An Explanation for the Efficacy of Attack by Platinum Blue Drugs on Biopolymers

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Summary A study of the interaction of a platinum blue compound with protein crystals has demonstrated a possible mode of attack of these anti-tumour drugs.

A RECENT paper on polymeric Pt-containing anti-tumour agents[1] leads us to report a series of parallel observations on a quite different set of platinum polymers. The compounds

in question are the 'platinum blues' formed by reaction of platinum halides with amides. Despite the fact that they have been extensively examined as chemicals, the exact formula is unknown but they are polymeric. They are used as stains for biological specimens and are useful anti-tumour agents, and appear to be more useful clinically than monomeric platinum compounds in that they give less side effects.[2] In an attempt to understand the ways in which platinum blues could act which would distinguish them from monomeric platinum anti-tumour agents we have carried out some simple experiments.

It is well known that if crystals of proteins are exposed to monomeric platinum salts the protein often becomes labelled with the heavy atom in quite specific ways. In fact these derivatives are frequently the basis of *X*-ray structure determinations of proteins. However the method can be turned around and a known crystal structure of a protein can be used to follow incorporation of a metal complex. Both the rate of incorporation and the structure of the complex could then be found. (This is a matrix isolation structure determination as far as the complex is concerned). Our idea was that, as the structural nature of platinum blues was not known and they have not yet been crystallised, we would determine their structure in a protein matrix. The proteins used were lysozyme and prealbumin where we know the binding sites of monomeric Pt-complexes.[3] To this end platinum blue was dissolved in the mother liquor around the protein crystals. After soaking for 24 h the inky colour of the solution remained but the crystals were completely free from colouration. After several days during which a colour change occurred in the mother liquor, the crystals became brown. In both lysozyme and prealbumin crystals it was found by *X*-ray analysis that there was now platinum labelling at the sites where *monomeric anionic* platinum(II) salts bind.

We conclude that the platinum blues act on the proteins through slow release of monomers. We speculate that probably their mode of action as drugs is through slow release of monomers too as it is difficult to see how polymeric platinum blue compounds which cannot diffuse into crystals can penetrate membranes. Thus platinum blue could have advantages over monomeric platinum compounds through the control it exerts on the release of the effective monomeric drug which is released in a specific chemical form. In fact it has long been the dream of the pharmacologist to be able to supply a drug in polymeric form while it acted through slow release of the monomer yielding a constant low concentration of the effective drug. Platinum blues and, perhaps, the phosphazene complexes provide good illustrative examples of this principle. In any event our experiments illustrate a simple general way of following drug–protein interactions. Although our attempt to carry out a crystal struture determination in a protein matrix failed, this possibility should be kept in mind now that crystal structures of so many proteins are available.

The platinum blue compounds used by us were supplied by Dr. A. J. Thomson (University of East Anglia) and Dr. M. Cleare (Johnson Matthey Ltd.) and are closely related in physical chemical properties to previous preparations.[4]

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