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# Australian Radiation Laboratory

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Composition of Technetium-99 Complexes:  
Implications for  $^{99m}\text{Tc}$ -Radiopharmaceutical Preparation

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LOWER PLENTY ROAD  
YALLAMBIE VICTORIA 3085  
TELEPHONE: 433 2211

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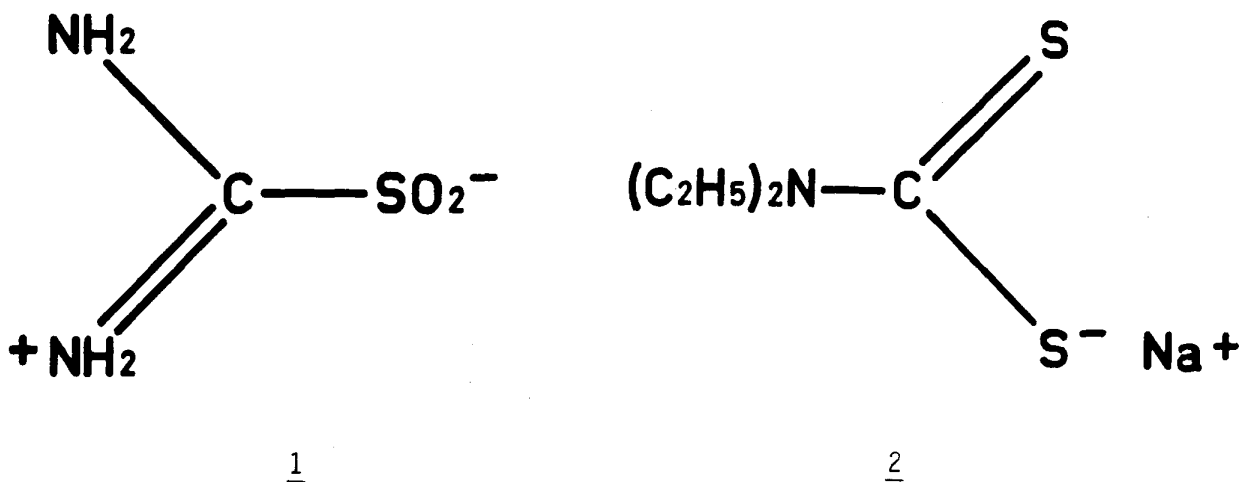
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YALLAMBIE, VIC., 3085  
TELEPHONE: 433 2211

## ABSTRACT

The use of hydrazine or formamidine sulphinic acid as reducing agents in the presence of  $^{99}\text{Tc}$ -pertechnetate anion and the diethyldithiocarbamate ligand has been found to yield complexes containing  $\text{Tc}\equiv\text{N}$  and  $\text{Tc}=\text{CO}$  bonds respectively. The nitrido nitrogen atom and the carbon monoxide incorporated in these complexes as ligands originate from the reducing agents themselves. It is apparent that when reducing agents such as hydrazine or formamidine sulphinic acid are used in the preparation of  $^{99\text{m}}\text{Tc}$ -radiopharmaceuticals, the possibility of the formation of complexes structurally different to those obtained by use of stannous chloride must be considered.

## INTRODUCTION

The preparation of  $^{99m}\text{Tc}$ -labelled radiopharmaceuticals generally requires the initial reduction of the pertechnetate anion ( $^{99m}\text{TcVIIIO}_4^-$ ) followed by reaction with an added complexing agent (Eckelman and Levenson 1977). Choice of the reducing agent is limited to non-toxic, water soluble species which do not result in appreciable amounts of  $^{99m}\text{Tc}$ -colloid formation. Stannous chloride is widely used but ascorbic acid/ferric ion (Stern et al. 1965), hydrazine (Galateanu et al. 1977), and electrolytic methods (Steigman et al. 1974) have been proposed. In some instances, such as penicillamine (Tubis et al. 1975) and pyridoxal derivatives (Baker et al. 1975), the reductant is also the complexing agent. Fritzberg et al. (1977) have proposed formamidine sulphinic acid (FSA, 1) as an alternative general reducing agent to stannous chloride. This new reductant avoids some of the problems which may result from the tendency of stannous salts to hydrolysis and oxidation.



When non-metallic reducing agents are used the possibility of the reducing agent competing with the added ligand for complexing with reduced technetium must be considered. We have recently reported that when FSA is used to prepare the  $^{99m}\text{Tc}$ -HIDA complex a substantial amount of a FSA-derived  $^{99m}\text{Tc}$  complex is also produced (Baldas and Pojer 1981).

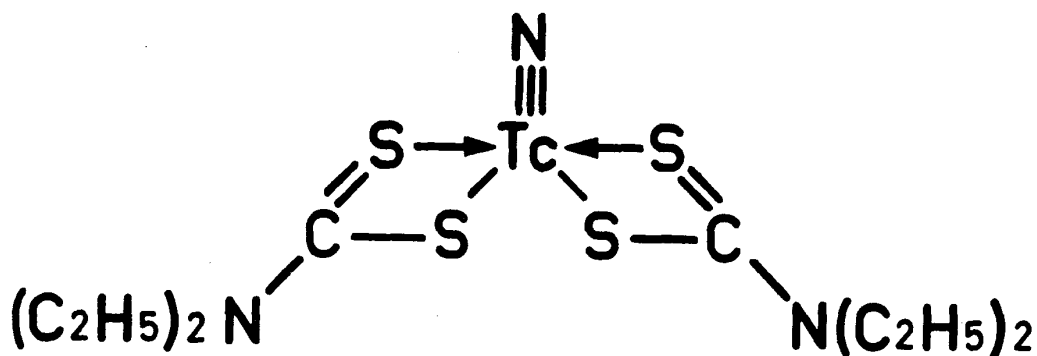
Deutsch et al. (1976) found that reduction of  $^{99}\text{Tc}$ -pertechnetate with stannous ion in the presence of dimethylglyoxime gave a complex containing both tin and technetium. The suggestion that  $^{99m}\text{Tc}$ -radiopharmaceuticals prepared using stannous chloride may contain  $^{99m}\text{Tc}(\text{Sn})$ -complexes has often

been made but the experimental evidence to date suggests that, in general, mixed metal complexes are not formed (Eckelman et al. 1972; Loberg and Fields 1978). Otherwise, the question of what effect the choice of reducing agent may have on the chemical structure of a  $^{99m}\text{Tc}$ -complex has received little attention.

