Palladium(II) and platinum(II) mixed ligand complexes of metronidazole and saccharinate or benzisothiazolinonate ligands, synthesis and spectroscopic investigation

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1. Introduction

Nitroimidazole compounds, especially 5- and 2-nitroimidazoles, were the first hypoxic cell radio sensitizers to show clinical promise [1-3], because they were of high electron affinity and exhibited relatively low toxicity to non-hypoxic cells. 5-Nitroimidazole is widely used in the treatment of an aerobic infections and has been shown to act as a hypoxic cell sensitizer in vitro [4,5] and gives significant sensitization of tumor response in several model murine tumor systems [6].

Several metal chelates are known to possess antibacterial, anti-fungicidal, antiviral and anticancer activity. In several cases, the metal chelates have been found to be more antimicrobial than the chelating agents themselves [7]. Also it is known that some drugs act via chelation or by inhibitory metallo enzymes but for most of the drugs that act as potential ligands, a lot of studies are being carried out to ascertain how metal binding influences the activities of the drugs [8]. However, metal ions play an important role in bioinorganic chemistry thus metals such as Fe, Co, Ni, Cu, Zn, and Cd may exist in trace amounts in biological systems. Structural studies of the complexes of these metals with biological compounds are extremely important [9]. Although, many papers have been published on the transition metal complexes of metronidazole ligand (mnz) alone or with other ligands as Co-ligands [10-19]. There are relatively little works reported on the mixed ligands as Co-ligands [10-19]. We describe in this paper the synthesis and characterization of new mixed ligand complexes of Pd(II) and Pt(II) metronidazole complexes with saccharinate (sac) or benzisothiazolinonate (bit) ligands, (Chart 1).

Chart 1
2. Experimental

2.1 Materials and Methods:
All chemical compounds and solvents were supplied and used without further purification. IR spectra were recorded on Shimadzu 8400 S FTIR spectrophotometer as KBr disc in 4000-400 cm⁻¹ range. NMR spectra (¹H-NMR) were recorded on Bruker av 400 NMR spectrometer in DMSO-d⁶ as a solvent. The conductivity measurement of the prepared complexes solutions (10⁻¹M) in DMSO was measured using digital conductivity meter CD 2005. Melting points were recorded on SMP40 - Stuart Company and were uncorrected.

K₂PtCl⁶, PdCl₂, metronidazole (mnz), benzisothiazolinone (Hbit) and sodium saccharinate (Nasac), were purchased and used as supplied. Sodium benzisothiazolinate (Nabit) [20] cis-[PdCl₂(DMSO)₂], trans-[PdCl₂(DMSO)₂] [21], trans-[PtCl₂(mnz)₂], cis-[PtCl₂(mnz)₂] [22], cis-[PtCl₂(Nabit)₂] [23], were prepared by literature methods.

2.2 Synthesis of complexes (1-6)

2.2.1 Synthesis of trans-[Pd(sac)₂(mnz)₂] (1)
A solution of sodium saccharinate (Nasac) (0.123g, 0.6mmol) in EtOH (10ml) was added to a yellow suspension of trans-[PdCl₂(mnz)₂] (0.156g, 0.3mmol) in EtOH (10ml) with stirring, a yellow clear solution was formed. The mixture was refluxed for 3h to afford a grey precipitate. The gray product was filtered off, washed with distilled water, and dried under vacuum (Yield: 0.188 g, 77%, m.p (°C): 285).

2.2.2 Synthesis of trans-[Pt(sac)₂(mnz)₂] (3)
A solution of sodium saccharinate (Nasac) (0.041g, 0.2mmol) in EtOH (10ml) was added to a yellow suspension of trans-[PtCl₂(mnz)₂] (0.061g, 0.1mmol) in EtOH (10ml) with stirring. The mixture was refluxed for 3h to afford a clear solution, which was left to evaporate at room temperature to dryness. The resulting creamy solid washed with distilled water, and dried under vacuum (Yield: 0.085 g, 94%, m.p (°C): 270).

trans-[Pd(bit)₂(mnz)₂] (2) was prepared and isolated by a similar method. cis-[Pt(sac)₂(mnz)₂] (5) and cis-[Pt(bit)₂(mnz)₂] (6) were prepared and isolated by similar methods starting with cis-[PtCl₂(mnz)₂] and Nasac or Nabit respectively.

