SYNTHESIS OF CARRIER-FREE RHENIUM-188(V)DMSA USING TRIPHENYL PHOSPHINE AS A FACILE REDUCING AGENT

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SUMMARY

Rhenium-188-labeled $ReOCl_3(PPh_3)_2$ is an important reactive complex which can be prepared in > 95% yield by the reaction of perrhenate ($^{188}ReO_4^-$) or perrhenic acid with triphenyl phosphine (PPh_3) and HCl with subsequent extraction into CH_2Cl_2 or $CHCl_3$. The yield is dependent upon a high HCl concentration. Because of the potential important use of ^{188}Re(V)DMSA for therapy of tumors of the head and neck, we have used the $^{188}ReOCl_3(PPh_3)$ intermediate for the facile synthesis of the $ReO(DMSA)_2$ complex.[1] Reaction of $ReOCl_3(PPh_3)_2$ with naturally abundant Re or carrier free Re-188, with DMSA (meso-1,2-dimercaptosuccinic acid) yields $ReO(DMSA)_2$ in high yield. The ^{188}Re(V)DMSA can also be prepared by reaction of Re-188 perrhenate or perrhenic acid with $SnCl_2$ in the presence of DMSA.

Key words: Rhenium-188, ^{188}Re(V)DMSA, Triphenyl Phosphine Reduction

INTRODUCTION

There is considerable interest in the use of small molecules such as ^{99m}Tc(V)DMSA for tumor imaging (Abrams, 1991). In particular, this radiopharmaceutical accumulates in medullary thyroid carcinoma (Ohta et al., 1984; Clarke et al., 1988) and in bone metastases (Ohta et al., 1988). The recent synthesis of Re(V)DMSA (Bisunadan et al., 1991) suggests that the possibility of a "matched pair" of diagnostic and therapeutic agents using Tc and Re radioisotopes may become a reality because of the chemical similarity of the two elements. Technetium-99m is produced carrier-free

[1]Although the $Re(V)O(DMSA)_2$ is a monovalent anion, for simplicity the charge is not included and the species denoted as Re(V)DMSA in this discussion.

0362–4803/93/010065–11$10.50

Received 30 July, 1992
Revised 22 September, 1992

from a $^{99}Mo/^{99m}Tc$ generator and is widely used in diagnostic nuclear medicine primarily because of its availability and the fact that it has perfect imaging qualities due to its short half life (6.02 hours), and decay characteristics (143 keV gamma ray). Both ^{188}Re and ^{186}Re decay with the emission of beta particles for therapeutic applications and also have gamma photons which can be efficiently detected with a gamma camera for biodistribution studies (155 keV for ^{188}Re and 137 keV for ^{186}Re). Rhenium-188 is available carrier-free from a $^{188}W/^{188}Re$ generator as perrhenic acid or sodium perrhenate (Ehrhardt et al., 1991; Kodina et al., 1991; Lisic et al., 1991; Coursey et al., 1990; Callahan et al., 1989) and ^{186}Re is produced by neutron irradiation of rhenium-185.

The chemical identity of Tc(DMSA) obtained from commercial "kit" preparations has been recently described in detail (Blower et al., 1991), and the preparation of ^{99m}Tc(V)DMSA by the aqueous alkaline reduction of pertechnetate by sodium dithionite in the presence of DMSA has been shown to actually result in the formation of the $[TcO(DMSA)_2]^-$ complex, which contains the $[Tc{=}O]^{3+}$ core. Recently, authentic, unlabeled Re(V)DMSA was synthesized and characterized for the first time and also radiolabeled with ^{186}Re (Bisunadan et al., 1991). Since ^{186}Re is reactor-produced from irradiation of ^{185}Re, it can contain significant levels of carrier. Rhenium-188 may thus be more attractive in radiopharmaceutical preparations, since it is carrier-free and can be repeatedly obtained from a tungsten-188/rhenium-188 generator system which has a shelf-life of several weeks. The initial preparation of Re(V)DMSA and ^{186}Re(V)DMSA involved stannous chloride reduction of perrhenate in the presence of DMSA by heating the reaction mixture to 100°C for 30 min to ensure completion. Because of the presence of $^{185/187}Re$ carrier in the preparation of ^{186}Re(V)DMSA, a significant excess of stannous ion is required to insure completion of the reaction compared to the relatively small amount of Sn(II) required needed to prepare carrier-free ^{99m}Tc(V)DMSA. As an example, the commercially available Amersham ^{99m}Tc(V)DMSA kits, which use stannous chloride as the reducing agent, can be used to synthesize ^{186}Re(V)DMSA but the total amount of Re must be limited to less than 0.1 mg and heating is required to ensure reaction.

