

Electrospray ionization mass spectrometric study of platinum(II) complexes with 1,3,4-thiadiazoles and dimethyl sulfoxide

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Abstract

By mixing 2,5-disubstituted-1,3,4-thiadiazoles (L) with platinum(II) chloride and dimethyl sulfoxide (DMSO) a number of complexes have been obtained and studied by the electrospray ionization mass spectrometry. Excellent correlation between the types of complexes observed and the arrangement of pyridine and thiadiazole nitrogen atoms has confirmed that we really deal with structurally defined complexes, not with electrostatic adducts which are very common in ESI. For platinum(II) coordinated by one nitrogen atom (from the thiadiazole ring or pyridine nitrogen atom), the observed complexes has been found to contain two DMSO molecules ($[\text{PtL}(\text{DMSO})_2\text{Cl}]^+$ ion). For the compounds containing 1,3,4-thiadiazole ring substituted by 2-pyridyl moiety, platinum(II) has been coordinated by two nitrogen atoms (one pyridine and one from the thiadiazole ring) and the complex formed contained one DMSO molecule ($[\text{PtL}(\text{DMSO})\text{Cl}]^+$ ion). The compounds containing 2,6-di(1,3,4-thiadiazol-2-yl)-pyridine moiety have formed non-DMSO containing complexes ($[\text{PtLCl}]^+$ ion) since the platinum(II) cation was coordinated by two nitrogen atoms of the thiadiazole ring and by one pyridine nitrogen atom. For the compounds able to form two types of complexes, their relative amounts have been shown to be substantially affected by the solvent used indicating that the recorded ESI mass spectra reflect the condensed phase. The compounds not containing pyridyl moieties but containing two thiadiazole rings have also yielded two types of complexes (containing one and two DMSO molecules), however, their relative amounts can be affected by the solvent used only if the thiadiazole rings are close to each other.

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Keywords: 1,3,4-Thiadiazoles; Platinum(II) complexes; Dimethyl sulfoxide; Electrospray ionization mass spectrometry