2.2.3 Synthesis of trans-[Pt(bit)₂(mnz)₂] (4)
A solution of sodium benzisothiazolinonate (Nabit) (0.025g, 0.164mmol) in EtOH (10ml) was added to a yellow suspension of trans-[PtCl₂(mnz)₂] (0.050g, 0.082mmol) in EtOH (10ml) with stirring. The mixture was refluxed for 4h, to afford a clear lemon solution within 25 min, then change to a yellow suspension after an hour. The yellow product was filtered off, washed with distilled water, and dried under vacuum (Yield: 0.034g, 50%, m.p (°C): 265).

3. Results and Discussions

3.1 Synthesis of complexes (1-6)
Treatment of trans-[MCl₂(mnz)₂] (M= Pd(II) or Pt(II)) with two equivalents of sodium saccharinate (Nasac) or sodium benzisothiazolinate (Nabit) in ethanol as a solvent afforded complexes of the types trans-[M(sac)₂(mnz)₂] (1,3) or trans-[M(bit)₂(mnz)₂] (2,4) in 50 to 94 % yield by chloride exchange under normal conditions as shown in Scheme 1. The reaction of cis-[PtCl₂(mnz)₂] complex with two moles of (Nasac) or (Nabit) afforded cis-[Pt(sac)₂(mnz)₂] (5) and cis-[Pt(bit)₂(mnz)₂] (6) respectively (Scheme 2).

Scheme 1: Preparation of trans-[M(sac)₂(mnz)₂] (1,3) or trans-[M(bit)₂(mnz)₂] (2,4)
The prepared complexes are air stable in the solid state and insoluble in common solvents such as methanol, ethanol, acetone, diethylether or distilled water but soluble in chloroform, dichloromethane, dimethyl sulfoxide, or dimethyl formamide. The prepared complexes have been characterized by infrared spectroscopy, $^1$H NMR spectra, molar conductivity, and elemental analysis (CHNS). The elemental analyses are listed in Table 1, they agreed well with the calculated data of the complexes. The molar conductivity values of the freshly prepared complexes measured in DMSO 25 °C temperature found to be within the range of non-electrolytes values [24].

### Table 1. Color, m.p.(°C), and elemental analysis of the prepared complexes (1-6)

<table>
<thead>
<tr>
<th>NO.</th>
<th>Complexes</th>
<th>Color</th>
<th>m.p.(°C)</th>
<th>Yield %</th>
<th>$\Lambda_{\text{mсол}}$ (Ohm $^{-1}\cdot$cm$^2$ $\cdot$mol$^{-1}$)</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>trans-[Pd(sac)$_2$(mnz)$_2$]</td>
<td>Gray</td>
<td>285</td>
<td>77</td>
<td>11.21</td>
<td>38.21 (38.41)</td>
</tr>
<tr>
<td>2</td>
<td>trans-[Pd(bit)$_2$(mnz)$_2$]</td>
<td>Orange</td>
<td>137</td>
<td>82</td>
<td>10.90</td>
<td>41.98 (41.69)</td>
</tr>
<tr>
<td>3</td>
<td>trans-[Pt(sac)$_2$(mnz)$_2$]</td>
<td>Creamy White</td>
<td>270</td>
<td>94</td>
<td>2.90</td>
<td>34.25 (34.63)</td>
</tr>
<tr>
<td>4</td>
<td>trans-[Pt(bit)$_2$(mnz)$_2$]</td>
<td>pale Yellow</td>
<td>265</td>
<td>50</td>
<td>4.37</td>
<td>37.41 (37.28)</td>
</tr>
<tr>
<td>5</td>
<td>cis-[Pt(sac)$_2$(mnz)$_2$]</td>
<td>White</td>
<td>304</td>
<td>90</td>
<td>13.09</td>
<td>34.25 (34.63)</td>
</tr>
<tr>
<td>6</td>
<td>cis-[Pt(bit)$_2$(mnz)$_2$]</td>
<td>Yellow</td>
<td>225</td>
<td>91</td>
<td>16.61</td>
<td>37.66 (37.28)</td>
</tr>
</tbody>
</table>

