Pd(II) and Pt(II) Ternary Complexes with Nucleosides and Amino Acids

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Metal ions in biological systems may promote, among other reactions, the interaction of proteins and nucleic acids through the formation of ternary complexes [1, 2]. The significance of such interactions, e.g. the formation of nucleic acid enzyme ternary complexes during DNA replication and RNA synthesis in the presence of bivalent metals, is already known [3, 4]. The formation of such ternary complexes may also induce selective interaction between amino acid residues and nucleic acid bases, even those far removed from the site of metal attachment [5].

The significance of such interactions is shown by the use of Pt(II), or its analogs Pd(II) or Au(III) as models of the former, due to the known antitumor action of Pt(II) complexes. The antitumor activity of *cis*-DDP is due to direct interaction of the drug with DNA during its replication. The presence, however, of protein DNA crosslinkages after treatment with *cis*-DDP was noted by Zwelling *et al.* [6, 7]. The nature and significance of such interactions are not at present completely understood.

We have therefore undertaken a study of the ternary complexes formed between these metals, nucleosides and nucleotides, on the one hand, and amino acids and peptides, on the other.

Results and Discussion

This is a preliminary report on the ternary complexes formed between *cis*-$Pt(ino)_2Cl_2$ [8] and *cis*-$Pd(guo)_2Cl_2$ [9] (ino = inosine and guo = guanosine), with the amino acids glycine, L-isoleucine, L-valine, L-proline, L-alanine and L-phenylalanine. New ternary complexes were obtained according to the general reaction (1), in methanolic solutions:

$$cis\text{-}M(nucl)_2Cl_2 + am\text{-}acNa \xrightarrow{25\,^\circ C} cis\text{-}[M(nucl)_2(am\text{-}ac)]Cl + NaCl \qquad (1)$$

where am-ac-Na is the sodium salt of the amino acid.

The complexes obtained correspond to the above empirical formulae, as shown by their elemental analyses, and they are 1:1 electrolytes in aqueous and DMF solutions.

They further react with 0.1 N HCl, in aqueous solution, according to:

$$cis\text{-}[M(nucl)(am\text{-}ac)]Cl + HCl \longrightarrow cis\text{-}[M(nucl)_2(am\text{-}acH)Cl]Cl \qquad (2)$$

The elemental analyses of the compounds of reaction (2) confirm their empirical formulae. They are also 1:1 electrolytes in aqueous and DMF solutions.

The N,O-coordination of the amino acids in the first series of compounds, as well as the N-coordination in the second series, are confirmed first by their IR spectra.

The IR spectra are clearer when the ino ligand is used and can be interpreted as follows. For example, for the compound *cis*-$[Pt(ino)_2(ala)]Cl$ of the first series, the skeletal $\nu C{=}O$ band appears at ~1700 cm^{-1}, while the coordinated νCOO^- and the δNH_2 bands of the amino acid coincide in a new band near 1630 cm^{-1} (See Fig. 1).

In the series *cis*-$[Pt(ino)_2(am\text{-}acH)Cl]Cl$, again in the compound with ala, the intensity of the band near 1630 cm^{-1} diminishes considerably, while the intensity of the near 1700 cm^{-1} band of the $\nu C{=}O$ of the purine ring is enhanced. The band at 1630 cm^{-1} disappears upon deuteration and it is therefore due

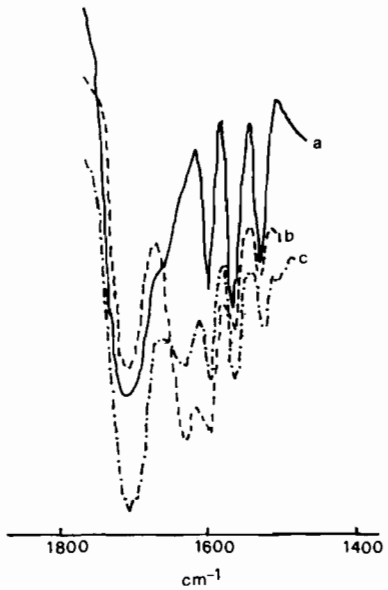

Fig. 1. IR spectra of the compounds: (a) —— *cis*-$Pt(ino)_2Cl_2$; (b) -----, *cis*-$[Pt(ino)_2(ala)]Cl$; and (c) –·–·–, *cis*-$[Pt(ino)_2(alaH)Cl]Cl$, in the region 1400–1600 cm^{-1}.

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to the δNH_2 vibration of the amino group coordinated to Pt(II) of the amino acid. On the other hand, the coordinated $-COO^-$ group of the amino acid, in the first series, is now free and protonated and its $\nu C{=}O$ band coincides with that of the purine skeleton (Fig. 1). Furthermore, a new weak band appears near 325 cm^{-1}, in these series, assigned to a $\nu Pt{-}Cl$. The situation is analogous in the other compounds.

