CHEMISTRY OF TECHNETIUM RADIOPHARMACEUTICALS.

I. EXPLORATION OF THE TISSUE DISTRIBUTION AND OXIDATION STATE CONSEQUENCES OF TECHNETIUM (IV) IN Tc-Sn-GLUCONATE AND Tc-Sn-EHDP USING CARRIER ^{99}Tc

Peter Hambright, James McRae, Peter E. Valk, Alan J. Bearden, and Barbara A. Shipley

*Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley, California
and Howard University, Washington, D.C.*

The distribution in rats of the renal agent Tc-Sn-gluconate using both ^{99m}Tc and carrier amounts of ^{99}Tc was similar. The same behavior was shown with the bone agent Tc-Sn-EHDP. The radiopharmaceutical consequences of the observed Tc(IV) oxidation state in these systems are explored.

The validity of using ^{99}Tc to study the chemistry of ^{99m}Tc radiopharmaceuticals in part depends on demonstrating that addition of carrier ^{99}Tc does not alter the biologic behavior of ^{99m}Tc compounds. Once this is established, insight into radiopharmaceutical behavior can be gained from classical kinetic and thermodynamic work on ^{99}Tc adducts. To this end, we report a study on the tissue distribution in rats of the renal agent Tc-Sn-gluconate (1,2) and the bone agent Tc-Sn-EHDP (3) using both ^{99m}Tc and carrier ^{99}Tc. The oxidation state of ^{99}Tc in these systems was determined. The chemical consequences of the oxidation level are discussed.

METHODS

Concentrations of ^{99}TcO$_4^-$ were measured spectrophotometrically using a molar extinction coefficient of 5,690 for the absorption bands at 40.32 and 40.98 kK (4). Gluconate was pure (> 99%) sodium gluconate (BHD Chemicals, Ltd.). The Sn(II) from SnCl$_2$·2H$_2$O was analyzed by iodometric titrations (5); K$_2$TcCl$_6$ and K$_2$TcBr$_6$ were synthesized (6).

For the oxidation state determinations, Sn(II) was dissolved in a tenfold molar excess of gluconate or EHDP at pH 5.5, filtered (0.22-micron Millipore), and added in excess to measured quantities (0.6–1.5 mg) of ^{99}TcO$_4^-$. The resulting solutions were titrated with I$_2$ to determine excess Sn(II).

The total amount of Sn(II) added was found by titration in the absence of pertechnetate. The number of equivalents of Sn(II) that react with a given weight of ^{99}TcO$_4^-$ in the Sn/TcO$_4^-$/gluconate, Sn/TcO$_4^-$/EHDP, and Sn/TcO$_4^-$ (5.0 M HCl) systems was calculated. With a sufficient excess of ^{99}TcO$_4^-$ to oxidize all of the added Sn(II), the titration endpoint was the same as that found with the starch-I$_2$ control itself in the absence of Sn(II). This indicates that I$_2$ does not rapidly oxidize the reduced technetium species. In addition, acidic solutions of Tc(IV) in the form of TcCl$_6^{2-}$ were not oxidized by I$_2$ nor further reduced by added Sn(II).

Throughout this section tin refers to SnCl$_2$·2H$_2$O. In all of the in vivo distribution studies, 4.0-ml stock solutions were prepared using different amounts of tin, ^{99}TcO$_4^-$, EHDP, and gluconate, and the same amount (300 μCi) of ^{99m}TcO$_4^-$. One-half milliliter of the agent was injected into the tail vein of male Sprague-Dawley rats weighing approximately 200 gm. The rats were sacrificed under ether anesthesia by exsanguination from the abdominal aorta. The organs, blood, and carcass were counted. Tissue distributions are shown in Tables 1 and 2.

