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Recent Advances in Technetium Chemistry: Bridging Inorganic Chemistry and Nuclear Medicine

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Recent research that bridges the apparently disparate disciplines of inorganic chemistry and nuclear medicine is described.

INTRODUCTION

Nuclear medicine is an enormously useful discipline wherein diagnostic and prognostic information is obtained by an essentially noninvasive (i.e., nonsurgical) procedure. In the practice of this discipline some chemical form of a gamma ray emitting isotope is administered to a patient (usually by intravenous injection) with the goal of having the isotope localize in a specific organ. Subsequent visualization of the organ with a gamma ray camera provides information about both the structure and functioning of the organ. This information, especially with respect to organ function, is difficult or impossible to obtain by other means. Diagnostic nuclear medicine thus provides a unique way of both assessing disease states and monitoring the effects of treatment, and therefore has become a very widely practiced discipline.

The chemical form of the isotope injected into a patient determines the mechanism and site of *in vivo* organ localization. This overall chemical form of the isotope is referred to as the radiopharmaceutical, and thus radiopharmaceuticals are the focus of this review. Of special concern to a chemical discussion of radiopharmaceuticals is the fact

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that these agents are almost always prepared and injected at very low concentrations, since it is the radioactivity of the radiopharmaceutical rather than its chemical mass which affects organ visualization. Thus, the effects of concentration of radioisotopes on the synthesis and efficacy of radiopharmaceuticals will be a continuing theme throughout this review.

Technetium-99m, where "m" stands for "metastable," is the preeminent isotope utilized in diagnostic nuclear medicine[1] for reasons which have to do with (a) the nuclear properties of ^{99m}Tc and ^{99}Tc, (b) the availability of ^{99m}Tc via an inexpensive generator system, and (c) the diverse chemistry of this Group VII transition metal which allows ^{99m}Tc to be converted into a variety of chemical forms that can then be used to image different organs. The first two reasons are discussed briefly. The third permeates this review and provides the underlying rationale for bridging inorganic chemistry and nuclear medicine.

NUCLEAR PROPERTIES OF ^{99m}Tc and ^{99}Tc

The nuclear properties of ^{99m}Tc are ideally suited to the requirements of diagnostic nuclear medicine. Technetium-99m emits a monoenergetic gamma ray, with no accompanying alpha or beta particle emission which would increase radiation dose to the patient. The energy of this gamma ray, 141 KeV, is sufficiently high to permit it to escape from even deeply seated organs, but also sufficiently low to allow collimation by lead and efficient trapping by 2″ thick NaI(Tl) crystals for scintillation counting. The physical half-life of ^{99m}Tc is only 6 hours, and thus relatively large doses (20–30 mCi) can be administered to patients without generating an unacceptably high radiation burden. Technetium-99m decays to ^{99}Tc which, with a half-life of 2.1 $\times$ 10^5 years, is effectively nonradioactive, and therefore does not add to the radiation burden of the patient (*vide infra*; 20 mCi of ^{99m}Tc decays to (20 mCi)(6.0 h)/(2.1 $\times$ 10^5 y) = 6 $\times$ 10^{-8} mCi of ^{99}Tc).

The gamma emission and short half-life of ^{99m}Tc make it impractical to use this isotope in macroscopic amounts for classical chemical procedures. However, the long-lived ^{99}Tc emits only a weak beta particle (0.29 MeV), is readily available from commercial sources at $\sim$ \$55/g and is therefore well suited for chemical investigations

employing macroscopic amounts of material. In milligram amounts ^{99}Tc does not present a serious health hazard since common laboratory materials provide adequate shielding. Bremsstrahlung is not a significant problem due to the low energy of the beta particle emission. Of course, normal radiation safety procedures must be used at all times to prevent contamination and inadvertent ingestion, and this places some practical limitations on the techniques that can be used to characterize and investigate coordination complexes of technetium-99.

THE ^{99}Mo/^{99m}Tc GENERATOR

Technetium-99m is readily available to all clinics and hospitals via the ^{99}Mo/^{99m}Tc generator.[2] This generator, developed at Brookhaven National Laboratory during the late 1950s, obviates the need for an onsite reactor or particle accelerator and has thus been the main reason for the dramatic growth of nuclear medicine over the last two decades. The ^{99}Mo/^{99m}Tc generator is based on the following ^{99}Mo $\rightarrow$ ^{99m}Tc $\rightarrow$ ^{99}Tc decay scheme, coupled with simple ion exchange separation of the -1 charged daughter and granddaughter pertechnetates from the -2 charged parent molybdate:

$$^{99}\left[MoO_4\right]^{2-} \xrightarrow[67h]{\beta^-} {}^{99m}TcO_4^- \xrightarrow[6h]{\gamma} {}^{99}TcO_4^-$$

$[^{99}MoO_4]^{2-}$, prepared either by neutron irradiation of ^{98}Mo or by fission of uranium, is adsorbed onto a sterile alumina column placed in a shielded container, and the resulting generator is shipped to the point of use. The 6 hour half-life of ^{99m}Tc is too short to allow shipment over long distances, but the 67 hour half-life of ^{99}Mo is long enough to allow transport to even the most remote institutions. Continuous beta decay of $[^{99}MoO_4]^{2-}$ yields $[^{99m}TcO_4]^-$ which then undergoes relatively rapid gamma decay to $[^{99}TcO_4]^-$. Both forms of pertechnetate build up on the column and then are simply eluted from the column with 0.15 M NaCl, leaving the parent molybdate behind. Thus, aqueous solutions of $[^{99m}TcO_4]^-$ (with $[^{99}TcO_4]^-$) are readily available at very low cost to even the smallest and most isolated nuclear medicine clinics.