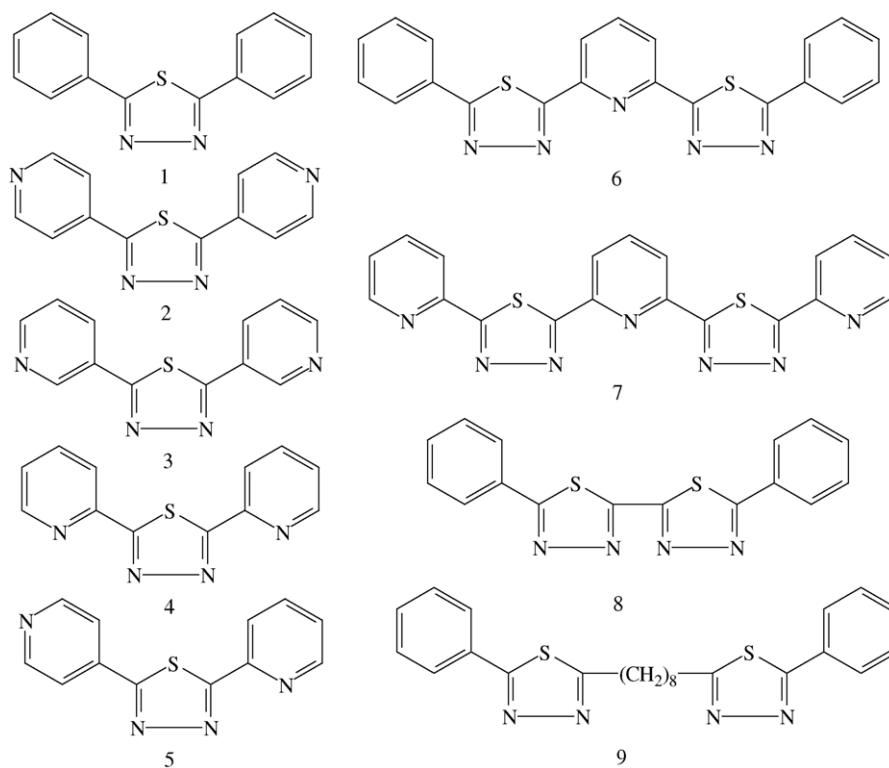
1. Introduction

The compound cis-diamminodichloroplatinum(II) (cis-platin) has been widely used in cancer therapy for over 30 years [1]. However, it shows a number of undesired side effects, therefore, other complexes of platinum(II) chloride with N donor ligands (L) have been considered for the cancer therapy research. From the biological activity point of view the presence of the dimethyl sulfoxide molecule (DMSO) may be desired [2–4]. The complexes of platinum(II) with L and DMSO are usually easily formed in the reaction of $\text{Pt}(\text{DMSO})_2\text{Cl}_2$ with L [4–8] or rarely, in the reaction (solvolysis) of PtL_2Cl_2 with DMSO [3,9]. There are also examples when substitution of DMSO (for $\text{Pt}(\text{DMSO})_2\text{X}_2$ complexes) by L yields biologically active PtL_2X_2 complexes [10,11]. It is well known

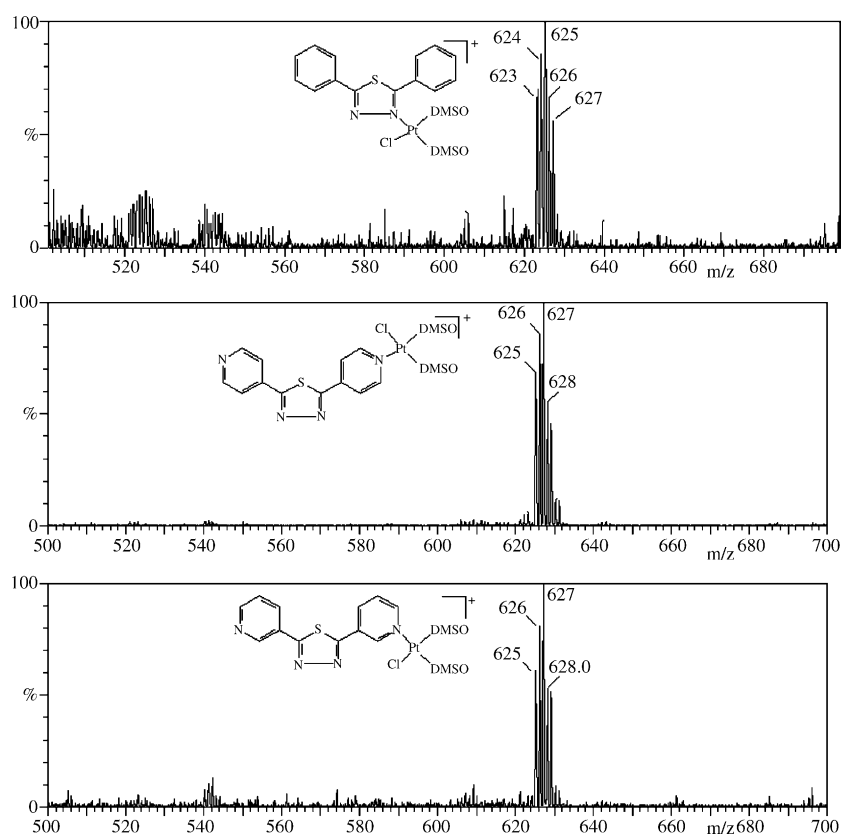
that DMSO is attached to the platinum by a sulfur atom [2,5–10].

Recently, a number of complexes of 2,5-disubstituted-1,3,4-oxa(thia)diazoles with platinum(II) has been reported [12–17]. In most cases 1,3,4-oxa(thia)diazoles were mercapto substituted and the sulfur atom from this group (not from the thiadiazole ring) was attached to the platinum cation. For 2-amino-5-methyl-1,3,4-thiadiazoles, the nitrogen atoms of thiadiazole ring were attached to this platinum [16]. None of the reported 1,3,4-oxa(thia)diazole-platinum(II) complexes contained DMSO molecule(s). Mass spectrometry with the use of the so-called soft ionization methods (especially electrospray ionization, ESI) was found to be very useful to study DMSO containing metal complexes [18–23]. In this work we report the ESI mass spectrometric study of platinum(II) chloride complexes with 2,5-disubstituted-1,3,4-thiadiazoles as N donor ligands L (Scheme 1) and DMSO. It is worth noting that some compounds containing 1,3,4-oxa- or 1,3,4-thiadiazole ring have shown anti-cancer properties [24–28].

