Prior work had documented that $^{99m}\text{TcCl}_6^{2-}$ could undergo ready ligand exchange reaction under non-aqueous condition. We now wish to report the ligand exchange reaction of bromine in $^{99m}\text{TcBr}_4^{2-}$ in non-aqueous solvents using 8-hydroxyquinoline (oxine) as the displacing ligand. Analysis of the products obtained by paper chromatography, HPLC and electrophoresis suggest that a 1:2 Tc:oxine complex appears to be the most stable of the complexes formed, probably $^{99m}\text{Tc(oxine)}_2\text{Br}_2$. However, displacement of bromine by polar solvents (both protic and aprotic) can also occur, both on $^{99m}\text{TcBr}_4^{2-}$ and in the above complex as a consequence of solvolytic reactions. Other Tc-oxine complexes can also be formed upon ligand exchange, but they appear to be stable only under aprotic, non-solvolytic conditions. These studies again document that hexahalotechnetate complexes exhibit ligand exchange reactions under non-aqueous conditions, that they allow the ready synthesis of novel technetium complexes, but that because of their high reactivity the effect of competing reactions must be considered.

Introduction

Complexes formed from $^{99m}\text{Tc}$ are widely used in Nuclear Medicine as imaging agents. Normally the preparation of these radiopharmaceuticals involves the aqueous reduction of $^{99m}\text{TcO}_4^{-}$ using an excess of SnCl$_2$, and in the presence of the ligand. This method of synthesis (known as classical synthesis) is simple and appears to ensure both a smooth reduction of Tc (VII), and, because the reduced Tc is trapped by the ligand, to prevent the formation of TcO$_2$. This classical method does, however, have several limitations, such as: it does not allow specific control over the final oxidation state, various complexes may be formed, including $^{99m}\text{Tc-Sn-radiocolloid}$; the reduced Tc is subject to reoxidation, and the excess of reductant remains in the final product and is injected into the patient. The other key consideration is that the above procedure requires the use of water-soluble ligands.
DEUTSCH\(^1\) has suggested that the synthesis of radiopharmaceuticals through the substitution route onto pre-reduced centers of technetium would avoid most of the above problems and that such a more flexible route of synthesis might permit the formation of new agents. Unfortunately, until now, very few studies have exploited such an approach.\(^2\)\(^3\)

Given the ready availability of technetium in most, if not all, nuclear medicine laboratories around the world, it is apparent that the exploitation of the full potential of technetium can best be attained by undertaking more extensive basic research on the chemistry of this element. The attainment of a single oxidation state during the reduction step, in a rapid and simple manner, might be key for the development of novel types of technetium complexes. The hexahalotechnetate intermediates, of the general structure TcX\(^2\)\(^+\), where X = Cl, Br or I, appear to be most promising. Previous studies of this laboratory\(^4\) had documented how such intermediates can be readily produced in non-aqueous medium.

We wish to report here the ligand exchange reaction on \(99^{m}\)TcBr\(^-\) by 8-hydroxyquinoline (oxine), and the behavior of the products formed in various solvent systems.

**Materials and methods**

**Chemicals**

The \(99^{m}\)Tc (NaTcO\(_4\)) was obtained by elution either from a dry generator (New England Nuclear) or from a fission generator (Mallinckrodt). To standardize the \(99^{m}\)Tc content, such generators were eluted every 24 hours. Stock solutions of oxine (ox) (Aldrich) \(10^{-2}\)M were prepared in chloroform and in acetonitrile. All chemicals used in this study were analytical grade and the solvents used as the mobile phase in HPLC studies were HPLC grade.

**Typical preparation of the technetium complexes**

0.5 ml of HBr, 8.8M, was added to an aqueous solution of 0.5–1 mCi of \(99^{m}\)TcO\(_4\) and the solution was warmed at 100 °C for 30 minutes. The solvent was evaporated to dryness under reduced pressure and warming at 35 °C. 1 mg of K\(_2\)CO\(_3\) and 1 ml of the oxine stock solution in chloroform \((10^{-2}\) M) were added to the dry residue and the mixture was warmed at 55 °C for 45 minutes with occasional shaking. The solution was centrifuged, and the supernatant chloroform solution was transferred into another vial. The reaction vial was washed with 1 ml of chloroform. The washing was added to the original chloroform solution. The organic solvent was then evaporated to dryness by the passage of a steady stream.