Synthesis of Spin-labelled Platinum Drugs and Interaction with Deoxyguanosine

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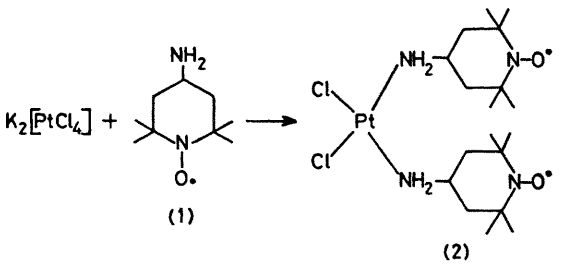
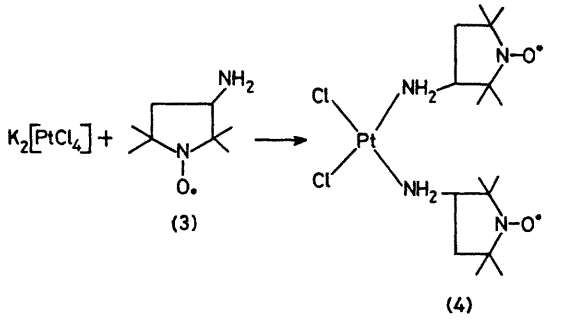
Summary Two novel spin-labelled *cis*-platinum drugs have been synthesized and allowed to react with deoxyguanosine to form a spin-labelled complex.

DURING the past few years there has been considerable interest in the binding of platinum complexes to nucleic acids and nucleic acid constituents,[1] and this has been studied so far by use of u.v.[2] and n.m.r. spectroscopy.[3]

E.s.r. spectroscopy could be used to obtain information about the binding of platinum complexes to nucleic acid constituents if a spin-labelled platinum complex were available. E.s.r. spectroscopy is able to detect as little as 10^{-13} moles of nitroxide spin label and spin label methods have been used successfully to study the viscosity and polarity of local domains, molecular ordering, rotational or translational motion, and interaction of molecular species.[4] We now report the synthesis of two nitroxide spin-labelled platinum drugs along with preliminary studies of their binding to deoxyguanosine.





4-Amino-2,2,6,6-tetramethylpiperidin-1-oxyl (**1**) was added to a solution of potassium chloroplatinite in water. Sufficient ethanol to obtain a homogeneous solution was then added and the mixture was stirred at room temperature for 24 h. The precipitated complex was filtered off and the mother liquor was extracted with chloroform to recover more of the spin-labelled complex. The crude product was further purified by cellulose column chromatography using butanol saturated with water as eluant. The spin-labelled platinum complex (**2**)† was obtained as a light-yellow powder [m.p. 257—260 °C (decomp); ν_{max} 3130, 3220, and 3450 cm^{-1}; λ_{max} (EtOH) 221—227 nm (ϵ 4760); mass spectrum, *m/e* 608].

The e.s.r. spectrum (Figure, a) consists of a triplet characteristic of the nitroxide. Additional low-intensity broad lines appear between the central and low-field lines and also between central and high-field lines. These additional lines are attributed to electronic exchange arising from spatial interaction of appropriately oriented nitroxyl biradicals.[5] This confirms the biradical nature of the compound and also its *cis*-geometry,[6,7] since the *trans*-isomer would allow no interaction and would not give additional lines.

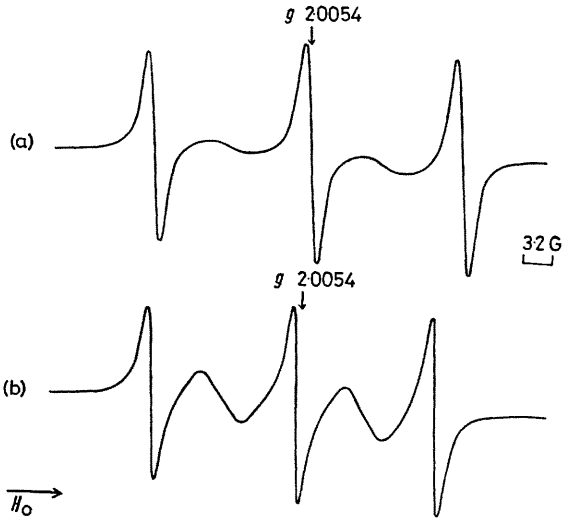


FIGURE. E.s.r. spectra of spin-labelled platinum complexes in water: (a) compound (**2**); (b) compound (**4**).

The anti-tumour activity and toxicity of platinum drugs are influenced by the nature of the co-ordinated amine, and structural and stereochemical variation.[8] Using a procedure similar to that described above, a *cis*-platinum complex (**4**) having pyrrolidineamine units co-ordinated to platinum was also prepared starting with potassium chloroplatinite and 3-amino-2,2,5,5-tetramethylpyrrolidin-1-oxyl (**3**) and purified as for (**2**). Compound (**4**) had m.p. 185—187 °C; ν_{max} (KBr) 3130, 3225, and 3450 cm^{-1}; λ_{max} (EtOH) 222—227 nm (ϵ 4750); mass spectrum, *m/e* 580, and its e.s.r. spectrum (Figure, b) also showed additional lines between those of the mono-radical triplet spectrum. The length and chemical structure of the connecting bridge influence the conformational proximity of the biradicals. In this compound, because of the relative closeness of the nitroxyl groups, the spin–spin interaction is expected to be greater than that in compound (**2**). This greater interaction is reflected in the increased intensity of the spectral lines between the components of the triplet spectrum.

A deoxyguanosine–*cis*-platinum spin-labelled complex was prepared by stirring complex (**2**) with deoxyguanosine in 0·06 M phosphate buffer (pH 6·8) for 2 days at room temperature. The product was purified by cellulose column chromatography to obtain a new, u.v.-absorbing product different from the reactants. This product exhibited a triplet e.s.r. spectrum characteristic of nitroxides, but the line width (W_{pp} 2·1 G) and hyperfine coupling constant (A_n 17·25 G) were different from those of free *cis*-platinum complex (W_{pp} 1·6 G; A_n 17·12 G). In the u.v. spectrum, the 254 maximum of deoxyguanosine was shifted to 258 nm. The carbonyl i.r. absorption was shifted to a lower wavenumber, indicating that N-7 is the possible binding site.[9] The n.m.r. spectrum of this compound, recorded after the reduction[10] of the nitroxide unit, showed proton signals arising from deoxyguanosine and tetramethylpiperidine unit. All this spectral information supports the hypothesis that a deoxyguanosine *cis*-platinum spin-labelled complex

† All new spin-labelled platinum complexes gave satisfactory analytical data.

has been formed, as reported in the case of unlabelled complexes.[11]

Preliminary studies indicate that the spin-labelled platinum complex is a very attractive candidate for studying the interaction of platinum drugs with DNA. The spectra of such complexes are capable of yielding both quantitative and qualitative information regarding molecular interaction.

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