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Short communication

Electrospray ionization mass spectrometric study of platinum(II) complexes with nucleobases and dimethyl sulfoxide

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Abstract

The electrospray ionization spectra of methanol solution containing adenine or guanine or cytosine (M) and $PtCl_2$ and DMSO at a low cone voltage value, have shown the singly charged ions, namely $[M + PtCl + 2DMSO]^+$. Analogous ions have been observed for adenosine, guanosine and cytidine. The data obtained from the mass spectra taken at a higher cone voltage and with the use of isotope labelled DMSO permit to discuss the fragmentation pathways of $[M + PtCl + 2DMSO]^+$. On the grounds of the experimental results and respective literature data, the structures of $[M + PtCl + 2DMSO]^+$ ions are proposed. In a methanol solution containing uracil or thymine (or their nucleosides), the ions containing deprotonated nucleobase (or nucleoside), namely $[M - H + PtCl + 2DMSO + Na]^+$ and $[M - H + PtCl + 2DMSO + K]^+$, have been detected. The higher acidity of uracil and thymine in relation to the other nucleobases may explain the existence of complexes containing deprotonated molecules. However, it has been difficult to propose their structures on the basis of the results obtained.

Keywords: Nucleobases; Nucleosides; Platinum(II) complexes; Dimethyl sulfoxide; Electrospray ionization mass spectrometry

1. Introduction

A number of platinum coordination compounds with N donor ligands (L) are widely used in cancer therapy. Electrospray ionization mass spectrometry has been successfully applied to characterize platinum based drugs, their metabolites as well as to study their interactions with nucleobases (nucleotides) [1–4].

Complexes of platinum(II) with N donor ligands (L) and dimethyl sulfoxide (DMSO) have been extensively studied [5]. These complexes are usually easily formed in the reaction of $Pt(DMSO)_2Cl_2$ with L or in the reaction (solvolysis) of PtL_2Cl_2 with DMSO. Nucleobases (Scheme 1), for obvious reasons, are the most important N donor ligands which are expected to form complexes with platinum(II) and DMSO.

This paper is devoted to electrospray ionization mass spectrometry (ESI/MS) study of such complexes. It is worth to add that the ruthenium(II)–DMSO complexes have shown anticancer properties and their interactions with nucleobases (nucleosides, nucleotides) have been successfully studied by ESI/MS [6,7].

2. Experimental

The ESI mass spectra were obtained on a Waters/Micromass (Manchester, UK) ZQ2000 mass spectrometer (single quadrupole type instrument, Z-spray, software MassLynx V3.5). The mass spectra were recorded in the mass range 100–1000. They are shown for the range of interest (Figs. 1, 2 and 4), however, at lower mass range the presence of abundant ions of protonated, sodiated and potassiated molecules of nucleobases, nucleosides and DMSO was observed. Because $PtCl_2$ is barely soluble in methanol (most common solvent for ESI), it was first dissolved in DMSO at the concentration of 10^{-2} M and 10 μl of this solution was added to 1 ml of methanol solution containing one of the nucleobases (or nucleosides) at the concentration of 10^{-4} M. The solution obtained was mixed in an ultrasonic bath and then directly infused into the ESI source using a Harvard pump, the flow-rate was 80 μl/min. The ESI source potentials were capillary 3 kV, lens 0.5 kV, extractor 4 V and cone voltage (CV) 10–80 V. The source temperature was 120 °C and the desolvation temperature was 300 °C. Nitrogen was used as

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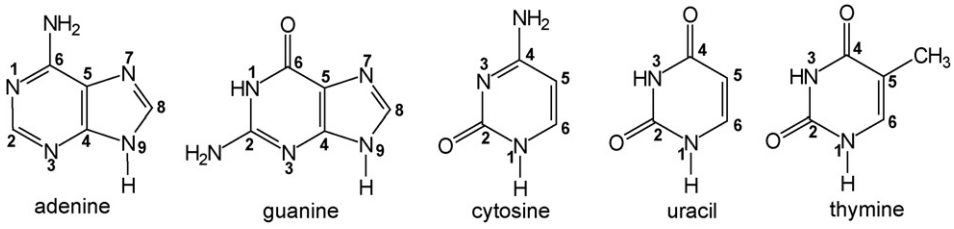


Scheme 1. Structures of nucleobases.