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Scheme 1. 2,5-Disubstituted-1,3,4-thiadiazoles used as N-donor ligands for platinum(II) complexes.

Fig. 1. ESI mass spectra obtained for methanol solutions containing PtCl_2 , DMSO and one of the ligands 1–3.

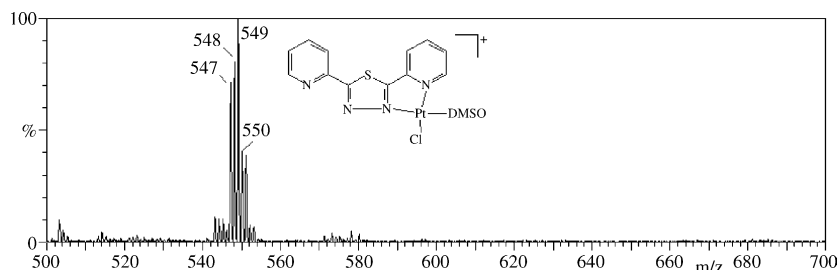


Fig. 2. ESI mass spectrum obtained for methanol solutions containing PtCl_2 , DMSO and **4**.

2. Experimental

Compounds **1–9** were prepared by using Lawesson's reagent according to the procedure described elsewhere [29]. The ESI mass spectra were obtained on a Waters/Micromass (Manchester, UK) ZQ mass spectrometer. Because PtCl_2 is barely soluble in methanol (most common solvent for ESI), it was first dissolved in DMSO at a concentration 10^{-2} M, and $10\ \mu\text{l}$ of this solution was added to 1 ml of methanol (or other solvent as stated further in the text) solution containing one of the ligands **1–9** at a concentration 10^{-4} M. The solution obtained was mixed by ultrasonic bath and then directly infused into the ESI source using a Harvard pump, the flow rate was $80\ \mu\text{l}/\text{min}$. The ESI source potentials were capillary 3 kV, lens 0.5 kV, extractor 4 V and cone voltage 30 V unless indicated otherwise. The source temperature was $120\ ^\circ\text{C}$ and the desolvation temperature was $300\ ^\circ\text{C}$ unless indicated otherwise. Nitrogen was used as the

nebulizing and desolvating gas at flow rates of 100 and $300\ \text{l h}^{-1}$, respectively.

3. Results and discussion

For each of the ligands **1–3** the ions of formulae $[\text{PtL}(\text{DMSO})_2\text{Cl}]^+$ were observed as shown in Fig. 1. The isotopic patterns characteristic for platinum- and chlorine-containing ions are clearly seen. The lowest signal to noise ratio observed for **1** suggest low stability of $[\text{Pt}(\text{DMSO})_2\text{Cl}]^+$ ion.

Ligand **1** is attached to the platinum cation by one of the nitrogen atom of thiadiazole ring, not by sulfur [16], but for **2** and **3** the coordination by pyridine nitrogen atom seems more likely. Simultaneous coordination by both pyridine nitrogen and the nitrogen of thiadiazole ring cannot be expected for **2** and **3**. ESI mass spectra shown in Fig. 1 were obtained at the cone voltage 30 V (standard value). This parameter is responsible for the so-

