Dimethyl Sulphoxide as Leaving Group: Applications in Transition Metal Chemotherapy

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Sulphur-bound dimethyl sulphoxide (DMSO) hydrolyses slowly in complexes of platinum; incorporation of DMSO into molecular species such as $[Pt(diamine)(DMSO)_2]^{2+}$ results in water-soluble, less toxic derivatives with equivalent chemotherapeutic activity to those of the parent chloro-complexes.

The discovery of the antineoplastic activity of *cis*-$[PtCl_2(NH_3)_2]$, and its subsequent clinical development, has inspired intensive research into the mechanism of action of this complex and the development of suitable analogues with better pharmacological properties by improvement of the lipophilicity, toxicity, and water-solubility of the parent drug.[1]

The presently accepted mechanism of action of this complex requires the presence of a *cis*-$[Pt(amine)_2]$ unit and the general methodology of variation of the amine and the anionic ligand (leaving group) in *cis*-$[PtX_2(amine)_2]$ has led to present clinical studies on 'second-generation' complexes such as [Pt(4-carboxyphthalato)(dac)][2] and $[Pt(cbdca)(NH_3)_2]$[3] (dac = 1,2-diaminocyclohexane, cbdca = 1,1′-cyclobutanedicarboxylate) from a large number of complexes synthesized. In this paper, we present initial results on the properties and relevance of a new series of complexes, *cis*-$[Pt(amine)_2(DMSO)_2]A_2$, based on DMSO (dimethyl sulphoxide) as leaving group.

DMSO is an ambidentate ligand which may bind to metal ions through either the sulphur or oxygen atom.[4] Oxygen-bound DMSO is more labile than the sulphur-bound ligand, but in aqueous solution the latter may also be dissociated, either in the presence of base (OH^-) or by increase in temperature, even in the absence of a strong incoming nucleophile [reaction (1)].[5]

$$[Ru(DMSO)_6]^{2+} \xrightarrow{H_2O} [Ru(DMSO)_4(H_2O)_2]^{2+}$$
4S, 2O-bound 4S-bound

$$\text{or } \xrightarrow[H_2O,\ 82\ ^\circ C]{OH^-,\ 32\ ^\circ C} [Ru(DMSO)_3(H_2O)_3]^{2+} \quad (1)$$
3S-bound

We have summarised the factors affecting the donor atom chosen in M–DMSO complexes and these also include steric[6] and electronic[7] effects of the other ligands in the co-ordination sphere. Further examples of the hydrolysis of S-bound DMSO have been observed for *mer*-$[RhCl_3(DMSO)_3]$[8] and $[PdCl_2(DMSO)_2]$,† the displacement occurring readily at room temperature for these more labile species.

In an extension of these studies we have recently studied DMSO complexes of platinum. The $[Pt(DMSO)_4]^{2+}$ cation is considered to have 2S- and 2O-bound ligands in a *cis*-arrangement as confirmed by i.r. and ^1H n.m.r. studies.[9] The ^1H n.m.r. spectrum in D_2O, however, shows a resonance for S-bound DMSO at τ 6.5 [^3J(Pt–H) = 24.1 Hz], with only a trace of the O-bonded ligand at τ 7.0. The S:O ratio is thus solvent-dependent, as observed for the $[Ru(DMSO)_6]^{2+}$ cation,[10] and the major species in aqueous solution contains all S-bound sulphoxides, and readily gives rise to the appearance of free DMSO (τ 7.4) upon addition of base. At room temperature in D_2O slow dissociation (*ca.* 24 h) of one ligand occurs.