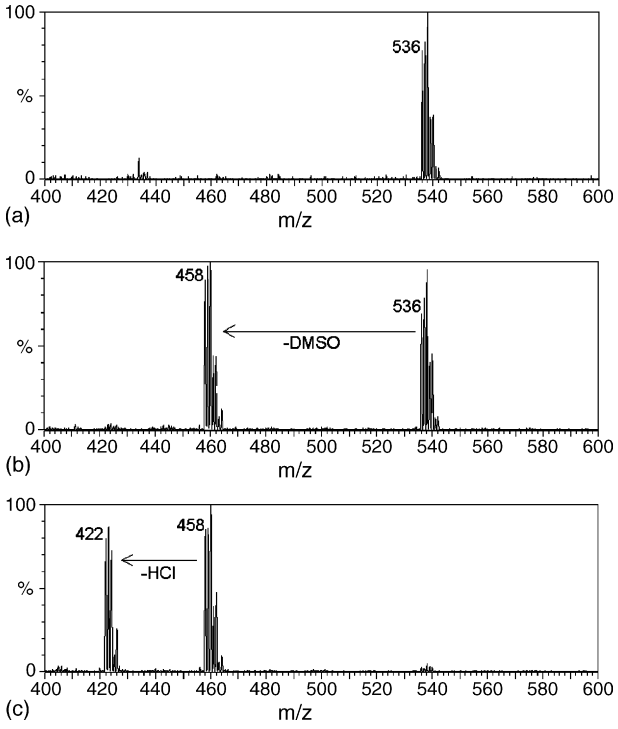


Fig. 1. ESI mass spectra obtained for methanol solutions containing $PtCl_2$, DMSO and guanine at different cone voltage (CV): (a) CV = 10 V, (b) CV = 30 V, (c) CV = 50 V. Signal at *m/z* 536 corresponds to the $[guanine + PtCl + 2DMSO]^+$ ion.

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

3. Results and discussion

It is well known that relative ion abundances can be affected by a number of parameters. Among these, the cone voltage has the most profound effect on ESI mass spectra. By increasing CV, the so-called dissociation "in-source" can be induced. On the other hand, too low CV may lead to the sensitivity loss because fewer ions reach the high vacuum region. However, for methanol solution containing the nucleobase (M), $PtCl_2$ and DMSO at a low CV value, namely 10 V, the singly charged ions $[M + PtCl + 2DMSO]^+$ were detected as shown in Fig. 1a for guanine-containing solution (characteristic isotopic pattern was observed for these ions). The ions of this type were also formed in the case of adenine and cytosine. The ions $[2M + PtCl + DMSO]^+$ may also be detected [3], however, only for a short time from the preparation of the solution studied. An increase in CV resulted in the DMSO molecule loss, producing $[M + PtCl + DMSO]^+$ ions (Fig. 1b). Further CV increase led to the HCl molecule loss, yielding $[M + Pt + DMSO - H]^+$ ions (Fig. 1c).

On the grounds of the mass spectrum obtained for the deuterated DMSO, namely $DMSO(D_6)$, it was found that the eliminated HCl molecule contained the hydrogen atom originated from DMSO, and not that from the nucleobase (Fig. 2).