The possibility of the presence of residual tin and its effect on radiopharmaceutical preparations of Tc(V)DMSA and Re(V)DMSA compounds is not well understood. For example, ^{99m}Tc(V)DMSA has been considered to be a polymeric material by gel filtration (Yokoyama et al., 1985), and this could possibly be due to the large excess of stannous and stannic ions and DMSA present in the radiopharmaceutical preparations. The excess reagents are not removed in the kit

formulations, and it is well known that tin forms complexes with DMSA presumably through the carboxylate group (Ikeda et al., 1976). Tin forms complexes with other carboxylic acids such as tartrate and oxalate. It is reasonable to assume that tin can coordinate with DMSA, ^{99m}Tc(V)DMSA and ^{188}Re(V)DMSA, which may thus affect chemical reactivity or biodistribution. Since rhenium will not complex with the carboxylates, the acid groups are available to bridge with tin. To address this problem, we have developed a new synthetic route for preparation of Re(V)DMSA via the extremely useful $ReOCl_3(PPh_3)_2$ intermediate (where PPh_3 is triphenyl phosphine). Preparation of carrier-free ^{188}Re(V)DMSA in the absence of tin ions is possible by using $^{188}ReOCl_3(PPh_3)_2$ in a simple one step procedure from generator-produced $^{188}ReO_4^-$.

EXPERIMENTAL

Materials and Methods

Stannous chloride and meso-dimercaptosuccinic acid (Aldrich Chemical Company) were used as purchased. A commercial DMSA kit (Amersham International) was used for the radiopharmaceutical preparation. The $ReOCl_3(PPh_3)_2$ was prepared by a literature method (Chatt and Rowe, 1962). Infrared spectra were obtained with Nujol mulls on a Nicolet spectrometer. The ^{1}H and ^{13}C were obtained with a Varian Gemini 200 instrument with TMS as internal reference. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Two systems were used for thin layer chromatography (TLC) analysis of radioactive and non-radioactive complexes. In system I, silica gel plates were developed with n-butanol:acetic acid:water (3:2:3), and in system II, silica gel plates were developed with acetone. The TLC plates were scanned for radioactivity (gamma) with the use of a model HY-3 Technical Associates Multichannel TLC Scanner. A calibrated 50-cm^3 high purity Ge detector (EG&G ORTEC, Oak Ridge, TN) coupled to a AccuSpec PC-based multichannel analyzer (Nuclear Data/Canberra Inc., Meriden, CT) and a Capintec Radioisotope Calibrator model (RC-7) were used for radioactivity measurements. Samples of constant liquid geometry were counted for sufficient duration to provide good counting statistics ($\leq$2% error).

$[NBu_4][ReO(DMSA)_2]$

A slurry of 0.2 grams (0.24 mmol) of $[ReOCl_3(PPh_3)_2]$ in 10 ml of CH_2Cl_2 was stirred in a 50 ml flask while a solution of 0.084 grams (0.48 mmol) of meso-2,3-dimercaptosuccinic acid (DMSA)

in 10 ml ethanol was slowly added. After stirring for 10 min, 5 ml of H_2O was added to the reaction mixture and the orange-colored product was immediately extracted into the aqueous layer. At this point a portion of the aqueous solution was removed, evaporated to dryness under argon, and analyzed by ^1H NMR in D_2O. The tetrabutyl ammonium salt, produced in the following step, is insoluble in water. The aqueous layer was separated from the organic phase and then treated with 0.077 grams (0.24 mmol) of tetrabutyl ammonium bromide in 1 ml. of water. The solution was concentrated to about 1 ml and allowed to stand overnight and the orange-colored microcrystalline $[NBu_4][ReO(DMSA)_2]$ was filtered and dried. Yield 0.158 gm (82%); NMR, see Figure 2. Found: C 35.7%; H 5.5%; N 1.8%. Calcd for $C_{24}H_{44}NO_9S_4Re$: C 35.8%, H 5.5%; N 1.7%.

