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**ARTICLE** *in* BIOPOLYMERS · JANUARY 2002

Impact Factor: 2.39 · DOI: 10.1002/bip.10091 · Source: PubMed



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# Density Functional Theory and Surface Enhanced Raman Spectroscopy Characterization of Novel Platinum Drugs

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*Received 8 September 2001; revised 26 Ocober 2001; accepted 11 November 2001*
*Published online 25 April 2002 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/bip.10091*

**ABSTRACT:** There is considerable interest in the development of novel platinum-based anticancer drugs that overcome the disadvantages associated with the widely used drug cisplatin, which are its inactivity against some types of tumors and its toxic side effects. In this study we show the suitability of normal Raman spectroscopy (NRS) and surface enhanced Raman spectroscopy (SERS), assisted by density functional theoretical (DFT) calculations, for the characterization of Pt complexes. The Pt complexes studied include the established drugs cisplatin and carboplatin, as well as five novel Pt complexes with anticancer activity. DFT calculations at the B3LYP/LanL2DZ level are a good prediction of the experimental NRS spectra of small and medium sized Pt complexes. The use of SERS allows the investigation of Pt complexes at physiological concentrations, and the binding strengths of the different ligands can be determined. The formation of positively charged hydrolysis products may be necessary for SERS activity. The exiting group in the hydrolysis reaction can be identified. © 2002 Wiley Periodicals, Inc. Biopolymers (Biospectroscopy) 67: 294–297, 2002

**Keywords:** surface enhanced Raman spectroscopy; density functional theory; anticancer drugs; cisplatin

## INTRODUCTION

*cis*-Diamminedichloroplatinum(II) (cisplatin, **1**) is one of the most widely used anticancer drugs in the world with applications in the treatment of a range of tumors including ovarian and testicular cancer.[1] Nevertheless, the therapeutic efficacy of cisplatin is limited by several disadvantages: strong nephrotoxic and neuropathic side effects, the need for intravenous application, and inactivity against a number of tumors (inherent and acquired resistance).[2] There is therefore considerable interest in the development of novel platinum-based anticancer drugs with fewer side effects and activity against cisplatin-resistant tumors.[3]

The aspects of the mechanism of action of cisplatin are well understood.[4] In the cell cisplatin is activated by the hydrolysis of one chloride ligand, and the primary target of the activated complex *cis*-$[Pt(NH_3)_2Cl(OH_2)]^+$ is the N7 of guanine bases. The major product formed with nuclear DNA is a 1,2-intrastrand crosslink involving two adjacent guanines, *cis*-$[Pt(NH_3)_2\{GpG\}]$. This bifunctional cisplatin–DNA adduct distorts the DNA structure and affects a range of cell functions, such as DNA replication, DNA transcription, and the DNA repair mechanism, eventually leading to cell death.

The aim of this study is to investigate the applicability of surface enhanced Raman spectroscopy (SERS) and density functional theory (DFT)

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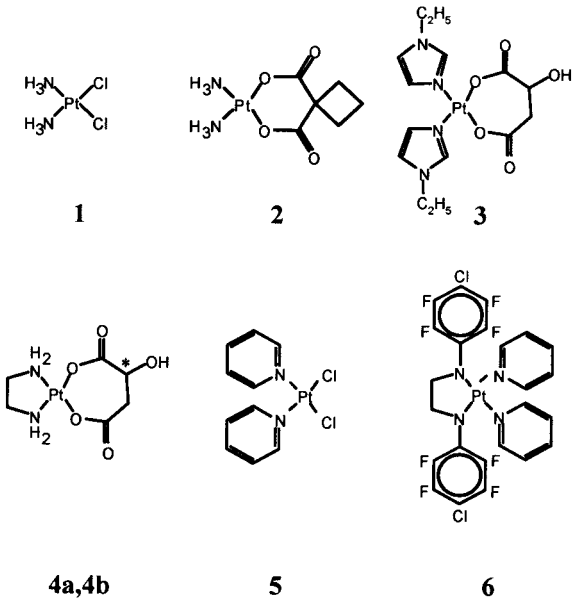


**Figure 1.** The Pt complexes investigated in this study.

calculations to characterize the structure of novel Pt complexes with potential antitumor activity (Fig. 1).