It should be expected that the eliminated HCl molecule would contain the hydrogen atom from the nucleobase because hydro-

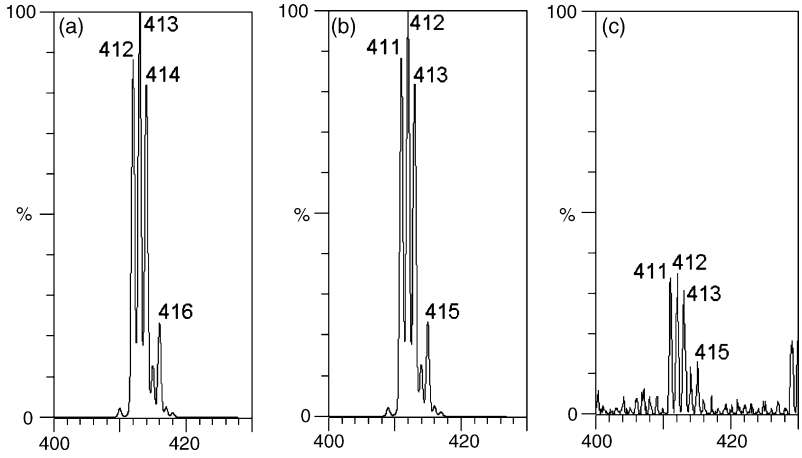


Fig. 2. Theoretically calculated isotopic pattern obtained by loss of HCl from $[adenine + PtCl + DMSO(D_6)]^+$ ion (a), theoretically calculated isotopic pattern obtained by loss of DCl from $[adenine + PtCl + DMSO(D_6)]^+$ ion (b), isotopic pattern obtained experimentally (c).

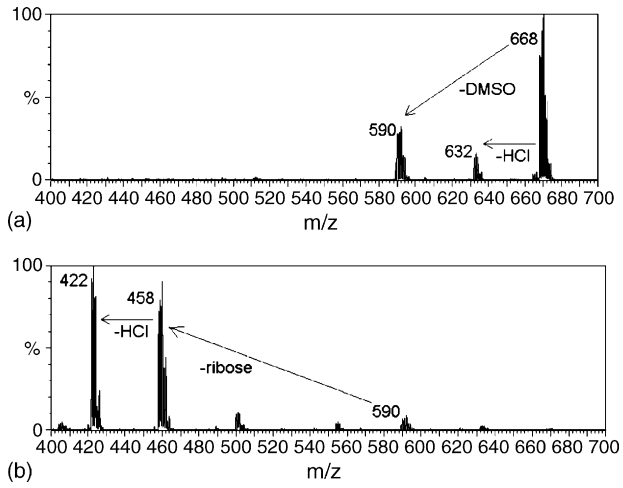


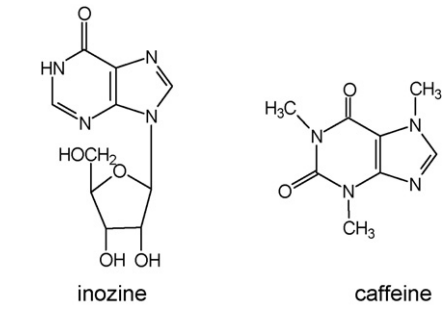
Fig. 3. ESI mass spectra obtained for methanol solutions containing $PtCl_2$, DMSO and guanosine at (a) CV = 30 V and (b) CV = 70 V. Signal at *m/z* 668 corresponds to the [guanosine + PtCl + 2DMSO]$^+$ ion.

gen atoms of the latter are more acidic atoms than those of DMSO [8,9]. This result indicates that the nucleobase is situated in *trans* position to Cl. For the ions [M + PtCl + 2NH_3]$^+$ containing the nucleobase situated in *cis* position to Cl, the hydrogen atom in the eliminated HCl molecule originated from the nucleobase [3]. It also worth to add that the role of platinum may consist on C–H bond activation leading to organometallic species [10].

For a solution containing nucleoside (guanosine, adenosine or cytidine) the [M + PtCl + 2DMSO]$^+$ ions were also observed at a low CV value (Fig. 3), obviously respective peaks were at mass 132 units higher than those for the nucleobases. An increase in CV resulted in the elimination of the HCl molecule as well as in the elimination of the DMSO molecule followed by a sugar moiety loss (loss of mass 132) and further followed by the HCl molecule loss (Fig. 3).

The molecule of HCl eliminated directly from [M + PtCl + 2DMSO]$^+$ ions contained a hydrogen atom from the nucleoside (strictly speaking from the sugar moiety) and not from the DMSO molecule, while the HCl molecule eliminated after the sugar moiety loss contained a hydrogen atom originating from DMSO, as determined from the mass spectrum obtained for the deuterated DMSO.