$[^{188}ReOCl_3(PPh_3)_2]$

A 1 ml portion of $^{188}W/^{188}Re$ generator saline eluent (Callahan et al., 1991) containing 9.4 mCi of $^{188}ReO_4^-$ was placed in a separatory funnel containing 3 ml of CH_2Cl_2. A solution of 10 mg of triphenyl phosphine in 3 ml of conc. HCl was then added, and the funnel capped and shaken for 5 min. The total HCl concentration was 9 M in the separatory funnel (aqueous layer). The CH_2Cl_2 layer was separated and contained 7.3 mCi of the product.

$[^{188}ReO(DMSA)_2]^-$

A 3 ml CH_2Cl_2 solution containing 6.6 mCi of $[^{188}ReOCl_3(PPh_3)_2]$ was placed in a separatory funnel containing 3 mg of DMSA slurried in 3 ml of 10% ethanol in water and the mixture shaken for 5 min. The aqueous layer was separated and contained 5.9 mCi of activity (89%). This layer was passed through an amino (-NH_2) Sep-Pak® prepared by washing with 1 ml of ethanol and 10 ml of 0.01 N HCl. The radioactivity remained on the Sep-Pak® which was then washed with 5 ml of water. The water wash contained no radioactivity. The ^{188}Re(V)DMSA (5.3 mCi) was then eluted from the Sep-Pak® with 2 ml of 0.5 M KOH. An additional 0.3 mCi was eluted with an additional 2 ml of KOH solution. The product was analyzed for purity by TLC silica gel plates stationary phase with acetone as the mobile phase and showed no trace of perrhenate [R_f = 0 for Re(V)DMSA; R_f 0.9 for perrhenate, (ReO_4^-)].

$[^{188}ReO(DMSA)_2]^-$[Sn]

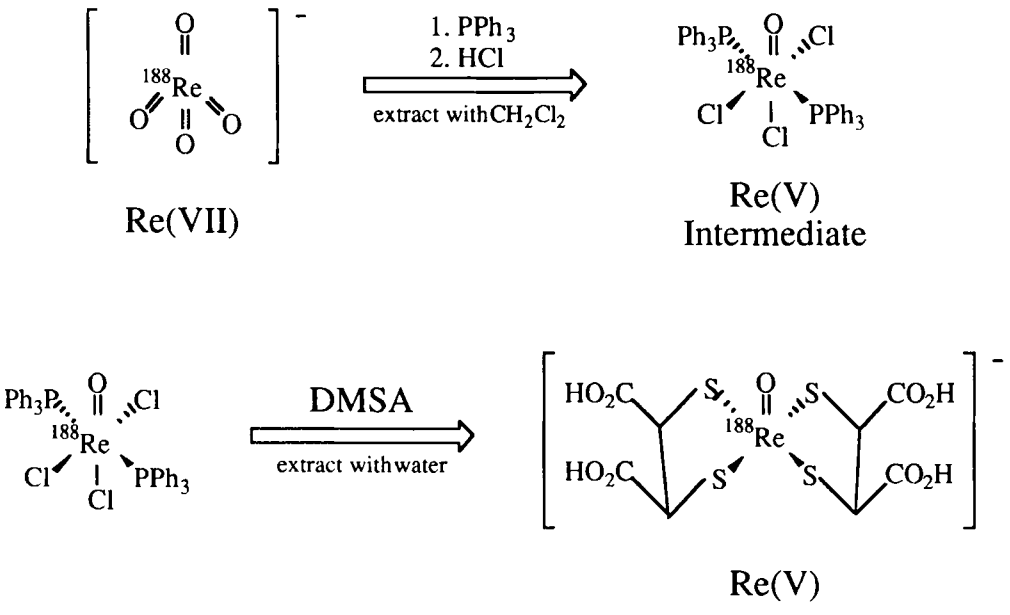
A 4 ml portion of $^{188}W/^{188}Re$ generator eluent containing 6.51 mCi of $^{188}ReO_4^-$ was placed in a 5 ml reactivial that had been charged with 4.0 mg (0.023 mmol) of meso-2,3-dimercaptosuccinic