## MATERIALS AND METHODS

Cisplatin (**1**), carboplatin (**2**), and guanine were purchased from Sigma Chemical Co. Bis(1-ethylimidazole)L(-)malatoplatinum(II) (**3**), ethylenediamine-D(+)malatoplatinum(II) (**4a**), and ethylenediamine-L(-)malatoplatinum(II) (**4b**) were synthesized and purified as described earlier.[5] The syntheses of *cis*-[Pt(pyridine)$_2$Cl$_2$] (**5**) and [Pt(*p*-ClC$_6$F$_4$NCH$_2$)$_2$(pyridine)$_2$] (**6**) were described by Buxton.[6] All reagents were the highest grade commercially available and were used without further purification.

All solutions were freshly prepared in 18 MΩ high purity water containing $5 \times 10^{-2}$ *M* $NaClO_4$. The surface substrate used in the SERS measurements was a citrate reduced silver colloid (pH 7.8).[7] Normal Raman spectra (NRS) were obtained from polycrystalline powders. All Raman spectra were recorded on a Renishaw Raman microspectrometer system 2000 with 632.8-nm laser excitation and CCD detection.

DFT calculations were performed at the B3LYP/LanL2DZ level using the Gaussian 98 software package.

## RESULTS AND DISCUSSION

The theoretical MP$x$ ($x$ = 2–4)[8] and DFT[9] calculations for the structure and vibrational spectrum of complex **1** were performed using a range of basis sets, which were published previously. For a comparison we revisited those calculations at the B3LYP/LanL2DZ level of theory, because this basis set allows us to carry out calculations on a larger range of Pt complexes. The predicted and experimental NRS spectra of cisplatin are illustrated in Figure 2. Despite the use of the relatively small LanL2DZ basis set, the agreement between the theory and experiment is comparable to that found for higher level calculations.[8,9] The Pt—N stretching vibrations at 525 (symmetric) and 506 $cm^{-1}$ (asymmetric) are predicted at considerably lower wavenumber values because of an overestimation of the Pt—N bond length common for these kind of calculations.[9] A similar discrepancy was found for the N—Pt—N bending mode at 254 $cm^{-1}$. The Pt—Cl stretching mode is predicted more accurately. The predicted splitting of 10 $cm^{-1}$ between the symmetric and the asymmetric stretching modes was not resolved in the experimental spectrum of polycrystalline cisplatin. The vibrations arising from the $NH_3$ ligands can be divided into four groups: N—H stretching (>3000 $cm^{-1}$, not shown), degenerate deformation, symmetric bending, and rocking.

The theoretical and experimental NRS spectra of pyridine in its free form and as a ligand in complex **5** are presented in Figure 3. The agreement between theory and experiment is excellent. The NRS spectrum of pyridine changes substantially when coordinated to Pt, and all wavenumber shifts and intensity changes are predicted well by DFT calculations at the B3LYP/LanL2DZ level. The most noteworthy change upon Pt coor-