### 3.2 Infrared spectroscopic studies

The infrared data of the free ligands and their prepared complexes are listed in Table 2 and Fig. 1, 2. The infrared spectra of the metronidazole complexes showed the $\nu$(C=N) stretching within (1544-1566) cm$^{-1}$ range, which shifted to higher frequencies, in all complexes due to the coordination of imidazole nitrogen atom to the metal ions [12-19]. The vibration frequency of the $\nu$(C=O) band appeared within the (1670-1683) cm$^{-1}$ range for the complexes 1, 3 and 5. The $\nu$(C=O) stretching was shifted to high frequency region compared to that of the free saccharinate ligand, indicates that the carbonyl group doesn't participate in the coordination to metal ions[25-27]. The $\nu$(SO$_2$)$_{xy}$ and $\nu$(SO$_2$)$_{xyy}$ stretching appeared within (1151-1159) cm$^{-1}$ and (1246-1255) cm$^{-1}$ range shifted slightly wave number side relative to that in the free ligand, indicating non-coordination of the SO$_2$ group with the metal ion [25,26].

In the trans-[Pd(bit)$_2$(mnz)$_2$] (2), the $\nu$(C=O) stretching vibration observed at (1649) cm$^{-1}$, indicates that the carbonyl group doesn't involved in coordination to the Pd(II) ion, as compared with that of the free Nabit which appeared at (1591) cm$^{-1}$ [26-29]. Whereas the vibration frequency of the $\nu$(C=O) band in the platinum complexes (4 and 6) appeared at (1153) and (1149) cm$^{-1}$, indicating that (C-O) group participate in coordination with Pt(II) ion [26-29].
Table 2: Selected IR stretching vibration bands (cm\(^{-1}\)) of the free ligands and their complexes.

<table>
<thead>
<tr>
<th>NO.</th>
<th>compounds</th>
<th>(v) (OH)</th>
<th>(v) (C=H)</th>
<th>(v) (C=O)</th>
<th>(v) (C=(\equiv)N)</th>
<th>(v) (SO(_2))</th>
<th>(v) (CNS)</th>
<th>M-N</th>
<th>M-O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ar.</td>
<td>Alph.</td>
<td>-----</td>
<td>1535s</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>1</td>
<td>Mnz</td>
<td>3221s</td>
<td>3099s</td>
<td>2956w</td>
<td>-----</td>
<td>1535s</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>2</td>
<td>Nasac</td>
<td>-----</td>
<td>3099w</td>
<td>-----</td>
<td>1645s</td>
<td>1450m</td>
<td>1257s</td>
<td>1149s</td>
<td>1336m</td>
</tr>
<tr>
<td>3</td>
<td>Na[btt]</td>
<td>-----</td>
<td>3061w</td>
<td>1591m</td>
<td>1435s</td>
<td>-----</td>
<td>1317m</td>
<td>877m</td>
<td>-----</td>
</tr>
<tr>
<td>4</td>
<td>trans-[PtCl(_2)mnz(_2)]</td>
<td>3420s</td>
<td>3110w</td>
<td>2991w</td>
<td>-----</td>
<td>1562s</td>
<td>-----</td>
<td>-----</td>
<td>432w</td>
</tr>
<tr>
<td>5</td>
<td>trans-[PtCl(_2)mnz(_2)]</td>
<td>3410s</td>
<td>3144m</td>
<td>2953w</td>
<td>-----</td>
<td>1558s</td>
<td>-----</td>
<td>-----</td>
<td>428w</td>
</tr>
<tr>
<td>6</td>
<td>cis-[PtCl(_2)mnz(_2)]</td>
<td>3392s</td>
<td>3134m</td>
<td>2962w</td>
<td>-----</td>
<td>1560s</td>
<td>-----</td>
<td>-----</td>
<td>422w</td>
</tr>
</tbody>
</table>