Platinum at +2 oxidation state has a coordination number of 4, so the existence of [M + PtCl + 2DMSO]$^+$ ions is reasonable.



Scheme 2.

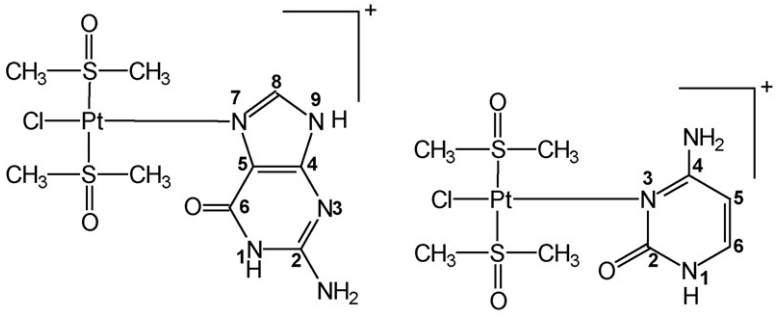
It is also known that Pt(II) binds to N-7 atom of adenine or guanine and N-3 atom of cytosine as well as it can also bind to N-1 atom of adenine [3,6]. In order to confirm that –NH_2 groups or oxygen atoms are not involved in the formation of the observed cationic complexes, the ESI mass spectra were recorded for a solution containing DMSO, $PtCl_2$ and inozine or caffeine (Scheme 2).

Results obtained for inozine, which has no NH_2 group, were analogous to those described above for guanosine, adenosine or cytidine. Caffeine has three nitrogen atoms substituted by a methyl group, thus they are not able to coordinate to the platinum cation, and this is why no complexes have been observed. The unsubstituted nitrogen atom was not able to form a complex.

On the grounds of the above described experimental results and the literature data, the structures of cationic complexes observed for cytosine and guanine are shown in Scheme 3. However, it is not yet clear whether the platinum atom in the adenine complex is attached to the N-7 or N-1 atom.

Fig. 4 shows the dependence of the [M + PtCl + DMSO]$^+$/[M + PtCl + 2DMSO]$^+$ ratio on the cone voltage. As results from Fig. 4, the presence of the sugar moiety does not affect the DMSO molecule loss in adenine and cytosine complexes. In guanine complexes the presence of sugar makes the DMSO molecule loss more difficult. These findings suggest that adenine complex is more similar rather to cytosine complex than to guanine one. Thus it is proposed that the platinum atom in adenine complex is attached to the N-1 atom (Scheme 4). However, the attachment to N-7 atom cannot be definitely ruled out.

For solutions containing uracil, thymine, uridine or thymidine the results obtained were different from those described above for guanine, adenine, cytosine and their nucleosides. At a low CV



Scheme 3. Plausible structures of cationic complexes containing guanine and cytosine.