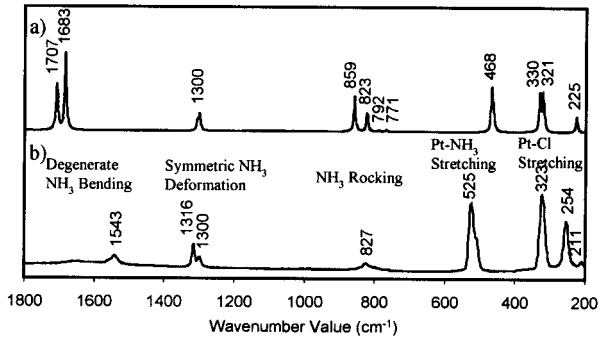


**Figure 2.** The theoretical (spectrum a) and experimental (spectrum b) NRS spectra of cisplatin (**1**).

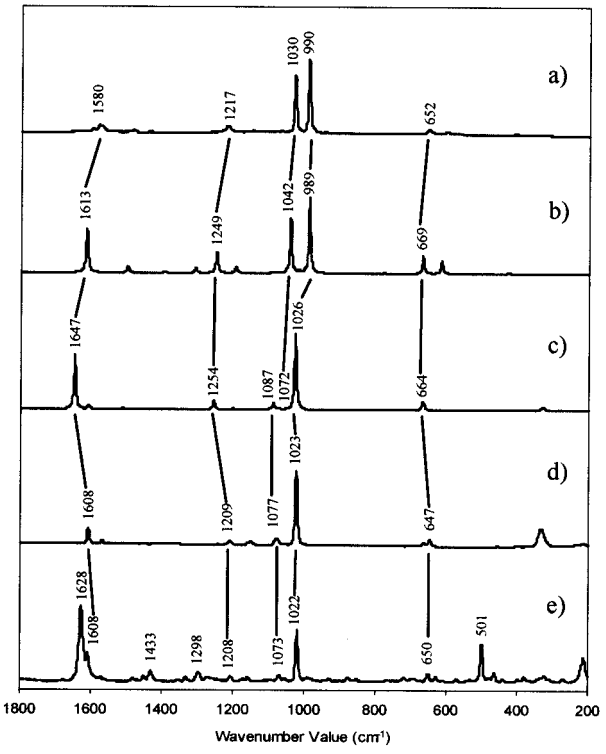


**Figure 3.** The theoretical (spectra b and c) and experimental (spectra a, d, and e) NRS spectra of pyridine in its free form (spectra a and b) and in the Pt complexes **5** (spectra c and d) and **6** (e)

dination is the almost complete disappearance of the strong NRS band at 1030 $cm^{-1}$ and the blueshift of the strong band at 990 $cm^{-1}$. This band appears at 1023 $cm^{-1}$ in the NRS spectrum of complex **5** and can be used as a marker band for coordinated pyridine compared to the characteristic doublet at 1030 and 990 $cm^{-1}$ in the NRS spectrum of free pyridine. The absolute predicted wavenumber values in the high wavenumber region deviate from the experimental SERS wavenumber values by up to 40 $cm^{-1}$. These discrepancies arise mainly from systematic errors, such as anharmonicity of the vibrations and the finite character of the basis set, and could be corrected for by a suitable scaling procedure. No scaling was performed in this work. However, because scaling factors for the same mode in the complex and in the free ligand should be almost identical, the predicted wavenumber shifts are expected to be significant. This is clearly demonstrated by the quantitatively correct prediction of the blueshift upon coordination of the pyridine NRS band at 1580 $cm^{-1}$.

The experimental NRS spectrum of polycrystalline **6** is also illustrated in Figure 3. A comparison with the NRS spectrum of **5** shows that the vibrational modes of coordinated pyridine are scarcely affected by the ligands in the trans position. Apart from the bands arising from pyridine, the NRS spectrum of **6** also exhibits contributions from the $(p\text{-}ClC_6F_4NCH_2)_2$ ligand, notably the strong bands at 1628 and 501 $cm^{-1}$.

The theoretical spectrum of complex **6** could not be predicted at the B3LYP/LanL2DZ level because of its large size. The NRS spectra of the Pt complexes containing the malato ligands (**3**, **4a**, **4b**) could be calculated, but the agreement with the observed NRS spectra was very poor (results not shown).

All Pt complexes included in this investigation were SERS active. SERS spectra (Fig. 4) with a good signal to noise ratio could be obtained at low concentrations ($<5 \times 10^{-7}$ *M*). It is most likely, though, that the observed SERS spectra do not arise from the original Pt complexes but rather from their hydrolysis products. The evidence for this hypothesis is threefold. First, freshly prepared complex solutions are not SERS active, but SERS spectra can only be recorded after incuba-