Technetium-Sn-gluconate is normally made (1,2) by mixing 1 ml 10% calcium gluconate (stabilized with 0.25% calcium d-saccharate), 1 ml of a fresh solution containing 0.1 mg of tin in distilled water, and 2 ml ^{99m}TcO$_4^-$. In distilled water tin oxidizes by less than 2% after standing in air for 2 hr. An equivalent quantity of tin in saline rapidly precipitates. The organ distributions of normal gluconate reagent is the same as shown in Experiment 1 (Table 1) where 1 ml of 10% sodium gluconate, 1 ml of 0.2

TABLE 1. DISTRIBUTION OF ^{99m}Tc ACTIVITY IN RATS GIVEN Tc-Sn-GLUCONATE

| Experiment (No.) | Reagent mixing order* | Percent of injected dose—average of four rats | | | | | | |
		Kidneys†	Liver†	Stomach†	Bowel†	1 cc Blood	1 cc Plasma	Carcass‡
1	G-Sn-^{99m}Tc	20.0	0.72	0.054	3.99	0.083	0.12	7.0
2	G-Sn-^{99m}Tc-^{99}Tc	21.0	0.78	0.14	4.67	0.013	0.11	7.0
3	G-Sn-(^{99m}Tc + ^{99}Tc)	10.7	3.7	8.5	5.8	0.70	0.93	—
4‖	Sn-^{99m}Tc-G	10.9	14.1	0.26	3.18	0.47	1.18	18.5
5‖	Sn-^{99m}Tc-G	13.7	3.8	0.23	4.39	0.39	0.64	9.2
6§	^{99m}Tc	1.02	4.25	17.1	7.16	0.53	—	—

* G is sodium gluconate, Sn is SnCl₂·2H₂O, ^{99m}Tc is ^{99m}TcO₄⁻, and ^{99}Tc is ^{99}TcO₄⁻. The amounts are given in the Methods section. The rats were sacrificed 1 hr after injection. Representative standard deviations for Experiments 1 and 2 are kidneys ± 1.2, liver ± 0.12, stomach ± 0.04, bowel ± 0.35, blood ± 0.021, plasma ± 0.038, and carcass ± 1.8.
† Percent of injected dose per total organ.
‡ Carcass represents skin, muscle, and skeleton.
‖ Experiments 4 and 5 are the distributions immediately and 5 min after preparation, and the distribution from the mixture in Experiment 4 after the reagent stood 1 hr was identical to Experiment 1.
§ Experiment 6 is data from Ref. 8.

TABLE 2. DISTRIBUTION OF ^{99m}Tc ACTIVITY IN RATS GIVEN Tc-Sn-EHDP

| Experiment | Reagent mixing order* | Percent of injected dose—average of four rats | | | | | | | |
		Femur†	Kidneys†	Liver†	Stomach†	Bowel†	1 cc Blood	1 cc Plasma	Carcass‡
A	E-Sn-^{99m}Tc	1.63	0.67	0.34	0.06	0.47	0.041	0.063	38.0
B	E-Sn-^{99m}Tc-^{99}Tc	1.78	0.75	0.30	0.17	0.63	0.044	0.071	40.0
C‖	E-Sn-^{99m}Tc-G	1.15	3.80	0.17	0.04	1.16	0.032	0.048	22.0

* E is EHDP, Sn is SnCl₂·2H₂O, ^{99m}Tc is ^{99m}TcO₄⁻, ^{99}Tc is ^{99}TcO₄⁻, and G is sodium gluconate. The amounts are given in the Methods section. Rats were sacrificed at 2 hr after injection. Representative standard deviations for Experiments 1 and 2 are femur ± 0.22, kidney ± 0.17, liver ± 0.10, stomach ± 0.08, blood ± 0.004, plasma ± 0.006, carcass ± 3, and bowel ± 0.17.
† Percent of injected dose per total organ.
‡ Carcass represents skin, muscle, and skeleton.
‖ The distribution of mixture C at preparation is the same as in Experiment A. Experiment C is the distribution after the reagent stood for 3 hr.

mg of tin dissolved in 10% sodium gluconate, 1 ml ^{99m}TcO₄⁻, and 1 ml of saline were used. In Experiment 2, 1 ml containing 0.2 mg ^{99}TcO₄⁻ was substituted for the 1 ml of saline. For Experiment 3, the ^{99m}TcO₄⁻ and 0.2 mg ^{99}TcO₄⁻ were premixed prior to adding to the tin-gluconate solution. In another series of experiments, the mixing order of the reagent was 1 ml tin (0.1 mg), 1 ml ^{99m}TcO₄⁻, 1 ml 10% sodium gluconate, and 1 ml saline. This preparation was injected immediately (Experiment 4), after 5 min (Experiment 5), and after standing for 1 hr (same results as Experiment 1). Similar trends were observed in comparable experiments.

