Nickel(II)-Tyrosine- and -Tryptophan-Nucleobase Ternary Complexes

M. C. Apella, A. Terron, J. J. Fiol, V. Moreno, E. Molins

I. Introduction

The bioinorganic chemistry of nickel is a topic of increasing interest owing to the presence of nickel in enzymes and the absolute requirement for this element proved for urea metabolism and urease synthesis in several higher plants [1, 2]. The interactions in solution with amino acids or peptides and nucleotides and related bases regarding ternary nickel-amino acid-base complexes have been studied by different authors [3, 12]; the complexity of Ni(II) with peptides, on the one hand, is of great relevance to the knowledge of nickel transport mechanisms, and with bases, on the other hand, for the understanding of the carcinogenicity of nickel. Very few studies have been reported up to date on ternary complexes [12, 15]. As a follow up of previous solution and solid state studies on the coordination chemistry of nickel (II) with nucleotides, nucleosides and amino acids, where the interaction between Ni(II) and two GMP or IMP was established to be in the cis conformation [15, 23] in the present work the interactions of nickel (II) with tyrosine, tryptophan and bases or nucleosides (Fig.1) have been studied in order to investigate the stacking interaction between the bases as a driving force in the formation of ternary compounds [24].

II. Experimental

Preparative method

Synthesis of 1: [Ni(tyr)2(9EtAde)2] × 4H2O. L-Tyrosine (0.61 mmol) (Merck), 0.61 mmol of KOH (3 ml of a 0.2 M solution) and 0.61 mmol of 9-ethyladenine (Sigma) were mixed in 37 ml of water. The mixture was heated at 60 °C with stirring for an hour until all the reagents were perfectly solubilised. A 10 ml solution containing 0.61 mmol of nickel(II) nitrate (Merck) was drop-wise added to this solution. The resulting solution was heated with stirring at 60 °C for 1 h. The final reaction pH was 6.1. When the reaction solution was allowed to...
stand for two days, pale lilac crystals appeared. The crystals were filtered out, washed with water and dried over silica gel in a desiccator. The yield was approximately 20%. Elemental analysis: found (calculated) for \( \text{Ni} \): C 44.43(44.30); H 5.62(5.68); N 20.57(20.56). The obtained compound is slightly soluble in both water and methanol and exhibits a weight loss between 30-120 °C corresponding to the loss of four water molecules per formula unit (mass loss calculated 8.82%, mass loss found 8.37%). The final residue at 660 °C, considered as NiO, was in agreement with the proposed formula (residue calculated 9.14%, found 9.48%).

**Synthesis of 2**: \([\text{Ni} \text{(tryr)}(9\text{EtGua})_2] \times 5\text{H}_2\text{O}\). The complex was obtained using the same procedure as in 1 but refluxing for 10 h, being the final pH 8.3. A pale violet micro crystalline precipitate appeared after two days, which was filtered off and dried over silica gel in a desiccator. The yield happened to be very low, approximately 6.2%. Elemental analysis, found (calculated) for 2: \([\text{Ni} \text{(tryr)}(9\text{EtGua})_2] \times 5\text{H}_2\text{O}\): C 44.43(44.30); H 5.31(5.59); N 19.25(19.38). The compound obtained exhibits a weight loss between 30 - 100 °C corresponding to the loss of five water molecules per formula unit (mass loss calculated 15.02 %, mass loss found 15.83 %); the final residue at 660 °C, considered as NiO, was in agreement with the formula proposed (residue calculated 13.13 %, found 12.11 %). The two water molecules lost below 110 °C can be tentatively assigned to hydration waters, and the remaining three as coordinated waters.

**Synthesis of 5**: \([\text{Ni} \text{(trp)}(9\text{EtGua})] \times 3\text{H}_2\text{O}\). A solution containing 1 mmol of tryptophan, 9-ethylguanine and 2 mmol of KOH in 40 ml of water was heated at 60 °C for 1 h. 1 mmol of nickel nitrate was added to the former solution. The mixture was heated to reflux for 14 h, final pH = 7.25. The precipitate obtained was filtered off and washed with water and dried over silica gel. Elemental analysis found (calculated) for 5: \([\text{Ni} \text{(trp)}(9\text{EtGua})] \times 3\text{H}_2\text{O}\): C 49.15(49.87); H 4.91(5.35); N 18.48(18.05). The compound obtained exhibits a weight loss between 30-235 °C corresponding to the loss of three water molecules per formula unit (mass loss calculated 15.62 %, mass loss found 15.83 %); the final residue at 660 °C, considered as NiO, was in agreement with the formula proposed (residue calculated 15.62 %, found 15.83 %).
Table I. Infrared data for the ternary complexes (in cm$^{-1}$).