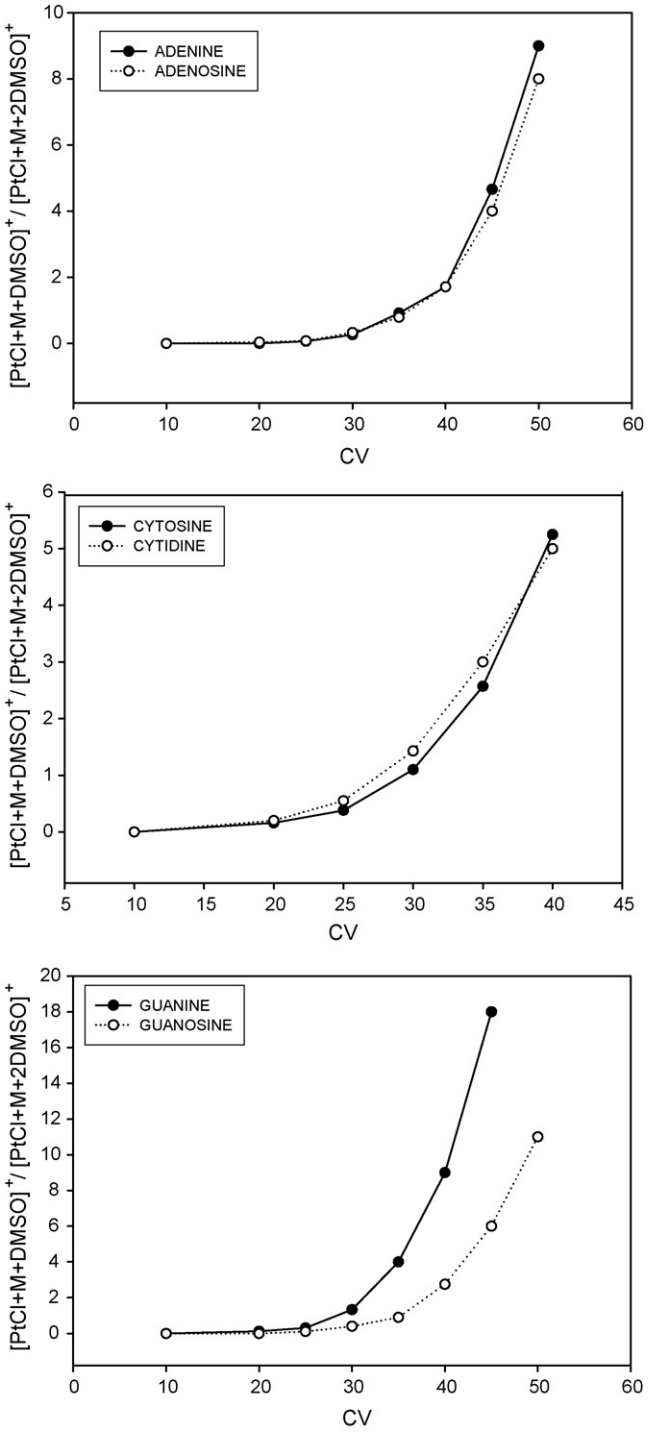
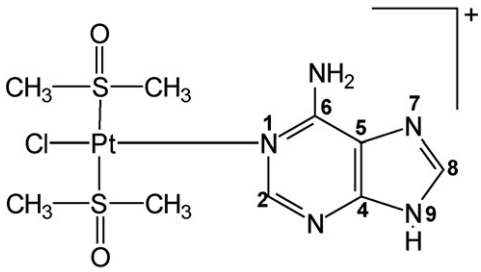


Fig. 4. Relationships between $[M + PtCl + DMSO]^+/[M + PtCl + 2DMSO]^+$ ratio and cone voltage (CV).

value, the ions containing a deprotonated molecule of the nucleobase (or nucleoside), namely $[M - H + PtCl + 2DMSO + Na]^+$ and $[M - H + PtCl + 2DMSO + K]^+$ ions, were observed as shown in Fig. 5 (Na^+ and K^+ were not added, but they were present as impurities and it is rather surprising that the potassium containing ion is more abundant than the sodium containing one, since the K^+ concentration should be much lower than that of Na^+).



Scheme 4. Plausible structure of cationic complex containing adenine.

The observed ions were characterized by low abundances and there was always a high background level. In order to confirm the composition of these ions, the ESI mass spectra were taken for solutions containing either an excess of Na^+ (by adding NaCl) or an excess of K^+ (by adding KCl). For the former, only the $[M - H + PtCl + 2DMSO + Na]^+$ ion was observed, while for the latter only the $[M - H + PtCl + 2DMSO + K]^+$. At a higher cone voltage, the fragment ions corresponding to the loss of DMSO, HCl and the sugar moiety (loss of mass 132 for uridine and loss of mass 116 for thymidine) were detected, however, because of their low signal to noise ratio, the fragmentation pathways of $[M - H + PtCl + 2DMSO + Na]^+$ and $[M - H + PtCl + 2DMSO + K]^+$ ions cannot be proposed as yet.