acid and 16 mg (0.089 mmol) of stannous chloride powder. The vial was capped tightly and placed in a heating block (preheated to 100°C) for 30 minutes. The mixture obtained a faint yellow color during the heating. After cooling, the mixture was analyzed by TLC, which demonstrated the absence of perrhenate. The reaction mixture was drawn into a 10 ml syringe containing 2 ml of 0.01 N HCl. The mixture was then loaded onto a pre-prepared amino Sep-Pak® and washed with 5 ml of water. The orange/yellow color of the product was even more evident when the product was trapped on the Sep-Pak®. The product, 6.20 mCi of ^{188}Re(V)DMSA [Sn], was eluted off the Sep-Pak® with 4 ml of 0.5 N KOH. Yield, 95.2%; only one radioactive component on TLC co-chromatography with the unlabeled standard.

RESULTS AND DISCUSSION

The $ReOCl_3(PPh_3)_2$ is an air stable, readily formed yellow solid that is reactive with many different ligands to form hosts of new complexes containing the oxo, nitrido, and organoimido Re cores (Rouschias, 1974; Fergusson, 1966). This intermediate has been described as being the most important Re(V) compound in rhenium chemistry. The synthesis of $ReOCl_3(PPh_3)_2$ on a preparative scale is best conducted by the procedure of Chatt and co-workers or a modification of their procedures where triphenyl phosphine reacts with perrhenate in an alcoholic or acetic acid solution containing HCl (Chatt and Rowe, 1962). The yield of $ReOCl_3(PPh_3)_2$ is reduced, however, when H_2O is present in any appreciable concentration. This approach is therefore not practical when performing a synthesis of [^{188}$ReOCl_3(PPh_3)_2$] using carrier free $^{188}ReO_4^-$ in saline eluent. An alternate synthesis of [^{188}$ReOCl_3(PPh_3)_2$] is accomplished by the addition of a concentrated HCl solution of triphenyl phosphine to an aqueous perrhenate or perrhenic acid solution as shown in Scheme I (triphenyl phosphine is soluble in concentrated HCl solutions). On a macroscopic scale a problem with this synthesis is the difficult separation of excess triphenyl phosphine from the product.

However, the synthesis of carrier-free [^{188}$ReOCl_3(PPh_3)_2$] is readily accomplished by this simple method since triphenyl phosphine is present in excess and separation from the product is not required if the [^{188}$ReOCl_3(PPh_3)_2$] is being used as a synthetic intermediate. This route works exceptionally well for the synthesis of ^{188}Re(V)DMSA, where the product is extracted into aqueous solution, and therefore separated from the triphenyl phosphine which is insoluble in water. Several



Scheme 1. Reaction of Perrhenate Ion to Form a Reactive Intermediate.

workers have noted that triphenyl phosphine, even in excess, will not reduce ReO_4^- past the Re(V) oxidation state (Rouschias, 1974). However, more basic and smaller phosphines such as diethyl phenyl phosphine, trimethyl phosphine, etc., can reduce ReO_4^- to the Re(III) oxidation state.

Synthesis of the $[^{188}ReOCl_3(PPh_3)_2]$ intermediate is complete within 5 min at room temperature. An important advantage in comparison to the use of stannous ion is that an oxygen-free atmosphere is not required. The compound is rapidly completely extracted into either CH_2Cl_2 or $CHCl_3$. The synthesis requires a significant amount of triphenyl phosphine (5-20 mg give the best results), but the yield of $[^{188}ReOCl_3(PPh_3)_2]$ has been found to be directly dependent upon the total HCl concentration in the reaction mixture. The yield of $[^{188}ReOCl_3(PPh_3)_2]$ can routinely be obtained over 70% when the total HCl concentration is greater than 6 M. When the HCl concentration is greater than 10 M the product yield is >95%. Yields of $[^{188}ReOCl_3(PPh_3)_2]$ in reaction mixtures with lower HCl concentrations can be increased with subsequent extractions by CH_2Cl_2 containing additional triphenyl phosphine. The $ReOCl_3(PPh_3)_2$ product is formed from the reaction of HCl and excess triphenyl phosphine with perrhenate or perrhenic acid at any concentration. The carrier-free $^{188}ReOCl_3(PPh_3)_2$ has the same mobility as the authentic $ReOCl_3(PPh_3)_2$ on TLC analysis, and

