



PS6.3 — TH

J.P. ALBERTINI

A. GARNIER-SUILLEROT

Laboratoire de Chimie bioinorganique
U.E.R. de Médecine et Biologie Humaine
Université Paris Nord
93012 Bobigny Cedex
France

**INTERACTION OF BLEOMYCIN
WITH Pd(II) COMPLEXES
([PdCl₄]²⁻, [cis-Pd(NH₃)₂Cl₂],
[Pd(en)Cl₂]) AND WITH [cis-Pt(NH₃)₂Cl₂].
ANTITUMOR ACTIVITY OF THE BLM-
[cis-Pt(NH₃)₂Cl₂] SYSTEM**

Bleomycin (BLM) and *cis*-diamminodichloroplatinum(II) (*cis*-DDPt) are used in combination chemotherapy to treat malignant tumors [1-3]. The two drugs exhibit synergism. The biological target for both *cis*-DDPt and bleomycin is believed to be DNA.

In this communication we address the question of whether prior covalent binding of *cis*-DDPt to BLM might alter the interaction of these two drugs with DNA and their antitumor activity.

Because of the slowness of Pt(II) ligand exchange reactions, parallel studies were conducted on the corresponding Pd(II) complexes which react 10⁵ times faster.

In this communication we report experiments showing that [PdCl₄]²⁻ as well as [cis-Pd(NH₃)₂Cl₂] and [Pd(en)Cl₂] reacts with bleomycin in a three steps process forming a 1:1 BLM.Pd(II) complex. In the same way a similar complex is obtained between BLM and [cis-Pt(NH₃)₂Cl₂]; its antitumor activity has been tested.

Interaction of BLM with Pd(II) complexes

The addition of [PdCl₄]²⁻ to an aqueous BLM solution gives rise to the immediate formation of

a first complex (**I**). The most striking features of this formation are i) the release of two protons, ii) the quenching of the pyrimidine fluorescence, iii) the appearance of a CD band at 367 nm which can be assigned to d-d transition. As time elapses this complex evolves to a second one (complex **II**); this occurs without any modification of the pH value but with noticeable change in the CD spectrum. The half life time of complex **I** is about 7 minutes. The last step, giving rise to the ultimate complex (**III**), is slower. Here again this occurs without modification of the pH value and, at pH 3, about three days are necessary to reach its complete formation. However if the pH is raised to about 7 the transformation of complex **II** to **III** occurs at once (it should be noticed that complex **III** is obtained directly by addition of [PdCl₄]²⁻ to BLM in a pH 7 Hepes buffer).

When either [cis-Pd(NH₃)₂Cl₂] or [Pd(en)Cl₂] are substituted for [PdCl₄]²⁻ one still observes a three steps process (complexes **I'**, **II'** and **III'**).

On the contrary when [PdCl₄]²⁻ is added to depyruvamide bleomycin (depBLM) one still observes the release of two protons but no evolution with time: only one complex (**d**) is observed.

The striking feature is that the CD spectra of complexes **III**, **III'** and **d** are similar strongly suggesting that the same four ligands are involved in the coordination square, most probably the secondary amine nitrogen, the pyrimidine nitrogen and the two peptide nitrogens. It must be pointed out that these ligands are different from those usually found in metal bleomycin complexes (the metal being copper, iron and cobalt) [4,5].

Interaction of BLM.Pd(1:1) complex (III) with DNA

The addition of DNA to complex **III** gives rise to a quenching of the bithiazole fluorescence suggesting that it is still able to intercalate between the base pairs of DNA. Moreover an immediate modification in the 320-340 nm region (d-d transition) of the CD spectrum is observed which can be assigned to a modification of the ligand field around the Pd(II) ion. However no release of Pd(II) from the complex could be detected.

BLM.[cis-Pt(NH₃)₂Cl₂] system

The interaction of *cis*-DDPt with BLM is very slow and incomplete. After one week, at pH 7, only 30% of the 1:1 complex is obtained.

Antitumor activity of the BLM-CisDDPt complex

A mixture containing BLM and *cis*-DDPt in a 3:1 molar ratio was used. In that conditions we have estimated that all the Pt(II) ions are complexed to BLM. The mixture has been screened for anticancer activity against Lewis pulmonary carcinoma and L 1210 leukemia in a comparative study with BLM and *cis*-DDPt respectively. The percentage of inhibition by the BLM-*cis*DDPt (1:1) complex is reduced to 65% and 55% with regard to free BLM and *cis*-DDPt respectively.

REFERENCES

- [1] M.P. CORDER, G.H. CLAMON, *Cancer*, **54**, 202-206 (1984).
- [2] R. VRIESENDORP, J.G. AALDERS, D.T. SLEIJFER, P.H.B. WILLEMSE, J. BOUMA, N.H. MULDER, *Cancer Treat. Rep.*, **68**, 779-781 (1984).
- [3] P.K. MASCHARAK, U. SUGIURA, J. KUWAHARA, T. SUZUKI, S.J. LIPPARD, *Proc. Natl. Acad. Sci., USA*, **80**, 6795-6798 (1983).
- [4] J.P. ALBERTINI, A. GARNIER-SUILLEROT, *Biochemistry*, **21**, 6777-6782 (1982).
- [5] J.P. ALBERTINI, A. GARNIER-SUILLEROT, *Biochemistry*, **23**, 47-53 (1984).



PS6.4 — MO

OLE JØNS

ERIK SYLVEST JOHANSEN

Royal Danish School of Pharmacy

Department of Pharmaceutical Chemistry AD

2 Universitetsparken, DK-2100 Copenhagen

Denmark

ALUMINIUM COMPLEXES
WITH PICOLINIC ACID

Aluminium has long been regarded biologically inert, but the aluminium absorption and consequent accumulation in the brain of patients with dialysis dementia is now well documented [1]. Aluminium intoxication has also been implicated in various neurological disorders such as Alzheimer dementia. Little is known about the mechanism of aluminium uptake. It is supposed that only dissolved aluminium is able to cross the mucosa barrier in the gastrointestinal tract [2]. Experiments with rats fed on diets containing suboptimal levels of zinc and elevated levels of aluminium showed increased aluminium concentrations in the rat brains. Probably aluminium in gut competes for binding sites on zinc or iron binding ligands. Investigation has showed that picolinic acid (2-pyridiniumcarboxylic acid) probably plays an important role in the absorption process of zinc [3]. The aim of the present work is to investigate the ability of aluminium to form complexes with picolinate ions.

EXPERIMENTAL

Potentiometric titrations with glass electrode were performed in 0.150 M KNO₃ at 25.0°C. Concentration of each component were of the order 10⁻³ M. The metal-to-ligand ratio varied between 1:1 and 1:4, and the mixtures were titrated in the pH range 3 to 7.