3.2 NMR spectroscopic studies

The \(^1\)H NMR spectra of the complexes trans-[Pd(sac)\(_2\)mnz\(_2\)] (1) (Fig. 3) and cis-[Pt(sac)\(_2\)mnz\(_2\)] (5) (Fig. 4) display a singlet peak within (62.46-2.47) ppm range assigned to the proton of the methyl group, whereas the methylene groups of the (mnz) ligand, NCH\(_2\) and OCH\(_2\) appeared with in (63.69) and (64.36-4.41) ppm respectively, Integrations under signals indicated that these signals represent 6H, 4H and 4H respectively. The saccharinate protons appeared as three multiplets at 7.59, 7.78 and 7.91 ppm for the complex 1 and at 7.58, 7.65 and 7.77 ppm for the complex 3. Complex 5 showed three multiplets at 7.59, 7.65 and 7.72 ppm for the four protons of the phenyl ring.

The \(^1\)H NMR spectrum of the trans-[Pd(bit)\(_2\)mnz\(_2\)] (4) (Fig. 5) displayed the protons of bit ligand as three multiplets at 67.67, 7.41 and 7.23 ppm, these signals represent 4H, 2H and 2H respectively, Integrations under signals are in agreement with the number of protons. The methyl group of the (mnz) ligand in 4 appeared as a singlet at 2.47 ppm, the protons of methylene groups appeared at 3.65ppm and 4.38ppm for NCH\(_2\) and OCH\(_2\) respectively. The \(^1\)H-NMR spectra of 2 and 6 complexes displayed the expected signals for the mnz ligand as well as the bit ligand (data are given in Table 3).

Table 3: \(^1\)H NMR chemical shifts (\(\delta\) ppm) for the prepared complexes (1-6) measured in DMSO-d\(_6\)