Metal complexes with DMSO as ligand are water-soluble species and the lipophilicity of DMSO and its low toxicity prompted us to examine the behaviour of the $[Pt(amine)_2(DMSO)_2]^{2+}$ cation as an analogue of *cis*-$[PtCl_2(NH_3)_2]$, especially to see if hydrolysis would occur in this species. Although complexes of the type $[Pt(amine)_2Cl(DMSO)]^+$ are known[11] the bis-DMSO complexes with weak non-co-

† A solution of *cis*-$PdCl_2(DMSO)_2$ in D_2O shows one absorbance at τ6.45 and free DMSO at τ7.4. A similar situation arises in $CDCl_3$: W. Kitching, C. J. Moore, and D. Doddrell, *Inorg. Chem.*, 1980, **8**, 541.

ordinating nucleophiles (*e.g.* BF_4^-) have not been reported. Addition of a chelating diamine such as 1,2-diaminocyclohexane (mixture of geometric isomers) to a methanolic solution of $[Pt(DMSO)_4]^{2+}$ readily gives upon reduction to half-volume and addition of ether the $[Pt(dac)(DMSO)_2]^{2+}$ cation [reaction (2)] with both DMSO ligands bound through sulphur [τ (Me_2SO) 6.4 in D_2O, ^3J(Pt–H) 26.0 Hz; ν(NH) = 3280, 3229 cm^{-1}, ν(SO) = 1150, 1070 cm^{-1}]. The complex is

$$[Pt(DMSO)_4]^{2+} + dac \xrightarrow{MeOH} [Pt(DMSO)_2(dac)]^{2+} \quad (2)$$

very soluble in water and alcoholic solvents and only sparingly soluble in chloroform and acetone. Similar results are obtained for 1,2-diaminoethane. With $[Ru(DMSO)_6]^{2+}$ the $[Ru(dac)_2(DMSO)_2]^{2+}$ cation [λ_{max} = 470 nm, τ (Me_2SO) 6.56] is obtained.[12]

The behaviour of $[Pt(diamine)(DMSO)_2]^{2+}$ species parallels that of $[Pt(DMSO)_4]^{2+}$. Slow dissociation (18 h, 25 °C) of one DMSO ligand occurs in D_2O, with concomitant changes in intensity ratios. Thus, the kinetic inertness of the diamine ligand favours DMSO hydrolysis even though this S-bonded ligand would be considered to have a greater *trans*-influence. It is especially interesting to note that use of DMSO as solvent for *cis*-$[PtCl_2(NH_3)_2]$ gives a complex mixture[13] whereas incorporation of DMSO into a well defined molecular species greatly enhances the water-solubility of the [Pt(diamine)] moiety which remains intact even upon initial hydrolysis.

In a related study of aspects of transition metal complexes in chemotherapy we have shown[14] that *cis*-$[PtCl_2(NH_3)_2]$, $[PtCl_2(dac)]$, and $[Pt(dac)(DMSO)_2]^{2+}$ are all active *in vivo* and *in vitro* against *Trypanosoma Rhodesiense*, the causative agent of sleeping sickness in man. The DMSO complex shows biological activity of the same order as the chloro-species but is significantly less toxic. The $L.D._{50}$ values[15] are 28 mg kg^{-1} (confidence limit = 17.5—44.8) for $[PtCl_2(dac)]$ and 140 mg kg^{-1} (confidence limit = 112—174) for the DMSO-substituted complex as its BF_4^- salt. The similar biochemistry of trypanosome and tumour cells[16] results in a good coincidence of activity between trypanocidal and anti-tumour agents.[17] This relationship holds for the platinum complexes and we note that $[PtCl_2(dac)]$ has been shown to have an equivalent therapeutic index to that of the original *cis*-$[PtCl_2(NH_3)_2]$.[18]

To summarise, substitution of DMSO for Cl in the $[Pt(amine)_2L_2]$ unit results in a more water-soluble, less toxic derivative with equivalent therapeutic activity. The general principle is clearly applicable to other systems besides trypanosomiasis and anti-tumour tests on a number of complexes are presently under way and the results awaited with interest. The results discussed represent an example of the application of basic chemical principles in the design of new, more effective chemotherapeutic transition metal agents.

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