ultraviolet analysis of the carrier-added synthesis of the product is in agreement with the spectrum observed for $ReOCl_3(PPh_3)_2$. One note of caution on the synthesis of $^{188}ReOCl_3(PPh_3)_2$ and $ReOCl_3(PPh_3)_2$ is that the CH_2Cl_2 or $CHCl_3$ extract must not be washed with water to remove minute amounts of HCl, since water hydrolyzes the product to form $ReO(OH)Cl_2(PPh_3)_2$ and other products which are soluble in the aqueous phase (Chatt et al., 1962).

The use of CH_2Cl_2 or $CHCl_3$ as the solvent for extracting the $^{188}ReOCl_3(PPh_3)_2$ intermediate is crucial. The solvents provide for excellent extraction of the intermediate in a clean and timely manner, and being more dense than water allows easy drainage from separatory funnels. The subsequent use of the CH_2Cl_2 or $CHCl_3$ solvents as the reaction media for the $ReOCl_3(PPh_3)_2$ intermediate is also crucial for the reaction with DMSA to proceed quickly and at room temperature. The unique beneficial behavior of CH_2Cl_2 and $CHCl_3$ as solvents for $ReOCl_3(PPh_3)_2$ in ligand substitution reactions where the $[Re=O]^{3+}$ core is maintained has been described (Parker et al., 1988). This behavior is probably due to the fact that the triphenyl phosphine ligand is readily soluble in these solvents and thus facilitates ligand lability. When a triphenyl phosphine ligand is lost from $ReOCl_3(PPh_3)_2$, a coordinatively unsaturated and highly reactive 5-coordinate complex is formed in equilibrium with the parent complex. The reactive 5-coordinate complex reacts with any available added ligands such as the chelating ligand DMSA in a stepwise fashion to give the final product after loss of the monodentate chloride and triphenyl phosphine ligands.

On a preparative scale, the $[ReOCl_3(PPh_3)_2]$ can be used to synthesize Re(V)DMSA by a simple exchange reaction as described in the experimental section. The orange-colored product extracted into the aqueous layer is the $[ReO(DMSA)_2]^-$ anion, but there is no cationic counter ion except for H_3O^+. If the solution is concentrated and a saturated aqueous solution of tetrabutylammonium bromide then added, the $[NBu_4]$ $[ReO(DMSA)_2]$ product precipitates out immediately as the yellow solid. This compound is identical by IR, UV, TLC, and elemental analysis with the compound reported using Sn^{2+} as the reducing agent (Bisunadan et al., 1991). The aqueous extract of Re(V)DMSA, before addition of tetra n-butyl ammonium bromide, yields a crystalline orange product when taken to dryness. As mentioned above, the cationic counter ion for Re(V)DMSA in this system is the hydronium ion, so we formulated the orange crystalline product as $[H_3O][ReO(DMSA)_2]$. The IR spectrum of this compound shows a (Re=O) stretching frequency at 948 cm^{-1} which is shifted significantly from the [Re=O] stretching frequency of

$[NBu_4][ReO(DMSA)_2]$ which is at 974 cm^{-1}. This evidence would support a structure for $[H_3O][ReO(DMSA)_2]$ where the H_3O^+ is coordinated *trans* to the oxo group in the solid thus lowering the (Re=O) stretching frequency. We have no evidence for a strong coordination of H_2O or H_3O^+ for Re(V)DMSA in solution, however, it may be reasonable to assume that a weak coordination of H_2O or H_3O^+ with Re(V)DMSA in equilibrium with the free five coordinate complex occurs in aqueous solution.

The choice of solvent and counter ion for Re(V)DMSA significantly affects the ^1H NMR spectrum of the complex. The ^1H NMR spectrum in D_2O of Re(V)DMSA prepared by phosphine reduction appears more well resolved than that observed previously (Blower et. al., 1991) for Re(V)DMSA prepared by stannous reduction. Significantly, the ^1H NMR spectrum shown in Figure 1 for Re(V)DMSA prepared by phosphine reduction is essentially identical to that observed for Tc(V)DMSA which was prepared by dithionite reduction of pertechnetate (Bisunadan et al., 1991).