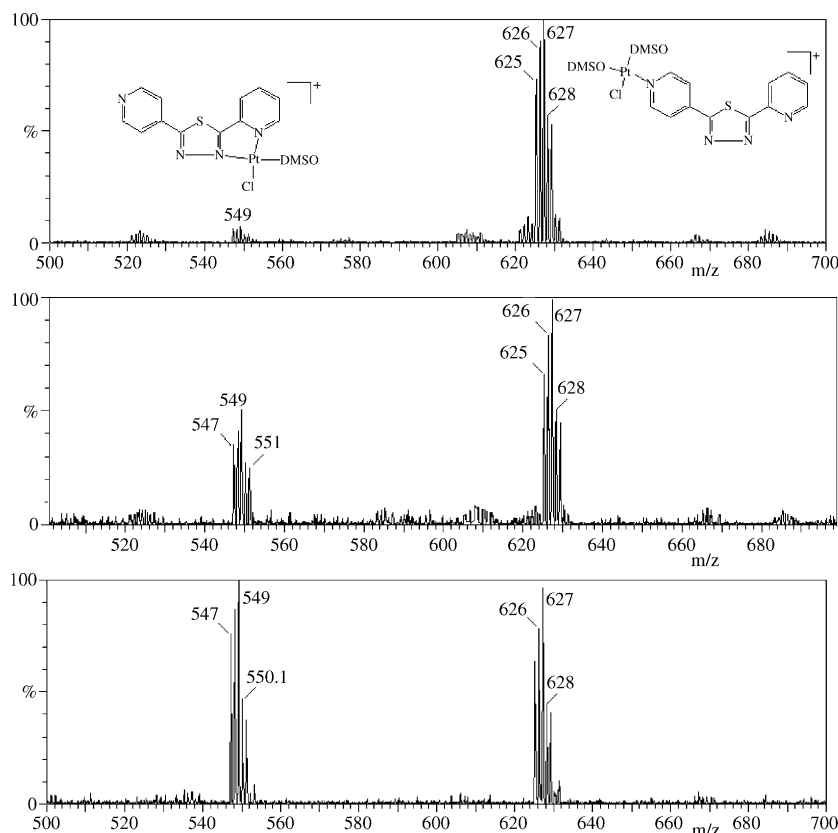


Fig. 3. ESI mass spectra obtained for a solution containing PtCl_2 , DMSO and **5**, for different solvents: methanol (top), methanol/chloroform 1/3 (middle), chloroform (bottom).

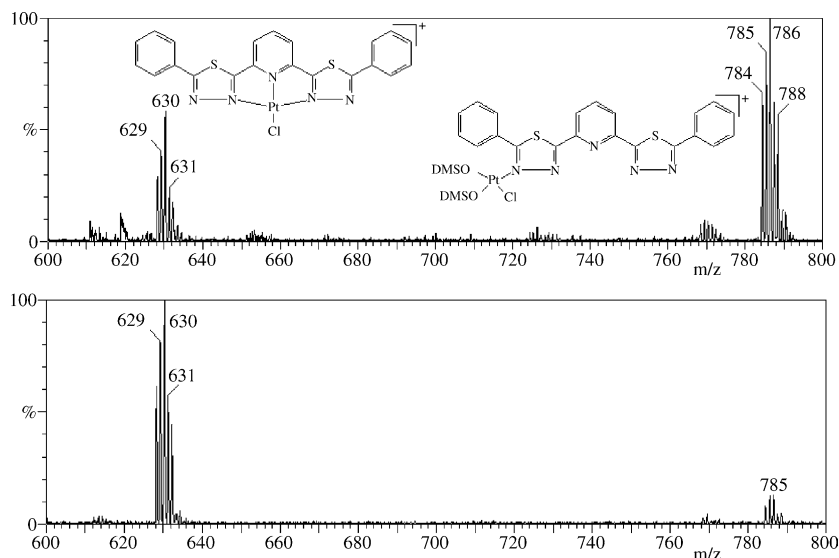


Fig. 4. ESI mass spectra obtained for methanol (top) and chloroform (bottom) solution containing PtCl_2 , DMSO and **6**.

called collision induced dissociation “in-source” and gives some insight into the stability of the ions detected. At the cone voltage 50 V, the ion $[\text{Pt1}(\text{DMSO})_2\text{Cl}]^+$ was not detected, however, the abundances of $[\text{Pt2}(\text{DMSO})_2\text{Cl}]^+$ and $[\text{Pt3}(\text{DMSO})_2\text{Cl}]^+$ ions were not affected until 60 V and they were detected even at 100 V. Thus, the nitrogen atoms of the thiadiazole ring are less prone to form platinum(II) complexes than the pyridine nitrogen atoms.

