Mixed Ligand Complexes of Al(III) & Ga(III) with Tripolyphosphate as Primary Ligand & Amino Acid & Peptides as Secondary Ligands†

M. M. TAQUI KHAN* & AMJAD HUSSAIN
Department of Chemistry, Nizam College (Osmania), Hyderabad 500 001

Received 30 April 1979; accepted 3 July 1979

Formation constants of mixed ligand complexes of Al(III) and Ga(III) with tripolyphosphoric acid (TPP) and amino acids and peptides are reported at 35° and $\mu = 0.10$ (KNO₃). Al(III) and Ga(III) do not form binary complexes with amino acids and peptides. Al(III)-TPP, Ga(III)-TPP, however, react with amino acids to form mixed ligand complexes. The order of stability of these complexes follows, in general, the order of basicity of the amino acids. Al(III) complexes are in general more stable than Ga(III) complexes.

In our earlier paper complexes of Al(III), Ga(III) and In(III) with aminopolycarboxylic acid were reported. As mentioned earlier very little is known about the aqueous solution chemistry of the complexes of Al(III) and Ga(III). This prompted us to study the interaction of these metal ions with amino acids and peptides in solution. A few workers have reported the formation of binary complexes by the interaction of Al(III), Ga(III) and In(III) with amino acids. However, the present studies indicate that the reported interaction of these metal ions with amino acids results from the hydrolysis of the metal ions and there is no true interaction with these ligands. During our investigations we have found that 1:1 complexes of Al(III), Ga(III) react with amino acids and peptides to form mixed ligand complexes. The present paper describes the investigation of these mixed ligand complexes.

Materials and Methods

Aluminium nitrate (BDH, AR) solution was standardised by EDTA titration and also by gravimetric method as oxinate. Specpure gallium and indium metals were obtained from K & K Laboratories. Metal nitrate solutions were prepared as described earlier. The ligands, $\alpha$-alanine and lysine monohydrochloride both BDH (England) products, were found to be chromatographically homogeneous. Valine, phenylalanine, proline, hydroxyproline, threonine, tyrosine, aspartic acid, glutamic acid were obtained from E. Merck (Germany). Glycylglycine, glycylphenylalanine were obtained from Mann Research Laboratories and tripolyphosphoric acid (TPP) was a product of Sigma Chemical Company. Purity of all the ligands was checked by titration with standard sodium hydroxide.

Procedure — The method consisted of titration of a given ligand in the absence and presence of an equivalent amount of metal ion with standard sodium hydroxide.

The $\phi$H meter (Elico) employed and its calibration have been described earlier. All the measurements were done at 35° and 0.10 M ionic strength. Nitrogen passed over acarite and presaturated with water was bubbled throughout the course of the titration.

Calculations

The equations used for calculating the dissociation constants of ligands have been given in our earlier publication.

For the calculation of the formation constants or mono-protonated 1:1 complexes the following equations were used:

$$K_{MLA} = \frac{[MLA]}{[ML][HA]} \quad \text{(1)}$$

$$K_{MLAH} = \frac{T_M - Y[A]}{Y[A][H^+]^2/k_{1a}} \quad \text{(2)}$$

where

$$Y = \frac{[H^+]^2}{k_1k_{2a}} + \frac{[H^+]}{k_{2a}} + 1$$

$$[L] = \frac{(1-a)T_L - [H^+] + [OH^-]}{[H^+]^2/k_{1a}k_{2a} + [H^+]^2/k_{2a}}$$

and $k_a's = \text{dissociation constants of ligand.}$

Formation of a "normal" 1:1:1 complex takes place according to the reaction

$$K_{MLA} = \frac{[MLA]}{[ML][A]} \quad \text{(3)}$$

†Work supported by CSIR grant.
proline, valine and threonine - The titration curve of lysine is also similar. Dissociation of a monoprotonated complex the following expressions hold good.

\[
Y = \frac{[H^+]^n}{k_{1a}k_{2a}\cdots k_{na}} + \frac{[H^+][n-1]}{k_{2a}\cdots k_{na}} + \cdots \frac{[H^+]}{k_{na}} + 1
\]

\[
[L] = \frac{(n-a)TA - [H^+] + [OH^-]}{n[H^+]k_{1a}k_{2a}\cdots k_{na} + \frac{(n-1)}{k_{2a}\cdots k_{na}} + [H^+]/k_{na}}
\]