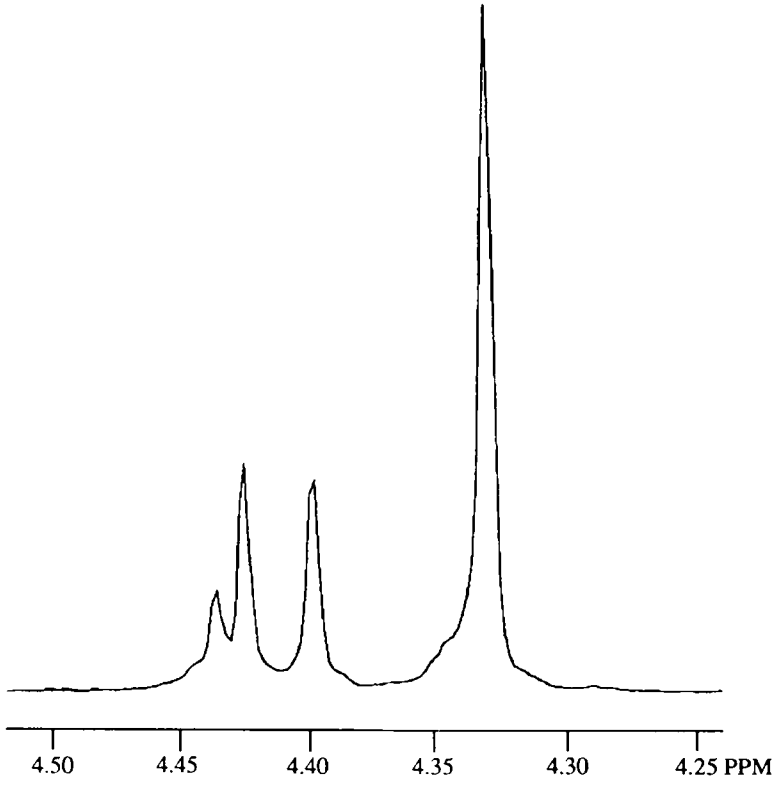


Figure 1. ^1H NMR Spectrum of $ReO(DMSA)_2^-$ in D_2O.

The ^{1}H NMR spectrum of Re(V)DMSA shown in Figure 1, like that of Tc(V)DMSA, suggests the presence of three isomers for the square pyramidal metal complex. The major dominant isomer is clearly one of the *syn* isomers which are symmetrical. The two singlets at 4.39 and 4.42 ppm are assigned to the anti-isomer. The ^{1}H NMR of $[NBu_4][ReO(DMSA)_2]$ in D_6 DMSO prepared by phosphine reduction of perrhenate is shown in Figure 2. The spectrum again is better resolved than that of Bisunadan et al., for the same complex, who report only the resonances at 3.90 and 3.88 ppm in varying ratio. We also observed these resonances, and the spectrum also shows resonances at 3.83 and 3.79 indicating the presence of all three isomers. The resonances are, however, in reverse order in relative chemical shift than those seen in Figure 2 for $[H_3O][ReO(DMSA)_2]$ in D_2O. This suggests weak coordination of either or both H_2O and DMSO with the five coordinate Re(V)DMSA complexion solution.