In the ^1H NMR spectra of the compounds, the chemical shifts of the protons of the free and metal coordinated amino acids are not significant, in all the series. On the one hand, metal coordination causes a downfield shift of the protons near the coordination site, whereas the expected hydrophobic interaction of the aliphatic side chain of the amino acids used with the adjacent nucleosides [1], causes an upfield shift to their protons. The observed small chemical shifts are consequently the results of these opposite effects.

Taking as an example the compound with L-valine, the α-CH of the amino acid in the *cis*-[Pt(ino)$_2$(val)]Cl complex appears at 3.59 ppm, shifted by 0.01 ppm from its position in the free amino acid, in D_2O solutions. The same resonance appears at 3.61 ppm in the *cis*-[Pt(ino)$_2$(ValH)Cl]Cl compound, where L-valine is expected to be only N-coordinated, with its aliphatic side chain further away from the nucleosides. The two methyl doublets of L-valine also shift downfield by ~0.01 ppm in *cis*-[Pt(ino)$_2$(Val)Cl] and by ~0.02 ppm in *cis*-[Pt(ino)$_2$(ValH)Cl]Cl. For the β-CH_2 protons, the chemical shifts are 2.24, 2.27 and 2.28 for the free ligand, the N,O-chelated and the N-coordinated complexes, respectively.

For the analogous compound *cis*-[Pd(guo)$_2$(Val)]Cl in D_2O solutions, a downfield shift of 0.06 ppm for the α-CH, 0.01 ppm for the β-CH_2 and an upfield shift of ~0.01 ppm and ~0.03 ppm for the two methyl protons are observed.

The most characteristic feature in the ^1H NMR spectra of the Pt(II) and Pd(II) complexes of both series is the appearance of multiple bands for almost all the protons (including those from the sugar) in the Pd(II) series in D_2O solutions (Fig. 2).

In all the complexes, including the achiral amino acid glycine, the H(8) proton of guo shows 3 to 4 lines. They may be assigned to different rotational isomers, stabilized by hydrogen bonding between the amino acids and the nucleosides in the same molecule, and/or intramolecular stacking interactions of the nucleoside molecules [10–12]. These isomers should correspond to the possible head-to-head and head-to-tail arrangements of the guo ligands. The number of ^1H NMR lines increases in the series *cis*-[Pd(guo)$_2$(am-acH)Cl]Cl, as expected, due to the different *cis*-ligands near the two guo molecules [11]. Thus, a new set of 4 lines appears in the *cis*-[Pd(guo)$_2$(ValH)Cl]Cl compound, located between the two main ones of the *cis*-[Pd(guo)$_2$(Val)]Cl compound. These collapse into one broad band at 80 °C. The $\Delta G^{\ddagger}$ value at the interconversion temperature for the different rotational isomers is estimated to be larger than 76 kJ/mol.

The phenomenon is not observed in DMSO-d_6 solutions, where only one band for the H(8) proton is observed. DMSO-d_6 is known to minimize the stacking interactions of guanine rings [13].

The fact that the Pt(II) analogues do not present the same behavior, can in the first place be attributed to its larger size, making hydrogen bonding between the amino acids and the nucleosides within the same molecule unimportant. The influence, however, of the different nucleosides used, e.g. inosine and guanosine, on the stabilization of the various conformers, cannot be excluded and is under investigation.

The possible antitumor action of these complexes is also under investigation, since they are analogous to the recently reported antitumor compounds of the type [M(bip)(am-ac)]Cl, with M = Pd(II) or Pt(II)

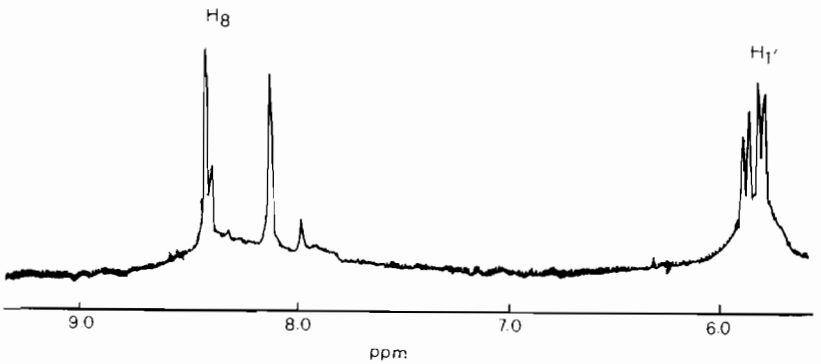

Fig. 2. ^1H NMR spectrum of the various rotational isomers of the compound *cis*-[Pd(guo)$_2$(isoleucine)]Cl in D_2O, showing the H_8 protons of the guanosine molecule.

and bip = bipyridine [14, 15]. The results of these studies, as well as of the detailed influence of temperature, pH and concentration, on the stabilization of the various rotational isomers of Pd(II), will be forthcoming.

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