When a "normal" complex is formed by the dissociation of a monoprotonated complex the following equations develop by Khan and Martell\(^{10}\).

\[
K_{MLA}^{MLAH} = \frac{MLA[H^+]}{[MLAH]} \quad ... (4)
\]

\[
T_A = T_M = [MLAH] + [MLA] \quad ... (5)
\]

\[
aT_A + [H^+] - [OH^-] = [MLA] \quad ... (6)
\]

All the unknowns in Eq. (4) can be calculated using Eqs. (5) and (6) and thereby the dissociation constant.

\[
K_{MLA}^{MLAH} \text{ is related to } K_{MLA} \text{ by Eq. (7)}
\]

\[
K_{MLA} = \frac{K_{MLA}^{MLAH}}{k_{2a}} \quad ... (7)
\]

Where the formation and subsequent dissociation of the protonated complexes took place in overlapping steps, equations developed by Khan and Martell\(^{10}\) were used.

Hydrolysis of metal chelates may lead to the formation of simple hydroxo chelates or high molecular weight polymers. If a polymer is formed it may be thought of as having a core and several links represented by general formula \(ML[ML(OH)]_n\). If such a species is formed then a plot of \(Z\), the average number of hydroxo bridges per link, versus \(-\log \text{T}_{ML}\) values should give a series of parallel lines. \(Z\) is given by

\[
Z = aT_A + [H^+] - [OH^-]/T_{ML} \quad ... (8)
\]

\(t\), the number of links is calculated from the slope of the plot of \(-\log \text{T}_{ML}\) vs \(-\log [H^+]\). If the value of \(t\) obtained is the correct value then a linear plot should be obtained on plotting \(Z/t\) versus (log \(T_{ML} - t \log [H^+]\)).

Results

Glycine, α-alanine, phenylalanine, proline, hydroxyproline, valine and threonine — The titration curve of glycine (Fig. 1, curve a) and of other ligands are similar. The curves start with an inflection which is followed by a buffer region. The dissociation constants of the ligands were calculated in the buffer region after \(a = 0\) by algebraic method. The results are presented in Table 1.

Tyrosine and lysine monohydrochloride — The titration curve of tyrosine (Fig. 2, curve a) also starts with an inflection followed by a buffer region. The titration curve of lysine is also similar. Dissocia-

<table>
<thead>
<tr>
<th>Ligand</th>
<th>(pK_{1a})</th>
<th>(pK_{2a})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>8.89 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Threonine</td>
<td>9.52 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>α-alanine</td>
<td>9.52 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Proline</td>
<td>10.17 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>9.20 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td>9.22 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>9.37 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>9.30</td>
<td>10.15</td>
</tr>
<tr>
<td>Lysine monohydrochloride</td>
<td>8.13</td>
<td>9.36</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>4.44 ± 0.01</td>
<td>9.37 ± 0.01</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>4.10 ± 0.01</td>
<td>9.37 ± 0.01</td>
</tr>
<tr>
<td>Glycylglycine</td>
<td>3.65 ± 0.01</td>
<td>7.15 ± 0.01</td>
</tr>
<tr>
<td>Glycylphenylalanine</td>
<td>4.13 ± 0.01</td>
<td>8.63 ± 0.01</td>
</tr>
</tbody>
</table>
the regions before the inflections at \( a = 1.0 \) and 2.0 respectively and the results are presented in Table 1.

**Interaction of Al(III), Ga(III), In(III) with amino acids** — The potentiometric titration curves of Al(III), Ga(III), In(III) with amino acids in 1:1 molar ratio show much depression in pH as compared to the free ligand titration curves apparently indicating a very strong interaction between amino acids and these metal ions. In order to distinguish the hydrolysis of the metal ion from that of its interaction with ligand, titrations of these metal ions with NaOH have been carried out in the absence of the amino acids. The hydrolysis curves thus obtained are horizontally added to free ligand titration curves. The synthetic curves thus obtained are then compared with the experimental 1:1 titration curves of the metal ions and amino acids. The synthetic and the experimental curves are found to overlap indicating that there is no interaction between the metal ions under investigation and amino acids. Had there been any interaction the experimental 1:1 curve would be lower than the synthetic curve.