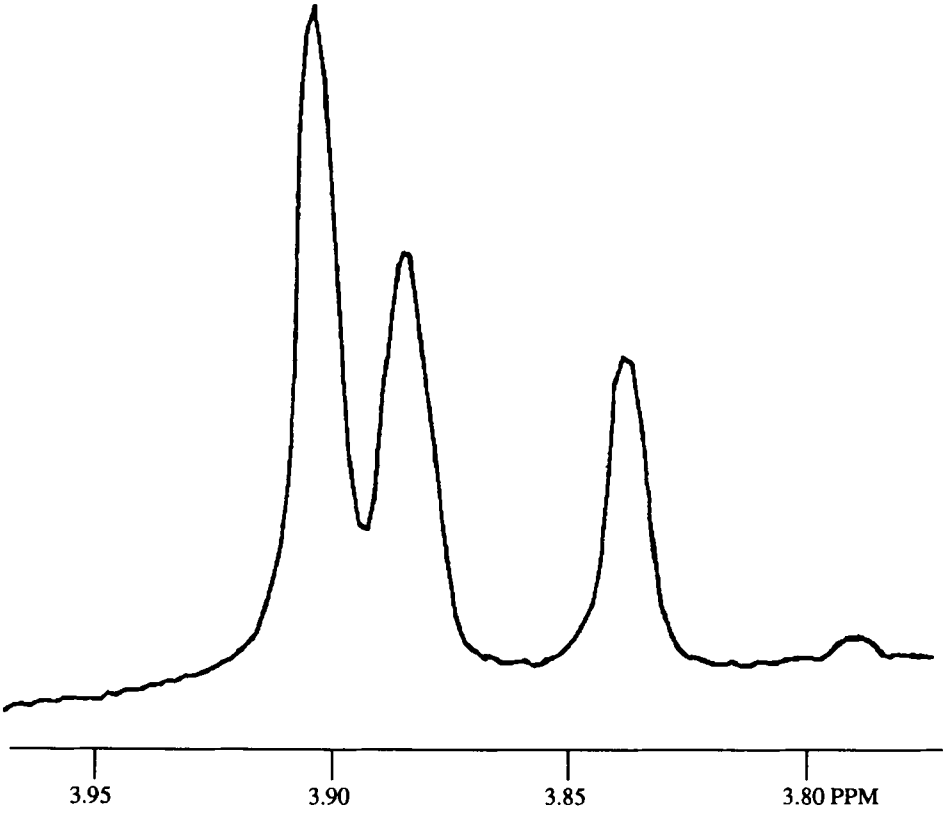


Figure 2. ^{1}H NMR Spectrum of $ReO(DMSA)_2^-$ in DMSO-d_6.

The synthesis of the ^{188}Re(V)DMSA complex using excess stannous ions as reductant proceeds easily, but the yellow color that develops suggests the presence of coordinating tin in the products. When the synthesis is performed using less than 1 mg of stannous chloride the color is difficult to see even when the product is captured on the amino Sep-Pak®, however, preliminary atomic absorption tests for Sn show that the ion is present after Sep-Pak® cleanup. Reaction of Sn^{+2} with DMSA produces a yellow-orange uncharacterizable solid (Ikeda et al., 1976), and by coincidence the Re(V)DMSA complex is also orange colored. However, on the carrier-free scale with ^{188}Re, the color of Re compounds would of course be undetectable. The TLC analysis of ^{188}Re(V)DMSA was performed using both systems I and II. As reported previously, the complex remains at the origin using acetone as the mobile phase (system II) but travels on the plate using the more polar system I (Bisunadan et al., 1991). Comparisons were made with authentic Re(V)DMSA and showed the compounds were identical. We have found no acceptable TLC procedure for the $ReOCl_3(PPh_3)_2$ species using silica gel, reverse phase, or paper as the stationary phase. In all attempts the compound is either insoluble and immobile, or if it is soluble and mobile (such as with CH_2Cl_2) then it decomposes as it moves up the TLC plate. This behavior underlies the reactive nature of the compound.

CONCLUSIONS

We have prepared and characterized the Re(V)DMSA complex using the convenient $ReOCl_3(PPh_3)_2$ reactive intermediate. The material is identical to Re(V)DMSA prepared from previously published methods. We have also developed a synthesis of the ^{188}Re(V)DMSA radiopharmaceutical via the facile synthesis of $^{188}ReOCl_3(PPh_3)_2$. The facile synthesis of $^{188}ReOCl_3(PPh_3)_2$ from generator produced $^{188}ReO_4^-$ is rapid and proceeds to completion at room temperature, but is dependent upon high concentrations of aqueous HCl and also an organic solvent such as CH_2Cl_2 for extraction. Due to the useful nature of the reactive complex $^{188}ReOCl_3(PPh_3)_2$, we believe that it may be very important in the synthesis of new therapeutic radiopharmaceuticals for use in nuclear medicine procedures.

ACKNOWLEDGEMENTS

Research at ORNL is supported by the Office of Health and Environmental Research, U.S. Department of Energy, under contract DE-AC05-84OR21400 with Martin Marietta Energy Systems, Inc. The authors thank Ms. L. Ailey for typing the manuscript.

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