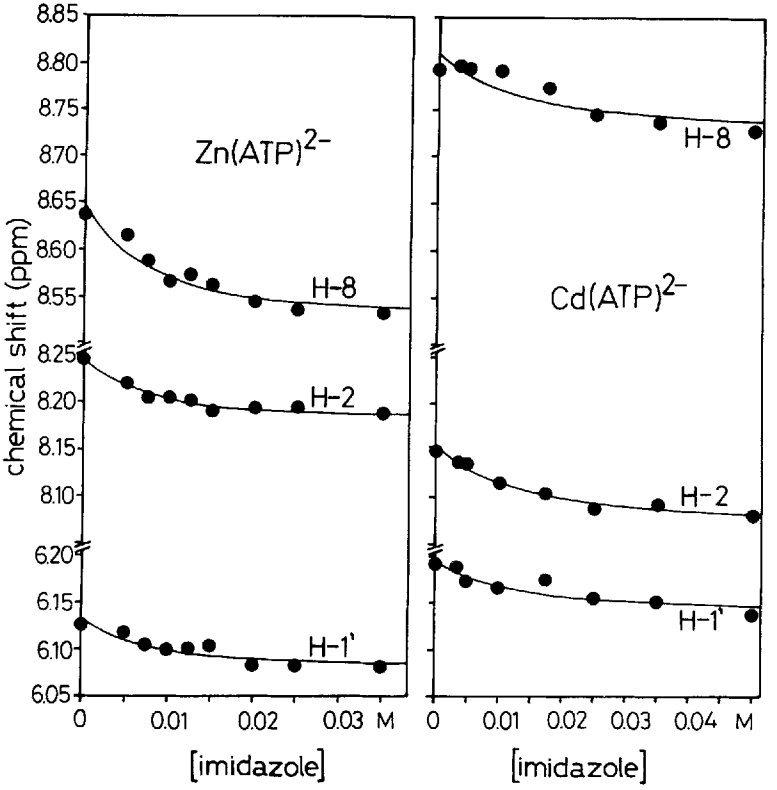


FIGURE 9 Corrected chemical shifts of H-2, H-8 and H-1′ of $M(ATP)^{2-}$ in dependence on increasing concentrations of imidazole. These chemical shifts represent the influence of imidazole on the purine residue upon formation of the ternary $M(ATP)(Im)^{2-}$ complexes (see Section 5).

6. CONCLUSIONS

This Comment provides clear evidence that the imidazole ring is well able to participate in stacking interactions with other aromatic-ring systems, as well as in hydrophobic interactions with aliphatic residues. Regarding biosystems this conclusion is important because it means that the imidazole residue of histidine has structuring effects like the indole or phenyl residues of tryptophan or

phenylalanine, respectively. Most important is the observation that the formation of stacking or hydrophobic adducts also occurs in the presence of metal ions; this means, coordination of a metal ion to the pyridine-like nitrogen of an imidazole ring does not invalidate its stacking properties and may in certain instances even produce a larger electron density difference between interacting rings. Clearly, this does not only hold for low-molecular-weight mixed ligand complexes, but is certainly also true for proteins, where the imidazole residue is an important binding site for metal ions.

Acknowledgments

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