ESI mass spectrum recorded for **4** shows a signal assigned to an ion containing one DMSO molecule namely to $[\text{Pt4}(\text{DMSO})\text{Cl}]^+$ ion, while no signal of an ion containing two DMSO molecules is detected (Fig. 2). It is expected that ligand **4** is attached to the platinum cation by both pyridine nitrogen and the nitrogen atom of the thiadiazole ring, therefore, the ion $[\text{Pt4}(\text{DMSO})_2\text{Cl}]^+$ was not formed since its formation would require five coordinated platinum(II) cations.

The mass spectra recorded at higher cone voltages show that the stability of $[\text{Pt4}(\text{DMSO})\text{Cl}]^+$ ion is comparable to that of

the ions $[\text{Pt2}(\text{DMSO})_2\text{Cl}]^+$ and $[\text{Pt3}(\text{DMSO})_2\text{Cl}]^+$. For ligand **5** formation of both $[\text{Pt5}(\text{DMSO})\text{Cl}]^+$ and $[\text{Pt5}(\text{DMSO})_2\text{Cl}]^+$ is expected. ESI mass spectrum recorded for methanol solution has shown these ions, the latter being much more abundant than the former (Fig. 3, top). Excellent correlation between the types of the ions observed and the arrangement of pyridine nitrogen atom for ligands **2–5** confirms that we really deal with structurally defined complexes, not with electrostatic adducts which are very common in ESI.

As results from Fig. 3 (top), in methanol, a simultaneous platinum coordination by the pyridine and thiadiazole nitrogen atoms is less favored than the coordination by only pyridine nitrogen. A number of solvents were tested for their influence on $[\text{Pt5}(\text{DMSO})\text{Cl}]^+$ and $[\text{Pt5}(\text{DMSO})_2\text{Cl}]^+$ ions. Acetone, water, ethanol did not affect the relative abundances of these ions. The use of acetonitrile resulted in the formation of complexes containing solvent [30], and the complexes with

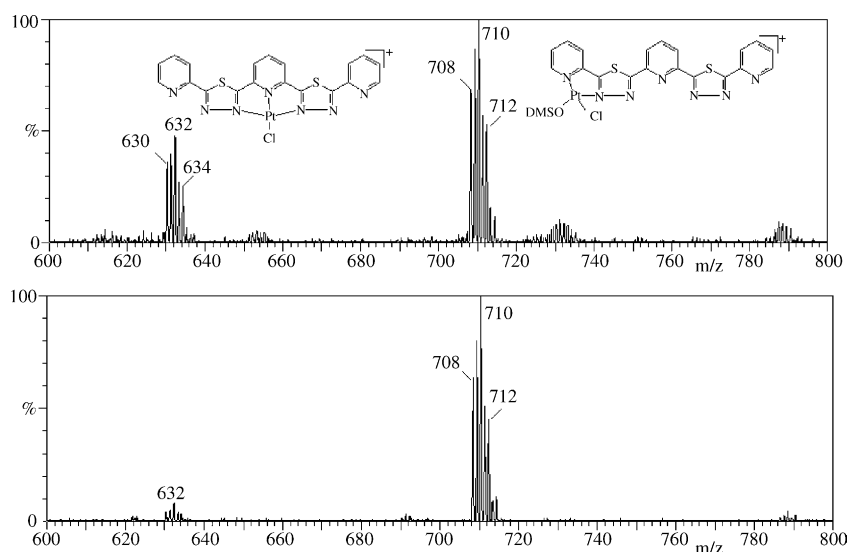


Fig. 5. ESI mass spectra obtained for methanol (top) and chloroform (bottom) solution containing PtCl_2 , DMSO and **7**.