Table 2 gives the data for the Tc-Sn-EHDP studies. This reagent (Experiment A) is made (3) by mixing 1 ml of EHDP in distilled water (0.5 mg of EHDP), 1 ml of tin (0.1 mg), 1 ml of ^{99m}TcO₄⁻, and 1 ml of saline. In Experiment B, 1 ml of distilled water containing 0.2 mg ^{99}TcO₄⁻ is substituted for the 1 ml of saline. To determine how rapidly gluconate replaced EHDP from ^{99m}Tc-Sn-EHDP, 1 ml of 0.4 M sodium gluconate was added in place of saline. This was injected immediately (same results as Experiment A), and after standing for 3 hr (Experiment C).

The Tc-Sn-gluconate and EHDP preparations with and without ^{99}TcO₄⁻ were flushed either with N₂ or O₂ for 1 hr and then injected. Solutions of TcCl₆²⁻ and TcBr₆²⁻ were made in 5.0 M perchloric acid, and 5.0 M hydrochloric acid at 27°C. Their absorption spectra were observed initially and after 1 hr.

RESULTS

When reduced to Tc(VI), Tc(V), Tc(IV), or Tc(III), ^{99}TcO₄⁻ would have an equivalent weight of 163, 81.5, 54.3, or 40.75 gm, respectively. From an average of ten determinations each, the equivalent weight of pertechnetate was found to be 52.9 ± 1.7 gm for Sn/TcO₄⁻/gluconate, 55.3 ± 2.0 gm for Sn/TcO₄⁻/EHDP, and 53.1 ± 1.5 gm for Sn/TcO₄⁻ (5.0 M HCl). The results are essentially the same and correspond to a final Tc(IV) oxidation state. The acid Sn/TcO₄⁻ data agree with previous measurements (7).

By definition, 1 meq of a reducing agent will reduce 1 meq of an oxidizing agent. Therefore 112.8

mg of the reductant $SnCl_2 \cdot 2H_2O$ (tin) is equivalent to 54.3 mg of the oxidant $^{99}TcO_4^-$ or 1 mg of tin will reduce 0.48 mg of $^{99}TcO_4^-$. In Table 1, Experiment 1 shows the tissue distributions of ^{99m}Tc-Sn-gluconate from a solution containing 0.2 mg tin and $\sim 1 \times 10^{-7}$ mg $^{99m}TcO_4^-$ (~ 300 μCi). In Experiment 2, $^{99m}TcO_4^-$ is first completely reduced to form ^{99m}Tc-Sn-gluconate. Excess $^{99}TcO_4^-$ (0.2 mg) is then added to react with the 0.2 mg tin to form approximately 0.1 mg of ^{99}Tc as ^{99}Tc-Sn-gluconate, leaving approximately 0.1 mg of $^{99}TcO_4^-$. The tissue distributions in Experiments 1 and 2 are essentially the same, and thus carrier ^{99m}Tc-Sn-gluconate in ratios of 10^6–1 does not influence the distribution of ^{99m}Tc-Sn-gluconate. Intermediate amounts of $^{99}TcO_4^-$, which left a fraction of tin unreduced, did not alter the tissue distribution.

In Experiment 3, 0.2 mg $^{99}TcO_4^-$ and $^{99m}TcO_4^-$ were premixed before reduction by 0.2 mg of tin in the presence of gluconate. The conditions are such that approximately 50% of the ^{99}Tc will be reduced, and thus half of the ^{99m}Tc activity should appear as ^{99m}Tc-Sn-gluconate, and half should remain as $^{99m}TcO_4^-$. With $^{99m}TcO_4^-$ alone, the stomach activity (8) is approximately 17%/organ/dose ($\sim 1\%$ kidney), whereas for ^{99m}Tc-Sn-gluconate alone, the kidney value is approximately 20% ($\sim 0.1\%$ in the stomach). Experiment 3 shows that the expected distribution is observed, with approximately 10.6% found in the kidneys and approximately 8.5% in the stomach. It is noted that, under the conditions of Experiment 3, a final Tc(V) oxidation state would produce 70% kidney agent, rather than the 50% expected and found, based on Tc(IV).