<table>
<thead>
<tr>
<th>Tentative assignement</th>
<th>L-tyr</th>
<th>1</th>
<th>9EtAde</th>
<th>2</th>
<th>9EtGua</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>1665s</td>
<td>1680s</td>
<td>1679s</td>
<td>1667s</td>
</tr>
<tr>
<td>$\nu$ COO$^-$ (asym)</td>
<td>1610s</td>
<td>1588s</td>
<td>1600s*</td>
<td>1603s</td>
<td>-</td>
</tr>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>1335,1306m</td>
<td>1330,1310m</td>
<td>1310w</td>
<td>1313m*</td>
</tr>
<tr>
<td>$\nu$ Tyr</td>
<td>1040s</td>
<td>1047m</td>
<td>-</td>
<td>1065m</td>
<td>-</td>
</tr>
<tr>
<td>$\nu$ Tyr</td>
<td>990m</td>
<td>998w</td>
<td>-</td>
<td>982m</td>
<td>-</td>
</tr>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>848m</td>
<td>840w</td>
<td>849m</td>
<td>859m</td>
</tr>
<tr>
<td>Ni-N + $\nu$ Tyr</td>
<td>500m</td>
<td>510w</td>
<td>-</td>
<td>513w</td>
<td>505w*</td>
</tr>
<tr>
<td>$\nu$ Ni-O</td>
<td>-</td>
<td>363w</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ni-N or Ni-N</td>
<td>310m</td>
<td>311,297vw</td>
<td>-</td>
<td>297w</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tentative assignement</th>
<th>L-tyr</th>
<th>3</th>
<th>Guanosine</th>
<th>4</th>
<th>Inosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>1734m</td>
<td>1733vs</td>
<td>1661s</td>
<td>1700vs</td>
</tr>
<tr>
<td>$\nu$ COO$^-$ (asym)</td>
<td>1610vs</td>
<td>1616s</td>
<td>1611vs</td>
<td>1601s</td>
<td>-</td>
</tr>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>1538w</td>
<td>1537s</td>
<td>1294w</td>
<td>1300s</td>
</tr>
<tr>
<td>$\nu$ C-O</td>
<td>1260s</td>
<td>1255w</td>
<td>-</td>
<td>1253m</td>
<td>1250m*</td>
</tr>
<tr>
<td>$\nu$ Tyr</td>
<td>990m</td>
<td>1000w</td>
<td>1003w</td>
<td>988w</td>
<td>-</td>
</tr>
<tr>
<td>$\nu$ Ring</td>
<td>-</td>
<td>819w</td>
<td>824w</td>
<td>775w</td>
<td>780m</td>
</tr>
<tr>
<td>Ni-N + $\nu$ tyr</td>
<td>500m</td>
<td>505w</td>
<td>506w</td>
<td>513w</td>
<td>520m*</td>
</tr>
<tr>
<td>$\nu$ Ni-O</td>
<td>-</td>
<td>-</td>
<td>367w</td>
<td>360w*</td>
<td>-</td>
</tr>
<tr>
<td>Ni-N or Ni-N</td>
<td>310m</td>
<td>310vw</td>
<td>-</td>
<td>307w</td>
<td>310w*</td>
</tr>
</tbody>
</table>

1: [Ni(tyr)$_2$(9EtAde)$_2$] × 4H$_2$O; 2: [Ni(tyr)$_2$(9EtGua)$_2$] × 5H$_2$O; 3: [Ni(tyr)(guo) × 5H$_2$O] and 4: [Ni(tyr)(ino) × 5H$_2$O]; * a band which also appears in the second ligand with different assignment.

spectra were registered in the solid state (KBr pellets) on a Perkin Elmer 683 with a PE 1600 IR data station and the electronic spectra registered on a PE 552 spectrophotometer. Thermogravimetric data within the temperature range 30-700 °C were recorded (heating rate 10 °C min$^{-1}$) on a PE TGA-2 thermobalance.

Crystallographic diffractions were performed on an Enraf Nonius CAD4 diffractometer using MoKα radiation (λ = 0.71068 Å). Compound 1 crystallises in lilac needles but it was not possible to obtain suitable crystals for X-ray structure determination. Parameters of the unit cell are $a$ = 11.353, $b$ = 12.341, $c$ = 14.723, $\alpha$ = 69.36, $\beta$ = 87.55 and $\gamma$ = 89.85 and $V$ = 1928 g/cm$^3$.