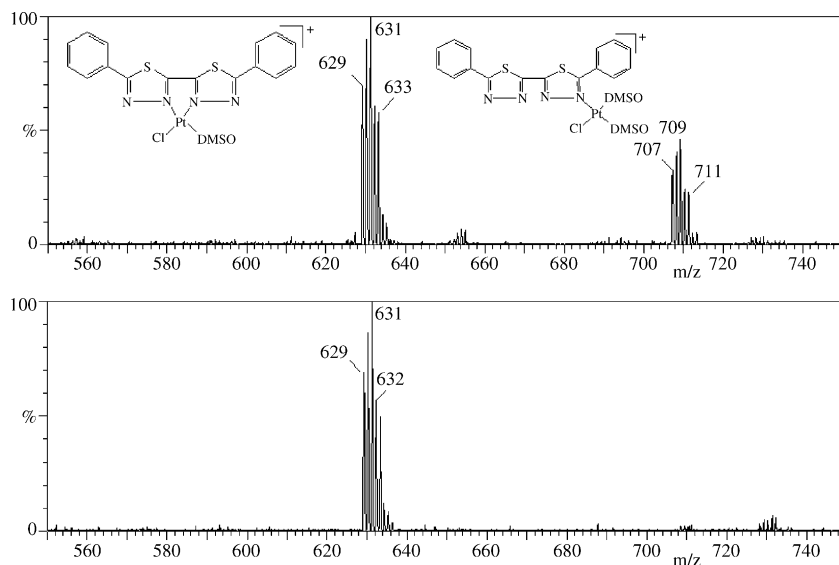


Fig. 6. ESI mass spectra obtained for methanol (top) and chloroform (bottom) solution containing PtCl₂, DMSO and **8**.

5 were not observed. The use of non-polar solvent without oxygen (chloroform or dichloromethane) caused a significant increase in the abundance of [Pt**5**(DMSO)Cl]⁺ as shown in Fig. 3 for chloroform/methanol 1/3 and chloroform solutions. The observed influence of the solvent used indicates that the complexes detected in the ESI mass spectra are formed in solution, not in the gas phase. The influence of solvent is rather not related with its physical properties, e.g., with its vapor pressure, since chloroform is less volatile than acetone but more volatile than methanol. The solvent effect is difficult to rationalize, however, it seems to be related, as mentioned above, to the absence or presence of an oxygen (or nitrogen) atom. This is strongly related to the effectiveness of the interaction between the solvent and the compounds solved.

Ligand **6** did not yield complexes containing one DMSO molecule but it yielded a complex containing two DMSO molecules (having platinum coordinated by nitrogen atom of

thiadiazole ring) as well as non-DMSO containing one (having platinum coordinated by two nitrogen atoms of thiadiazole rings and by one pyridine nitrogen atom). As shown in Fig. 4, the ions [Pt**6**Cl]⁺ and [Pt**6**(DMSO)₂Cl]⁺ were obtained, the latter was twice more abundant than the former in methanol solution, and the use of chloroform resulted in a significant increase in the former in comparison to the latter.

Ligand **7** is structurally similar to **6**, however, instead of phenyl moieties it has 2-pyridyl moieties. This difference yielded the complex containing one DMSO molecule (having platinum coordinated by one nitrogen atom of the thiadiazole ring and one pyridine nitrogen atom), which was not observed for **6**, and prevented the formation of a complex containing two DMSO molecules, which was observed for **6**. The different results obtained for ligands **6** and **7** are further evidence that the observed ions correspond to the structurally defined complexes. As shown in Fig. 5, the abundance of [Pt**7**(DMSO)Cl]⁺ is twice

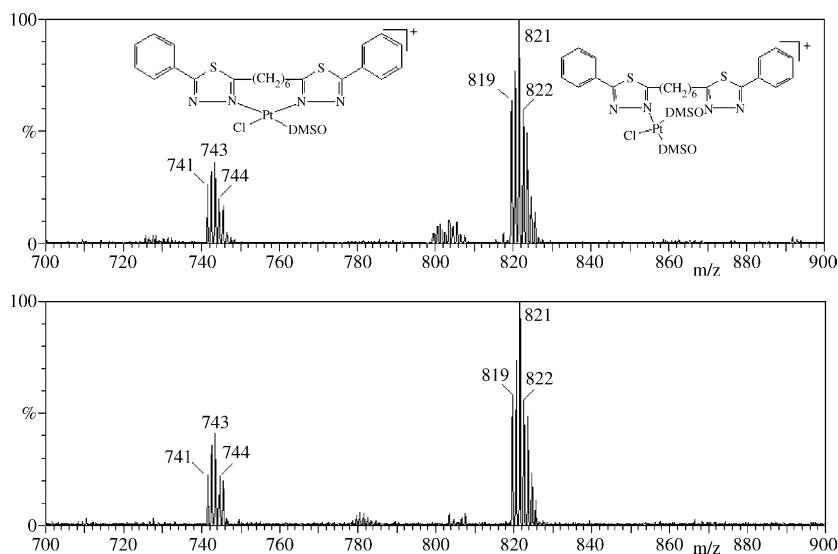


Fig. 7. ESI mass spectra obtained for methanol (top) and chloroform (bottom) solution containing PtCl₂, DMSO and **9**.

higher than that of $[\text{Pt}7\text{Cl}]^+$ in a methanol solution, while the use of chloroform results in a significant increase in the abundance of the former in comparison to that of the latter.