<table>
<thead>
<tr>
<th>NO.</th>
<th>Complexes</th>
<th>(\delta)H (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>trans-[Pd(sac)(_2)mnz(_2)]</td>
<td>8.80 (s, 2H, OH); 8.03 (s, 2H, CH-N); 7.88 (m, 2H, H-sac); 7.75 (m, 2H, H-sac); 7.58 (m, 2H, H-sac); 4.41 (m, 4H, CH-N); 3.69 (m, 4H, CH-O); 2.47 (S, 6H, CH(_3)).</td>
</tr>
<tr>
<td>2</td>
<td>trans-[Pd(bit)(_2)mnz(_2)]</td>
<td>8.05 (s, 2H, CH-N); 7.63 (m, 2H, H-bit); 7.39 (m, 4H, H-bit); 7.21 (m, 4H, H-bit); 5.03 (s, 2H, OH); 4.36 (m, 4H, CH-N); 3.69 (t, (\delta)J(_{HH}) = 8.88 Hz, 4H, CH-O); 2.51 (S, 6H, CH(_3)).</td>
</tr>
<tr>
<td>3</td>
<td>trans-[Pt(sac)(_2)mnz(_2)]</td>
<td>8.17 (s, 2H, OH); 8.04 (s, 2H, CH-N); 7.91 (m, 2H, H-sac); 7.79 (m, 4H, H-sac); 4.45 (t, (\delta)J(_{HH}) = 788 Hz, 4H, CH-N); 3.69 (m, 4H, CH-O); 2.46 (S, 6H, CH(_3)).</td>
</tr>
<tr>
<td>4</td>
<td>trans-[Pt(bit)(_2)mnz(_2)]</td>
<td>8.70 (s, 2H, OH); 8.03 (s, 2H, CH-N); 7.67 (m, 4H, H-bit); 7.41 (m, 2H, H-bit); 7.23 (m, 2H, H-bit); 4.38 (m, 4H, CH-N); 3.65 (m, 4H, CH-O); 2.47 (S, 6H, CH(_3)).</td>
</tr>
<tr>
<td>5</td>
<td>cis-[Pt(sac)(_2)mnz(_2)]</td>
<td>8.55 (s, 2H, OH); 8.03 (s, 2H, CH-N); 7.72 (m, 2H, H-sac); 7.65 (m, 2H, H-sac); 7.59 (m, 4H, H-sac); 4.36 (t, (\delta)J(_{HH}) = 8.88 Hz, 4H, CH-N); 3.69 (m, 4H, CH-O); 2.46 (S, 6H, CH(_3)).</td>
</tr>
<tr>
<td>6</td>
<td>cis-[Pt(bit)(_2)mnz(_2)]</td>
<td>8.43 (s, 2H, OH); 8.03 (s, 2H, CH-N); 7.66 (m, 4H, H-bit); 7.41 (m, 2H, H-bit); 7.22 (m, 2H, H-bit); 4.36 (t, (\delta)J(<em>{HH}) = 8.88 Hz, 4H, CH-N); 3.69 (q, (\delta)J(</em>{HH}) = , 4H, CH-O); 2.47 (S, 6H, CH(_3)).</td>
</tr>
</tbody>
</table>
References


معقدات البلاديوم (II) والبلاتين (II) مع مزيج من ليكاندات المترونيدازول والسكارينيت أو البنزايزوثايازولينونيت، تحضير وتشخيص طيفي

علي أحمد خضر الجبوري، صبحي عطية محمود الجبوري، أحمد شاكر مرموص الجنابي

قسم الكيمياء، كلية العلوم، جامعة تكريت، تكريت، العراق

فرع الكيمياء الحيائية، كلية الطب البيطري، جامعة تكريت، تكريت، العراق

الملخص

تست مستعدادات جديد البلاديوم (II) والبلاتين (II) الحاوية على مزيج من ليكاندات المترونيدازول والسكارينيت (Nasac) أو البنزايزوثايازولينونيت (Nabit) الصيغ trans-[M(sac)2(mnz)2] و cis-[Pt(sac)2(mnz)2] و M=Pd(II) أو Pt(II) حيث (M= Pd(II) أو Pt(II)) نتائج الصناعية ذات الصيد. و trans-[M(bit)2(mnz)2] و cis-[Pt(bit)2(mnz)2]، و من تفاعل المعقدات [PtCl2(mnz)]2 و trans-[PtCl2(mnz)]2 و cis-[PtCl2(mnz)2] و trans-[MCl2(mnz)]2 و cis-[MCl2(mnz)2] مع ليكاندات صوديوم سكارينيت (Nasac) أو ليكاندات بنزايزوثايازولينونيت (Nabit) و الببتيد بنزايزوثايازولينونيت (Nabit) أو صوديوم بنزايزوثايازولينونيت (Nabit) و نسب منتج عالية. تُستخدم المعقدات المحضرة باستخدام التحليل البصري واستهداف الموصلية المولارية وطبقة الأشعة تحت الحمراء للكشف عن الصيد. و鼠 اليسك، ليكاند المترونيدازول. يناسب مع الأيون (Nasac) أو ليكاند (bit) عن طريق ذرة النيتروجين؛ فإن ليكاند (Nasac) يناسب مع الأيون (bit) عن طريق ذرة النيتروجين. يناسب مع البلاديوم (II) أو البلاتين (II).