The bone agent Tc-Sn-EHDP results are in Table 2. Experiment A gives the organ distributions with 0.1 mg tin and approximately 10^{-7} mg $^{99m}TcO_4^-$ solutions and these are essentially the same as shown in Experiment B, where approximately 0.05 mg ^{99}Tc is formed as ^{99}Tc-Sn-EHDP by oxidation of the tin with excess $^{99}TcO_4^-$. Thus addition of a 10^5-fold excess of carrier agent does not significantly change the ^{99m}Tc-Sn-EHDP distribution.

When a preformed ^{99m}Tc-Sn-EHDP solution was made 0.1 M in sodium gluconate, the transformation of the bone agent into a kidney agent was slow. There was no detectable reaction at t = 0 (same results as Experiment A), and after 3 hr (Experiment C), the percent of the injected dose found in the kidney had increased from 0.7 to 4% while the femur activity had decreased from 1.6 to 1.1%.

Molecular O_2 and N_2 were bubbled through the bone and kidney agents for 1 hr both in the presence and absence of $^{99}TcO_4^-$. The resulting tissue distributions were, within experimental error, the same

as found in air as given by the first two experiments in Tables 1 and 2. Therefore, even in the absence of Sn(II), O_2 does not rapidly oxidize the Tc(IV) imaging agents. The "Tc-Sn-ligand" terminology is descriptive of the method of preparation and not necessarily the composition of the product. The fact that the agents are stable when all of the Sn(II) is oxidized [Sn^{2+} could be coordinated to gluconate or $(Cl_3Sn:)^-$ could be bound to Tc(IV)] implies that any tin present in the agent is Sn(IV).

The absorption spectra of $TcCl_6^{2-}$ and $TcBr_6^{2-}$ are readily distinguishable (6,9,10). After 1 hr at 27°C, there was no spectrophotometric evidence for the transformation of $TcCl_6^{2-}$ into the hexabromo compound in 5 M HBr, or the production of $TcCl_6^{2-}$ from $TcBr_6^{2-}$ dissolved in 5.0 M HCl, or self-dissociation in 5.0 M perchloric acid.

DISCUSSION

Workers focusing on the behavior of ^{99}Tc complexes (11,12) usually qualify their conclusions by stating that the chemistry at macro-^{99}Tc levels may be different than that shown by micro-^{99m}Tc. Our data on the renal agent Tc-Sn-gluconate and bone agent Tc-Sn-EHDP show that essentially the same organ distributions are found in rats at both the carrier and carrier-free levels. This implies that observations on the chemical properties of ^{99}Tc adducts are probably applicable to the physical-chemical behavior of ^{99m}Tc radiopharmaceuticals in these two systems.

It has been suggested, heretofore by indirect criteria (11–13), that the oxidation state of technetium in many radiopharmaceuticals is Tc(IV). We have directly established the Tc(IV) oxidation state in the gluconate and EHDP systems. Hence the occurrence of Tc(IV) may be fairly general for the types of oxygen-donor, hard base ligands used in many imaging studies when TcO_4^- is reduced by Sn(II).