**Ternary Chelates** — Various 1:1 metal-ligand systems were investigated to seek the possibility of 1:1:1 ternary complexes by the interaction of a 1:1 metal-ligand system with amino acids. It was found that 1:1 Al(III)-TPP and Ga(III)-TPP complexes interacted with amino acids to form ternary complexes under similar conditions. A precipitate was obtained with In(III), therefore, In(III) ternary systems were not investigated.

**Na₃TPP** — The titration curve of Na₃TPP shows an inflection at \( a = 1.0 \) (Fig. 6, curve a) followed by a buffer region. The first and second dissociation constants were calculated in the region before and after the inflection at \( a = 1.0 \) respectively by an algebraic method.

The titration curves of 1:1 Al(III)-TPP and Ga(III)-TPP systems (Fig. 6, curves b and c) show an inflection at \( a = 2.0 \). The pH at \( a = 0 \) shows...
The potentiometric titrations of Al(III)-TPP and phenylalanine is completely formed as mentioned earlier. There-fore the stability constants of 1:1 complexes could not be determined. In order to investigate the behaviour of the complexes after \( a = 2.0 \) various models for the hydrolysis and polymerisation were assumed. The model which best fitted the experimental observations was the formation of a Sillen’s “core link” species with the formula \( \text{M[ML}] \).

**Ternary chelates of Al(III)-TPP Ga(III)-TPP with amino acids and peptides** : Glycine, \( \alpha \)-alanine, phenylalanine, proline, hydroxyproline, valine and threonine — The potentiometric titrations of Al(III)-TPP and glycine in 1:1:1 molar ratio is shown in Fig. 1. The titration curve shows a slight inflection at \( a = 1.0 \) followed by a buffer region. The formation of “normal” 1:1:1 chelates was assumed in the region \( a = 2 \) to 3 and the stability constants calculated. In the region before \( a = 2.0 \), Al(III)-TPP complex is completely formed as mentioned earlier. Therefore the region between \( a = 0 \) and 2 was not taken into consideration in these and all the subsequent calculations.

In the case of 1:1:1 Ga(III)-TPP-amino acid systems titration curves did not show any inflection. But the horizontal addition of 1:1 Ga(III)-TPP and free amino acid curves and comparison with experimental 1:1:1 curves indicated interaction of Ga(III)-TPP with amino acids to form ternary complexes. Various equilibria were assumed and stability constants were calculated. The reaction for which stability constant showed least mean deviation was taken to be the one actually taking place. It was found that “normal” 1:1:1 complexes are formed with these amino acids. The results are presented in Table 2.

**Tyrosine and lysine monohydrochloride** — The potentiometric titration curves of 1:1:1 ternary systems of Al(III)-TPP-amino acid and Ga(III)-TPP-amino acid systems are shown in Fig. 2. The titration curves of Al(III) systems show a slight inflection at \( a = 1.0 \) followed by a buffer region. A monoprotonated species MLAH was assumed to be formed in the buffer region \( a = 2 \) to 3 and constant calculated using Eq. (6).

It may be seen from Fig. 2 (curve c) that titration curve of Ga(III) systems do not show any inflection. As in the case of monobasic amino acid systems discussed above various equilibria were assumed and the system which showed least mean deviation in stability constant was found to be 1:1:1 monoprotonated ternary complex MLAH. The formation constant of this protonated species MLAH is presented in Table 2.

**Aspartic acid and glutamic acid** — The potentiometric titration curves of these amino acids and Al(III)-TPP and Ga(III)-TPP systems in 1:1 molar ratios are shown in Fig. 3. The titration curves (b and c) did not show any inflection. Various assumptions were made regarding the species formed in solution and the corresponding models tested by mathematical equations and their solution to give a reasonably good constant. The model which best fitted the experimental observations was the formation of “normal” 1:1:1 ternary chelate. The results are presented in Table 2.