Ligands **8** and **9** do not have pyridyl moieties but due to the presence of two thiadiazole rings they are able to form complexes containing one and two DMSO molecules. The formation of $[\text{Pt}8(\text{DMSO})\text{Cl}]^+$ ion is slightly favored to that of $[\text{Pt}8(\text{DMSO})_2\text{Cl}]^+$ ion in a methanol solution and in a chloroform solution the latter ion is not detected, as shown in Fig. 6.

In contrast to the other ligands being able to form two types of complexes (**5–8**), the solvent used did not affect the relative abundances of $[\text{Pt}9(\text{DMSO})\text{Cl}]^+$ and $[\text{Pt}9(\text{DMSO})_2\text{Cl}]^+$ ion (Fig. 7).

There are two theoretically possible explanations. The first is that the ESI mass spectrum of ligand **9** complex better represents the gas phase than the solution, namely in solution we have only the complex having two DMSO molecules and during the ionization process one DMSO molecule is eliminated and the second thiadiazole ring is attached to platinum, while the second is that the complexation of platinum by **9** is much less dependent on the solvent used than for other ligands studied. If the first one is the case, the changes in the ESI source parameters like cone voltage, desolvation temperature or desolvation gas flow rate should have much more influence on the relative abundances of $[\text{Pt}9(\text{DMSO})\text{Cl}]^+$ and $[\text{Pt}9(\text{DMSO})_2\text{Cl}]^+$ ion than on those of $[\text{Pt}8(\text{DMSO})\text{Cl}]^+$ and $[\text{Pt}8(\text{DMSO})_2\text{Cl}]^+$ ion. However, it was not observed. For example, for desolvation temperature 300 °C the $[\text{Pt}8(\text{DMSO})\text{Cl}]^+ / [\text{Pt}8(\text{DMSO})_2\text{Cl}]^+$ and $[\text{Pt}9(\text{DMSO})\text{Cl}]^+ / [\text{Pt}9(\text{DMSO})_2\text{Cl}]^+$ ion ratios were about 2 and 0.4, respectively (Figs. 6 and 7) and for the desolvation temperature 250 °C they were about 1.5 and 0.3, respectively. Therefore, the second explanation seems to be reasonable. Ligand **9** is much more flexible than others and thus it is able to assume a proper arrangement needed for platinum cation complexation, irrespective of solvent used.

4. Conclusion

Each of compounds **1–9** tends to form complexes with platinum(II) chloride and dimethyl sulfoxide. Nitrogen atoms of the thiadiazole ring are able to bind platinum, however, they are less prone to do this than the pyridine nitrogen atom. The excellent agreement between the arrangement of nitrogen atoms (from pyridine and thiadiazole ring) in the ligands used and the types of the complexes observed confirmed that we really deal with structurally defined complexes. For the compounds able to form two types of complexes, their relative amounts can be substantially affected by the solvent used, indicating that the recorded ESI mass spectra reflect the condensed phase. The use of chloroform as a solvent results in a higher tendency to form complexes containing one DMSO molecule than those containing two or none DMSO molecules. The situation is the reverse in methanol solutions (Figs. 3 and 5). Compound **6** yielded a complex containing two DMSO molecules as well as a non-DMSO containing one. For methanol solutions the formation of the former is favored and the use of chloroform favors the

formation of the latter (Fig. 4). The compounds containing two thiadiazole rings (as the only coordinated moieties, **8** and **9**) also yielded two types of complexes (containing one or two DMSO molecules), however, their relative amounts can be affected by the solvent used only if the thiadiazole rings are close to each other (Figs. 6 and 7).

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