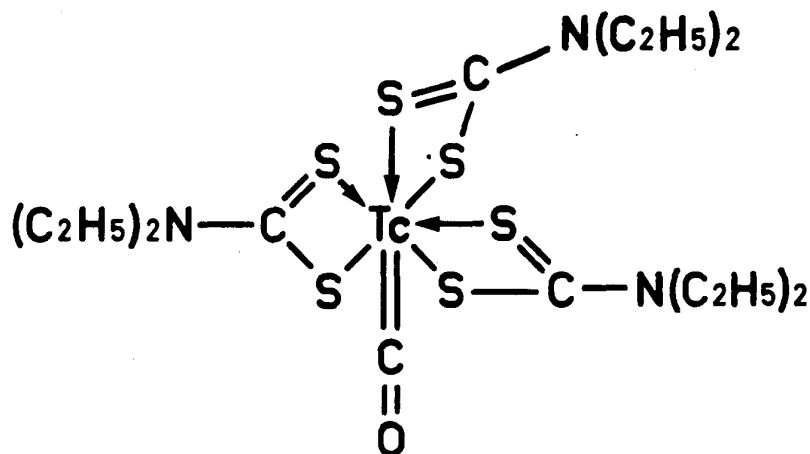
We have recently reported the preparation and biological behaviour of a highly lipophilic  $^{99m}\text{Tc}$ -diethyldithiocarbamate preparation (Pojer and Baldas 1981) and have now extended our chemical studies of this complex by use of technetium-99. The chemical composition of the complex formed was found to vary with the reducing agent used. Crystalline products were obtained by use of hydrazine and FSA as the reducing agents and the structures have been determined by single-crystal X-ray diffraction analysis. The products obtained from reduction with stannous chloride and sodium borohydride have been partially characterised by infrared spectroscopy.

#### RESULTS AND DISCUSSION

Reduction of  $^{99}\text{Tc}$ -pertechnetate by hydrazine in the presence of sodium diethyldithiocarbamate [ $\text{Na}(\text{dtc})$ , 2], described elsewhere (Baldas et al. 1981a), gave the yellow chloroform-soluble compound  $(\text{dtc})_2\text{TcN}$  (3) in high yield. The presence of the  $\text{Tc}\equiv\text{N}$  bond was indicated by an absorption at  $1070\text{ cm}^{-1}$  in the infrared spectrum. X-ray diffraction analysis (Baldas et al. 1981a) showed that the technetium atom, in the +V oxidation state, is in a distorted square-pyramidal environment. The nitrido nitrogen atom originates from the reductive cleavage of coordinated hydrazine; a reaction which has been previously used for the preparation of rhenium(V) nitrido compounds (Griffith 1972).



When FSA in aqueous solution was used as the reductant, a chloroform-soluble product was obtained. This was separated by alumina chromatography into ca. a 45% yield of the chloroform-eluted  $(dtc)_3TcCO$  and ca. 45% of a methanol-eluted compound. The presence of carbon monoxide coordinated to technetium in the chloroform eluate was clearly indicated by an intense absorption at  $1895\text{ cm}^{-1}$  in the infrared spectrum. Single-crystal X-ray diffraction analysis of  $(dtc)_3TcCO$  (4) shows that the technetium atom, in the +III oxidation state, has a distorted pentagonal-bipyramidal environment (Baldas et al. 1981b).



The formation of the carbon monoxide complex,  $(dtc)_3TcCO$ , was indeed unexpected. It is difficult to conceive a satisfactory mechanism for the formation of carbon monoxide by the decomposition of FSA in aqueous solution. It is probable that carbon monoxide is formed after FSA, or a decomposition product, has coordinated to technetium. This is discussed in detail elsewhere (Baldas et al. 1981b).

The methanol-eluted compound from the FSA reduction has not been crystallised for X-ray analysis. However, the infrared spectrum indicates the involvement of FSA in complex formation.

Reduction of  $^{99}\text{Tc}$ -pertechnetate by either stannous chloride or sodium borohydride in the presence of sodium diethyldithiocarbamate resulted in a product having infrared absorptions consistent with only coordinated dtc ligands. The deep purple chloroform extracts of the reaction mixtures slowly turned brown on standing or more rapidly in the presence of alcohols. With stannous chloride and sodium borohydride the evidence is against any involvement of the reducing agents in complex formation.

The extent to which results obtained with  $^{99}\text{Tc}$  can, in general, be extrapolated to the "carrier-free"  $^{99\text{m}}\text{Tc}$ -radiopharmaceuticals is not clear. It is, however, apparent that when reducing agents such as FSA or hydrazine are used, the possibility of the formation of radiopharmaceuticals structurally different to those obtained by use of stannous chloride must be considered. These unexpected complexes may have different biological properties which may be of value in diagnostic nuclear medicine.

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