**Glycylglycine** — The potentiometric titration of Al(III) TPP and glygly, gave a curve (Fig. 4) which showed an inflection at \( a = 3.0 \). A monoprotonated ternary complex was assumed to be formed between \( a = 2 \) and 3 and the formation constant calculated using Eq. (6). In the buffer region between \( a = 0 \) and 2, 1:1 Al(III)-TPP complex was completely formed. Therefore this region was not taken into consideration for calculations. In the buffer region after \( a = 3.0 \), proton from the protonated complex, formed before \( a = 3.0 \), dissociated giving rise to a ‘normal’ ternary chelates.

The titration curve of Ga(III)-TPP-glygly. system showed a long drawn out inflection at \( a = 4.0 \) (Fig. 4, curve c). Formation of “normal” and protonated 1:1:1 complexes were assumed to

---

Table 2 — Formation Constants of 1:1:1 Complexes

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Al(III)</th>
<th>Ga(III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylalanine</td>
<td>7.55 ± 0.05</td>
<td>7.21 ± 0.05</td>
</tr>
<tr>
<td>Threonine</td>
<td>7.55 ± 0.05</td>
<td>7.21 ± 0.05</td>
</tr>
<tr>
<td>( \alpha )-alanine</td>
<td>7.51 ± 0.04</td>
<td>8.94 ± 0.04</td>
</tr>
<tr>
<td>Proline</td>
<td>8.65 ± 0.05</td>
<td>8.53 ± 0.06</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>7.83 ± 0.06</td>
<td>7.55 ± 0.05</td>
</tr>
<tr>
<td>Valine</td>
<td>7.90 ± 0.06</td>
<td>7.88 ± 0.06</td>
</tr>
<tr>
<td>Glycine</td>
<td>7.97 ± 0.03</td>
<td>7.96 ± 0.02</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>7.95 ± 0.06*</td>
<td>7.62 ± 0.03*</td>
</tr>
<tr>
<td>Lysine HCl</td>
<td>6.13 ± 0.03**</td>
<td>6.56 ± 0.04**</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>7.97 ± 0.03</td>
<td>7.99 ± 0.04</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>8.29 ± 0.03</td>
<td>8.31 ± 0.03</td>
</tr>
<tr>
<td>Glycylglycine</td>
<td>4.18 ± 0.04*</td>
<td>3.91 ± 0.05*</td>
</tr>
<tr>
<td>Glycylphenylalanine</td>
<td>4.33 ± 0.04*</td>
<td>-</td>
</tr>
</tbody>
</table>

\*\log KMLAH
\**log KMLAH
\**log KMLA

Fig. 6 — Free ligand titration of TPP (a) and 1:1 titrations of TPP and metal ions. [(b) Al(III), (c) Ga(III), \( \mu = 0.1 \) (KNO₃), temp. = 35°]
be formed in the region between \( a = 2 \) and 4. The constants were determined by a graphical method using the equations developed by Khan and Martell. The results are presented in Table 2.

Glycylphenylalanine — The potentiometric titration curves of Al(III)-TPP-glyph. a and Ga(III)-TPP-glyph. a system is shown in Fig. 5 (Curves b and c) The titration curve of Al(III) system shows an inflection at \( a = 3.0 \). A monoprotonated 1:1:1 complex was assumed to be formed between \( a = 2 \) and 3. A proton from this chelate then dissociates between \( a = 3 \) and 4 and a "normal" ternary complex is formed.

A monoprotonated complex is completely formed at \( a = 2.0 \) in the case of Ga(III)-glyph. a system as shown by an inflection at \( a = 4.0 \) (Fig. 5, curve C). The pH at \( a = 2.0 \) shows complete displacement of one proton from the peptide. A "normal" 1:1:1 complex is formed between \( a = 3 \) and 4 by the dissociation of proton from the monoprotonated complex. The results are tabulated in Table 2.

Discussion

Glycine may be considered as the simplest member of the series of aminopolycarboxylic acids IMDA to TTHA. As pointed out earlier, the stability of the complexes increases with the increase in the number of -CH₂COOH groups from HIMDA to TTHA. There is no interaction of Al(III), Ga(III), In(III) with glycine and other amino acids though a five-membered ring can be formed in such complexes. It appears that these tervalent metal ions which are hard acids prefer a carboxylate oxygen over nitrogen for complex formation. In fact Al(III), Ga(III), In(III) do not form complexes with ammonia or amine ligand. The interaction results in extensive hydrolysis of these metal ions. This fact lends support to the possibility that the donor nitrogen in amino acids and aminopolycarboxylic acids may not be able to coordinate with the metal ions to the same extent as the carboxylate oxygen. Simple dicarboxylic acids like oxalic acid and hydroxy acids like tartaric, gluconic, citric, salicylic form very stable complexes with Al(III), Ga(III), In(III).