Electrochemical data for compounds 1 and 2 were obtained from cyclic voltammetry under argon at 20 °C using acetonitrile (HPLC grade) as solvent and tetrabutylammonium hexafluorophosphate (0.1 M) as supporting electrolyte. The half-wave potentials were referred to an Ag-AgNO$_3$ (0.1 M in acetonitrile) electrode, separated from the solution by a medium porosity fritted disk. A platinum wire auxiliary electrode was used in conjunction with a TACUSSEL-EDL platinum disk electrode, rotatory working electrode (3.14 mm$^2$). Cyclic voltammograms of 210-3 M solutions of the samples in acetonitrile were recorded with a VersaStat EGand G Princeton Applied research potentiostat. The reference electrodes were periodically checked against the ferrocenium/ferrocene couple (Fc+/Fc) in acetonitrile. The half-wave potentials of Fc+/Fc versus Ag/Ag+ in acetonitrile was 0.132 V.

III. Results and Discussion

The thermogravimetric data strongly support the ternary nature of these complexes as indicated in the experimental section.

The infrared spectra confirm the ternary nature of these compounds, including tyrosine, tryptophan [25, 28] and purine base bands [29, 31]. The stretching Ni-N and Ni-O bands corresponding to the interactions between Ni(II) and tyrosine can be tentatively assigned [32, 35]. In Table I, some infrared data for these complexes are summarised. Infrared spectra regarding ternary compounds are well-known for the presence of a large number of bands, being the intensity usually not as strong as in the ligand bands, and in the studied compounds it was possible to assign bands which belong to only one of the ligands.

For example, in compound 1, different adenine ring bands can be observed: at 1680 cm$^{-1}$ (corresponding to $\delta$ NH$_2$ + $\nu$ C$_5$ = C$_6$ + $\nu$ C$_6$-NH$_2$) of
Table II. Electronic spectra.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\nu_2$ (cm$^{-1}$) $^3A_2 \rightarrow ^3T_1(F)$</th>
<th>$\nu_3$ (cm$^{-1}$) $^3A_2 \rightarrow ^3T_1(P)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: [Ni(tyr)$_2$(9EtAde)$_2$] $\times$ 4H$_2$O</td>
<td>16.450 ($\varepsilon = 4$)</td>
<td>28.000 ($\varepsilon = 13$)</td>
</tr>
<tr>
<td>2: [Ni(tyr)$_2$(9EtGua)$_2$] $\times$ 5H$_2$O</td>
<td>16.500</td>
<td>29.400 (sh)</td>
</tr>
</tbody>
</table>

Table III. Electrochemical data for the ternary complexes 1 and 2: anodic ($E_a$) and cathodic ($E_c$); potentials in V.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E_a$ ($eV$)</th>
<th>$E_a$ ref. to $fc$</th>
<th>$E_c$ ($eV$)</th>
<th>$E_c$ ref. to $fc$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: [Ni(tyr)$_2$(9EtAde)$_2$] $\times$ 4H$_2$O</td>
<td>-0.05</td>
<td>0.13</td>
<td>-0.18</td>
<td>-0.20</td>
</tr>
<tr>
<td>2: [Ni(tyr)$_2$(9EtGua)$_2$] $\times$ 5H$_2$O</td>
<td>-0.07</td>
<td>0.13</td>
<td>-0.20</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

Compounds 1 and 2 exhibit an electrochemically quasi-reversible one electron oxidation process with $E_{1/2} = -0.19V$ and -0.24 V respectively versus ferrocinium/ferrocene.

Fig. 2. Cyclic voltammograms of complexes 1: [Ni (tyr)$_2$(9EtAde)$_2$] $\times$ 4H$_2$O (top) and 2: [Ni (tyr)$_2$(9EtGua)$_2$] $\times$ 5H$_2$O (bottom).

the free 9-Ethyladenine appears at 1665 cm$^{-1}$ in the ternary complex 1. The same is observed for other adenine ring bands such as the 1330 and 1310 cm$^{-1}$ 9-bands (assigned to $\nu N_7$-C$_5$ + $\nu$ C$_8$-N$_7$ and $\nu$ N$_9$-C$_8$ + $\nu$ N$_3$-C$_2$ + $\delta$ C$_8$-H, respectively) which appear at 1335 and 1306 cm$^{-1}$ in the ternary complex, the 840 cm$^{-1}$ band ($\delta$ N$_1$-C$_2$-N$_3$ + $\nu$ N$_7$-C$_5$) and the band at 540 cm$^{-1}$ ($\delta$ C$_5$-C$_4$-N$_3$ + $\delta$ C$_2$-N$_1$-C$_6$) in the free ligand) which appear at 848 and 543 cm$^{-1}$ in the ternary complex respectively. Bands owing to the amino acid can be also tentatively assigned as indicated in Table I. Several bands can be compared with those of the [Ni(Tyr)$_2$(H$_2$O)$_2$] $\times$ H$_2$O complex which also appear in the ternary derivative: 1226 (and 1223 in the ternary complex) cm$^{-1}$, 1102(1101), 1040(1047), 978(998), 879(882) and 740(740) cm$^{-1}$. The metal normal modes of the [Ni(Tyr)$_2$(H$_2$O)$_2$] $\times$ H$_2$O complex are also present in the ternary complex (1): $\nu$ Ni-N 502 (and 510) cm$^{-1}$, $\nu$ Ni-O 364 (and 363) cm$^{-1}$ and $\nu$ Ni-N or Ni-N at 310 and 318(311 and 297) cm$^{-1}$ respectively.