The Tc(IV) complexes are usually surrounded by six ligands in an octahedral environment (14,15) and have three unpaired 4d electrons, i.e., a d^3 state. Transition metal ions in d^3 (Cr^{3+}) or low-spin d^6 (Co^{3+}) configurations are generally substitution inert (16). For example, the room temperature half-life for substitution of water molecules between the bulk solvent and those coordinated in substitution inert $[Cr^{III} (H_2O)_6]^{3+}$ is greater than 30 hr. The corresponding rate for substitution labile Cr^{2+} (a d^4 configuration) is approximately 10^{-8} sec. Although the exact magnitudes of the rate constants for a given ion cannot be calculated, several theories (16) lead to a relative lability order for spin-paired complexes of d^1, $d^2 \gg d^5 > d^4 > d^3 > d^6$. Second-row transition metals are usually low spin (16).For the oxidation states of technetium, the order would be Tc(VI),

Tc(V) >> Tc(II) > Tc(III) > Tc(IV) > Tc(I). The "inertness" of an oxidation state also depends on the ligand type and configuration about the metal center: [Cr^{III} (H$_2$O$_6$)]$^{3+}$ is more inert (16) than [Cr^{III} (H$_2$O)$_2$(OH)$_2$]$^+$ while five coordinate Cr(III) porphyrins (17) are labile.

Once a Tc(IV) complex forms with a ligand (or ligands) L (such as EHDP, gluconate ....) to produce an imaging agent [Tc(IV)-L], the loss of this ligand or the substitution of a different ligand into the coordination shell of [Tc(IV)-L] should be slow, relative to the same reaction in a different oxidation state. This assumed substitution inertness of Tc(IV) predicts that [Tc(IV)-L] should remain a discrete entity for long periods of time following injection and subsequent dilution in the body. This dilution would rapidly dissociate any labile metal-ligand Tc(V) or Tc(VI) complexes into their equilibrium components, and even with moderate stability constants, a 1:5,000 dilution would favor the uncomplexed ion, whose imaging properties should be independent of the nature of L. In essence, the fact that the renal- and bone-imaging agents work, that is, they go to specific organs depending on the identity of L, argues that the (Tc-L) bond is intact upon dilution, which is consistent with substitution inert Tc(IV) behavior.

The chemistry of ^{99}Tc(IV) complexes in solution is difficult to study, primarily due to the instability of the complexes at neutral pH with respect to hydrolysis into insoluble technetium oxide (14,15). However, TcCl$_6$$^{2-}$ and TcBr$_6$$^{2-}$ [both Tc(IV)] are stable in acids and we have shown them to be substitution inert. There is no rapid exchange between the bromides in TcBr$_6$$^{2-}$ and the chloride from HCl under mild conditions. Boiling a solution of TcCl$_6$$^{2-}$ in HBr (more vigorous conditions) leads to the formation of TcBr$_6$$^{2-}$ (6). The renal agent ^{99m}Tc-Sn-EHDP is also substitution inert; after standing for 3 hr in 0.1 M sodium gluconate, less than 50% of the coordinated EHDP is replaced by gluconate to form ^{99m}Tc-Sn-gluconate.

The renal and bone agents are stable to oxidation by molecular O$_2$ for periods of at least 1 hr. This is consistent with observation (18) on the chemistry of TcCl$_6$$^{2-}$, which cannot be oxidized with platinum electrodes or Ce(IV) whereas the hydrolysis product, TcO$_2$, is readily oxidizable to TcO$_4$$^-$. Thus oxidation of radiopharmaceuticals to ^{99m}TcO$_4$$^-$ probably occurs by initial dissociation of the stable chelate into TcO$_2$ rather than by a direct interaction of the chelate with O$_2$.

Although no firm statements on the mechanisms of ligand binding to technetium can be made without detailed equilibrium and fast reaction kinetic studies, some general speculations are in order. If the

electron transfer reaction between Sn(II) and TcO$_4$$^-$ to form Tc(IV) is faster than ligand substitution into the coordination shells of the intermediate oxidation states, ligand addition will only involve Tc(IV). We have demonstrated that, while the same renal agent forms either by the mixing order ^{99m}TcO$_4$$^-$-Sn-gluconate, or gluconate-Sn-^{99m}TcO$_4$$^-$, the former reaction, which could initially produce Tc(IV), is much slower than the latter. This could indicate that the gluconate-Sn-^{99m}TcO$_4$$^-$ sequence does not directly produce Tc(IV) since the Tc(IV) reactivity is too low to account for the observed rate of renal agent formation. Alternatively, the Tc(IV) may be in a colloidal form and unavailable for rapid reaction with gluconate.