Interaction of Al(III) and Ga(III) with TPP makes these metal ions soft enough to interact with amino acids. The microscopic nature of this interaction cannot be ascertained with the data available for the ternary complexes. A comparison with other amino acids and peptides complexes indicate that in the ternary complexes carboxylate oxygen from the amino acids may be involved to fill the vacant coordination position on the metal ion with a weak interaction by the amino or peptide nitrogen. Al(III) and Ga(III) form very stable complexes with TPP and the formation of these complexes is complete even at low pH. At higher pH in the buffer region after \( a = 2.0 \), Al(III)-TPP and Ga(III)-TPP hydrolyse and form Sillen's core + link species having the formula ML [ML(OH)₂]ₙ. In the absence of a definite inflection after \( a = 2.0 \) it is not possible to determine the value of \( n \). In the interaction of Al(III)-TPP and Ga(III)-TPP with amino acids and peptides hydrolysis of Al(III)-TPP and Ga(III)-TPP seems to be suppressed since the stability constants are fairly constant. Probably binding of two ligands to the metal ions in ternary chelates makes them sufficiently soft acids. So much so that hydrolysis of the 1:1 binary complexes is either suppressed or negligible.

All amino acids except tyrosine and lysine monohydrochloride form 'normal' 1:1:1 ternary chelates. Tyrosine and lysine however form monoprotonated complexes. In lys, HCl a butylamine group is attached to C-2. The butylamine group prefers to be protonated rather than form a weak complex with the metal ion since such a complex would involve a nine-membered ring system and nitrogen has a poor tendency to coordinate with these metal ions. The butylamine group is not bound in the complex and remains free.

In tyrosine a p-hydroxybenzoyl group is attached to C-2. Therefore it is not possible for the -OH of this group to take part in coordination. The coordination of tyrosine to metal ion increases the acidity of the -OH proton due to the shift of electrons towards the metal ion. Thus the proton dissociates at a higher pH to form a 'normal' tyrosine complex.

In the case of aspartic and glutamic acids which have two carboxylate groups, both the groups are expected to be coordinated to the metal ion and can act as terdentate ligands. In these cases two protons are expected to be released from the ligands upon coordination to form 'normal' ternary complexes. Monoprotonated complexes are not expected for such ligands as the carboxyl groups are quite acidic and the acidity further increases upon coordination with metal ion. Aspartic acid complexes have higher stability than glutamic acid complexes even though the basicity of both the ligands is almost same. This is because of formation of a highly stable five-membered and a six-membered ring in aspartic acid complexes. In glutamic acid complexes a five-membered and a seven-membered ring, which has lower stability, are formed.

The order of stability of ternary Al(III) and Ga(III) complexes in general follow the order of basicities of the amino acids. Lysine and α-alanine complexes of Ga(III)-TPP are more stable than those of Al(III)-TPP. Stabilities of Al(III) and Ga(III) complexes are almost same.

Interaction of Al(III)-TPP with glycyglycine and glycyphenylalanine is similar as shown by the titration curves which show an inflection at \( a = 3.0 \). With these ligands a monoprotonated complex is first formed and dissociates at higher pH to form a 'normal' complex. In contrast to the Al(III)-TPP complexes those of Ga(III)-TPP show a marked difference in interaction. Glycyglycine forms a protonated complex which dissociates to form a 'normal' complex. In the case of glycyphenylalanine a monoprotonated complex is completely formed at \( a = 2.0 \) and then dissociates to form a normal complex. Thus the complex of glycyphenylalanine is more stable than that of glycyglycine. This may be due to the electron withdrawing effect of phenyl ring in glycyphenylalanine. In Al(III) complex no such effect is detected. In fact the correspon-
ding constants are same for Al(III)-TPP-glygly. and Al(III)-TPP-gly. ph.a.

References