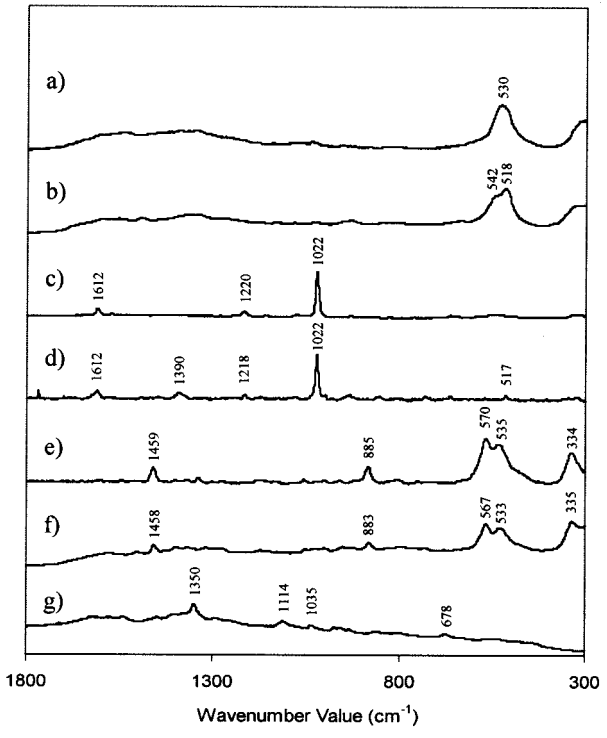


**Figure 4.** The SERS spectra of $10^{-6}$ *M* solutions of Pt complexes **1** (spectrum a), **2** (spectrum b), **5** (spectrum c), **6** (spectrum d), **4a** (spectrum e), **4b** (spectrum f), and **3** (spectrum g) in a silver colloid.

tion at 37°C for at least several hours. Second, the positive charge of the cationic hydrolysis products may be necessary to promote interaction with the negatively charged colloid surface ($\zeta$ potential = −40 mV). This kind of electrostatic interaction was previously postulated for $[Ru(bpy)_3]^{2+}$ adsorption on a Ag colloid.[10] Third, the SERS spectra of **5** and **6** are essentially identical. The latter contains no bands that can be clearly assigned to the complexed $(p\text{-}ClC_6F_4NCH_2)_2$ ligand, indicating that it may be replaced by $H_2O$ ligands prior to adsorption to the Ag colloid. There are weak peaks at 1390 and 517 $cm^{-1}$ in the SERS spectrum of **6** that are absent in the SERS spectrum of **5**. They may correspond to the NRS bands at 1433 and 501 $cm^{-1}$ that are assigned to the complexed $(p\text{-}ClC_6F_4NCH_2)_2$ ligand. It is therefore possible that the adsorbed species is a partly hydrolyzed complex. Alternatively, these SERS bands may be due to the coadsorbed free $(p\text{-}ClC_6F_4NCH_2)_2$ ligand. Hydrolysis of **1** and **5** would release $Cl^-$ ions and consequently lead to the occurrence of the characteristic Ag—Cl band at ~ 240 $cm^{-1}$. We observed strong SERS bands at 230–240 $cm^{-1}$ in the SERS spectra of all six Pt complexes, even in the SERS spectra of the complexes that did not contain any chloride. All Pt complexes were prepared from chlorides and the final products may still contain traces of these chlorides, leading to the characteristic Ag—Cl bands. Alternatively the $NaClO_4$ added to all solutions may contain traces of chloride. In any case, no information about the possibility of hydrolysis can be derived from this band.

The SERS spectra of the Pt complexes with $NH_3$ or en ligands are dominated by the strong Pt—N stretching bands at 500–580 $cm^{-1}$, which appear to be sensitive to the ligand in the trans position. For example, in the SERS spectrum of **4a** the strong band at 570 $cm^{-1}$ corresponds to the strong band at 573 $cm^{-1}$ in the NRS spectrum of the polycrystalline solid. In aqueous solution one carboxylate group is hydrolyzed and replaced by a $H_2O$ ligand, which in this case exerts a stronger trans influence and hence weakens the Pt—N bond in the trans position. The weakened Pt—N bond is manifested in the SERS spectrum by the appearance of a new band at about 540 $cm^{-1}$. During incubation the second carboxylate ligand is also replaced by $H_2O$ and the band at 540 $cm^{-1}$ increases in intensity while the original band at 570 $cm^{-1}$ decreases in intensity. After 10 days the latter band disappears altogether and only the band at 540 $cm^{-1}$ is observed. Considering this hydrolysis and adsorption behavior of complexes **4a** and **4b**, it is sensible to assign the bands in their SERS spectra (Fig. 4) to contributions from the en ligand.

## CONCLUSION

SERS is a very promising tool for the characterization of Pt-based anticancer drugs at physiological concentrations. DFT calculations at the B3LYP/Lanl2DZ level are very useful in the interpretation of experimental results for small and medium sized systems, but they fail for large complexes. This work forms the basis for our ongoing theoretical and experimental work on the interaction of Pt drugs with guanine and sulfur-containing amino acids, which are thought to be involved in drug resistance and undesirable side effects.

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