A mechanism consistent with our data could involve the rapid reduction of TcO$_4$$^-$ by Sn(II) to labile Tc(VI) or Tc(V). The Tc(VII) → Tc(VI) transformation should be very fast since the conversion TcO$_4$$^-$ → TcO$_4$$^=$ involves electron addition without a large change in TcO bond distances. The Tc(VI) → Tc(V) or Tc(V) → Tc(IV) reactions may be slower due to the possibility of the metal changing from a four-coordinate tetrahedral to a six-ligated configuration. If a ligand were bound to the technetium in a higher labile state, the subsequent electron transfer forming Tc(IV) would trap this group in the substitution inert Tc(IV) coordination shell to produce [Tc(IV)-L]. This process could occur by an adjacent electron transfer mechanism where the Sn(II) is coordinated to one oxygen and the Tc(VI) or Tc(V) bound to the other oxygen of the -COO$^-$ group in gluconate (19). Electrons would flow from the Sn(II) through the conjugated carboxylic acid group into the adjacent technetium, thus oxidizing Sn(II) and bringing the carboxylic acid group into the inert coordination shell of the newly formed Tc(IV). Many examples of adjacent attack have been demonstrated in inorganic systems (20). Alternatively, the disproportionations (14,15) of ligated Tc(VI) or Tc(V) into Tc(IV) and Tc(VII) could lead to labeling in the final reduced state. Another possibility is that inert Tc(IV) is always in rapid equilibrium with a trace amount of labile Tc(V) in which ligand addition occurs through the Tc(V) state. Similar suggestions (16) have been advanced for Co(III)-Co(II) systems. It is noted that thiocyanate addition to Tc(IV) forms both [Tc(IV)(SCN)$_6$]$^{2-}$ and [Tc(V)(SCN)$_6$]$^-$ which can exist as a redox couple (13,20).

Irrespective of the exact reduction mechanism, ligand addition must compete with the rate of the transformation of soluble, uncomplexed Tc(IV) into the insoluble, rather unreactive TcO$_2$ (21). Therefore, at low ligand concentrations where the soluble

Tc(IV)/L reaction is slow, the prereduction of TcO_4^- by Sn(II) to form soluble Tc(IV) followed by ligand addition should produce less specific initial technetium labeling than if Sn(II) is pre-equilibrated with the ligand prior to the addition of pertechnetate. In the former case, Tc(IV) has more time to precipitate and this "improper" order of reagent mixing produces significant amounts of liver-imaging impurities in both the Tc-Sn-gluconate and Tc-Sn-EHDP systems (3). To favor ligand binding to tin, which also prevents precipitation (22) of polynuclear chloro complexes, such as $[(Sn_3)(OH)_4]^{2+}$, the molar ratio of ligand to tin should be much greater than one. Thus pre-equilibration of the reductant and ligand using high ligand and low reductant concentrations should favor maximal labeling efficiency and hydrolytic stability.

The behavior of chromium radiopharmaceuticals can be analyzed by similar oxidation state considerations. Direct ligand addition to Cr(III) is generally limited by the slow rate of water loss from this substitution inert ion (16). A different mechanism may be followed in the Sn(II)-chromate [Cr(VI)] labeling of platelets (23) and the labeling of red cells (24) by the presumed enzymatic reduction of $^{51}CrO_4^{2-}$. The reduction of Cr(VI) could involve ligand substitution into the labile Cr(VI), Cr(V), Cr(IV), or Cr(II) coordination shells and the retention of these groups upon final Cr(III), (d^3) formation.

Bench-top studies with $^{99m}TcO_4^-$ are valuable in the preliminary elucidation of Tc-radiopharmaceutical properties. For example, the reaction of Sn(II) with $^{99}TcO_4^-$ in neutral solution rapidly forms a precipitate of TcO_2. The addition of $^{99}TcO_4^-$ to Sn(II) solutions of gluconate or EHDP produce clear, colored solutions whose acid stability ranges are readily determined by the color changes with pH. Thus the observable reactions of ^{99}Tc with ligands provide some insight into their potentialities as imaging agents.

ACKNOWLEDGMENTS

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