The existence of $[M - H + PtCl + 2DMSO + Na]^+$ and $[M - H + PtCl + 2DMSO + K]^+$ ions indicates that neutral complexes consisting of platinum cation, chloride anion, deprotonated nucleobase (nucleoside) and two DMSO molecules are present in the solution. As a result of the attachment of Na^+ or K^+ cations, the complexes are charged and can be detected by ESI/MS.

Thymine and uracil have lower proton affinity than the other nucleobases, and the same concerns the nucleosides [11,12]. On the other hand, thymine and uracil are stronger acids compared

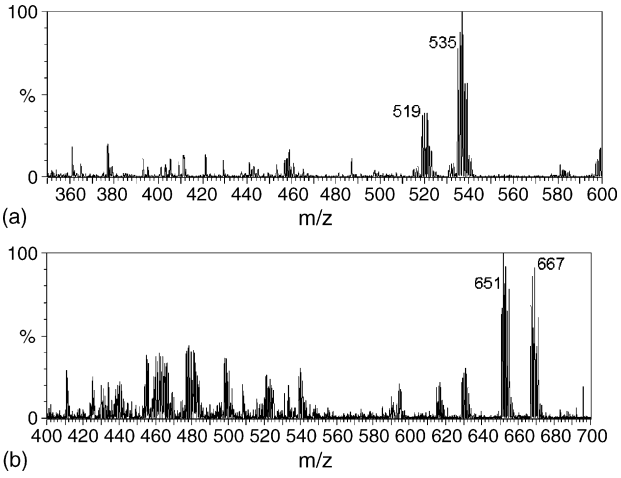


Fig. 5. ESI mass spectra obtained at CV = 10 V for methanol solutions containing $PtCl_2$, DMSO and (a) uracil, (b) uridine. Signal at *m/z* 519 corresponds to the $[uracil - H + PtCl + 2DMSO + Na]^+$ ion, at *m/z* 535 to the $[uracil - H + PtCl + 2DMSO + K]^+$ ion, at *m/z* 651 $[uridine - H + PtCl + 2DMSO + Na]^+$ ion and at *m/z* 667 to the $[uridine - H + PtCl + 2DMSO + K]^+$ ion.

to the other nucleobases [9]. The relative acidity of various kinds of organic compounds can be successfully checked by taking the ESI mass spectra in the negative ion mode. The lower the acidity, the lower the $[M-H]^-/[M+Cl]^-$ ratio [13,14]. The observed ratio confirmed the higher acidity of uracil and thymine in comparison to that of other nucleobases involved in this study, and the same referred to the nucleosides. This finding may explain why in the case of uracil and thymine the complexes formed contain deprotonated molecules. However, it is difficult to propose the structures of these complexes. For deprotonated molecules of uracil and thymine at least three resonance structures can be drawn, thus there are three potential sites of platinum cation attachment, namely two oxygen atoms and N-3 atom (N-1 atom is substituted in the nucleosides).

4. Conclusions

Adenine, guanine and cytosine (as well as their nucleosides) tend to form cationic complexes with platinum(II) and DMSO, namely $[M+PtCl+2DMSO]^+$ ions, observed on ESI mass spectra at low cone voltage values. At higher cone voltage values, the decomposition involving the loss of DMSO, HCl and sugar moiety (for nucleosides) is observed. It is reasonable to suppose that the nucleobase is situated in *trans* position to the chlorine and that platinum is attached to N-7 atom of guanine, N-3 atom of cytosine and to N-1 atom of adenine.

Uracil or thymine (or their nucleosides) form neutral complexes containing a deprotonated nucleobase (or nucleosides). Due to the Na^+ or K^+ attachment their presence can be observed in ESI mass spectra as $[M-H+PtCl+2DMSO+Na]^+$ and $[M-H+PtCl+2DMSO+K]^+$ ions, which are, however, characterized by low abundances. The higher acidity of uracil and thymine relative to that of the other nucleosides may explain the existence of complexes containing deprotonated molecules. On the grounds of the results obtained, it is difficult to propose structures of these complexes.

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