The same detailed discussion can be held with the remaining ternary compounds 2, 3 and 4. Thus, the infrared data provides a clear information of the ternary nature of these complexes, together with the interaction between Ni(II) and the amino and carboxylic groups of the tyrosine and the purine ring. It is difficult to decipher, from the infrared data only, the coordination atom of the purine ring, however, these data are in agreement with the existence of a metal-base interaction.

For complex 5: [Ni (trp)$_2$(9EtGua)] $\times$ 3H$_2$O the ring bands can be observed at 1645s, 1546s, 1489s, 1186w, 735w, 715w, 705w cm$^{-1}$; and the tryptophan bands at 1588s (sCO), 1458w, 1279w, 1046w, 1012w, 987w, 750w, 658w and 465w cm$^{-1}$. Besides, the normal modes Ni-N or Ni-O can be tentatively
The electronic spectra were determined in a 1:1 water/methanol solution. In this solution compound 1 was very soluble; however, compound 2 happened to be slightly soluble. The electronic spectra agree with a pseudo-octahedral geometry corresponding to N₄O₂ ligands [36] (the N7 imidazol ring, the amino and carboxylic tyrosine groups) (Table II), e.g. the bands appear at 17543 and 28089 cm⁻¹ for the [Ni (en)₂(cyt-O)₂]²⁺ complex¹⁷, at 16130 and 26880 cm⁻¹ for the glycine [Ni (gly)₂(H₂O)₂]²⁺ complex and at 18000 and 28000 cm⁻¹ for the histidine [Ni (his)₂] complex [37].

Cyclic voltammograms registered within the range (-1 to 0.7V) exhibit an anodic peak with a reduction in the reverse scan as shown in Fig. 2, which belongs to the intensity-potential curves for compounds 1 and 2. This peak is assigned to the oxidation process of Ni(II) to Ni(III). The experiments were carried out at different scan rates (from 0.20 to 1.00 Vs⁻¹) and the results were consistent with those expected for a simple and reversible one electron transfer process.

The oxidation potential (V) found for compounds 1 and 2 are given in Table III. The values obtained for ferrocene at the same experimental conditions have been also tabulated. Besides, the values referred to ferrocene are included. Holm [38] has published values of Ni(III)/Ni(II) in CH₃CN versus SCE with a value for the couple ferrocinium/ferrocene of 0.40 V. Making the conversion from ferrocene to SCE the E₁/₂ values obtained for 1 and 2 are +0.21 V and +0.14 V, respectively referred to SCE. These values are higher than those previously published in identical conditions for the couple Ni(III)/Ni(II) for NiN₂ complexes, where N is pyridine or an N oxime ligand, and NiN₂S₄, with sulphur ligands [38], as expected for a system with NiN₄O₂ ligands, where N is a puric nitrogen or amino group and O an amino acid carboxylic group. Besides, these values are also in agreement with the value of +0.40V (versus SCE) for the couple Ni(III,II) (H⁻₁GG)₂⁻ bis(dipeptido) complex measured in water [2]. In the latter a NiN₄O₂ complex is present, however, the N are amino or peptide groups, not as strong ligands as a N from the aromatic purine base ring which seems to strongly stabilise the Ni(III) oxidation state.

All data agree with the ternary character of the studied complexes. The electronic spectra and the voltammograms strongly agree with an octahedral geometry for the Ni(II) ions. In complexes 1 and 2, to four nitrogens (two from the purine ring and two amino groups from the amino acid) and two oxygens (from the carboxylic group of the amino acid). The two compounds are microcrystalline, however, the numerous attempts failed to yield suitable crystals for X ray diffraction analysis. The coordination of two bases, purine nucleosides or nucleotides in cis position to a metal ion is well-known in the literature [39]. For example, the X ray structure of the [Ni (5’GMPH)₂(H₂O)₂(en)] complex presents the two guanosine monophosphate ligands coordinated in cis position through the N(7) of the purine ring to the nickel ion [40]. The guanosine and inosine derivatives 3 and 4, seem to be also ternary compounds although possibly polymeric.

Acknowledgments

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