From the perspective of inorganic chemistry there are two salient features of clinically used $^{99}Mo/^{99m}Tc$ generators. (1) These generators define the starting material for all ^{99m}Tc radiopharmaceutical preparations to be an aqueous NaCl solution of $[^{99m}TcO_4]^-$ and $[^{99}TcO_4]^-$. (2) Because of the nature of the $^{99}Mo \rightarrow {}^{99m}Tc \rightarrow {}^{99}Tc$ decay scheme the concentrations of $[^{99m}TcO_4]^-$ and $[^{99}TcO_4]^-$ in this starting material are variable. The total technetium concentration in generator eluents depends on several parameters, especially on the time elapsed since the generator was last eluted. Recent experimental measurements[3,4] show that the total concentration of $[TcO_4]^-$ (as both ^{99m}Tc and ^{99}Tc) in generator eluents is in the range 10^{-8}–10^{-6} M. Because of the presence of the naturally occurring ^{99}Tc granddaughter, which functions as an innate carrier, these concentrations are much greater than those usually encountered in carrier free radiochemical solutions. Thus ^{99m}Tc derived from $^{99}Mo/^{99m}Tc$ generators is referred to as "no carrier added" to indicate the presence of variable amounts of ^{99}Tc. The relatively high concentrations of chemical technetium present in generator eluents enhances the possibility that inorganic chemistry developed using milligram amounts of ^{99}Tc can be directly transferred to the no carrier added ^{99m}Tc level encountered in radiopharmaceutical syntheses.

SYNTHESES OF ^{99m}Tc RADIOPHARMACEUTICALS

Many ^{99m}Tc imaging agents are already widely used in hospitals around the world, but there is also a great need for the development of new classes of ^{99m}Tc radiopharmaceuticals to image organs and disease states that are either inaccessible or only marginally accessible to current agents. This development will require enhanced knowledge of the inorganic chemistry of the relatively unstudied element technetium and very astute applications of this chemistry, since the synthesis of ^{99m}Tc complexes for use as radiopharmaceuticals must be conducted under incredibly stringent restraints. (1) The synthesis of new agents, be it either by the generation or interconversion of technetium complexes, must be conducted at very low concentrations of technetium, usually in the order of 10^{-8}–10^{-6} M (*vide infra*). (2) The synthesis must start with pertechnetate [i.e., technetium(VII) as TcO_4^-] in aqueous saline, since this is the chemical form of ^{99m}Tc

available in the clinic (*vide infra*). (3) The entire synthesis must be conducted within 1 or 2 hours, and preferably within 30 minutes, since ^{99m}Tc decays with a physical half-life of 6 hours. (4) The synthesis must proceed to a radiochemical yield of greater than 95%, since the injection of a mixture of radioactive agents decreases organ specificity, needlessly increases the radiation dose to the patient and makes the resulting images much more difficult to interpret. (5) Any reagents used in excess must be nontoxic and suitable for intravenous injection. (6) The synthesis must be conducted in a matrix suitable for intravenous injection. This is usually aqueous saline, although small concentrations of ethanol are also acceptable. (7) The synthesis must be conducted under sterile, pyrogen free conditions. This condition virtually eliminates any sort of chromatographic purification of the desired ^{99m}Tc radiopharmaceutical. (8) Finally, the synthetic procedure must be simple enough to be performed by a technician untrained in the techniques of inorganic chemistry, behind sufficient shielding to protect him from the ^{99m}Tc radiation. The procedure should preferably be based on an "instant kit" formulation wherein aqueous $^{99m}TcO_4^-$ is simply added to a sterile, sealed vial of lyophilized reagents and then either briefly heated or allowed to stand at room temperature to produce the desired radiopharmaceutical.

The synthesis of new, well defined technetium complexes under the above constraints presents unique challenges in inorganic chemistry. Especially challenging is the requirement of conducting and controlling transition metal chemistry at the 10^{-8}–10^{6} M concentration level. However, these challenges are being successfully met, partially through the use of new experimental techniques that give chemical and structural information at the 10^{-8}–10^{-6} M concentration level. In this article we discuss some of the recent developments in this area, emphasizing those methodologies and techniques that appear to be best suited for bridging inorganic chemistry to nuclear medicine.

BRIDGING INORGANIC CHEMISTRY AND NUCLEAR MEDICINE[1,5,6]

Technetium-99m radiopharmaceuticals are nothing more than coordination complexes of technetium prepared under the very dilute

conditions dictated by the use of no carrier added ^{99m}Tc. Therefore, a logical route to the development of new classes of ^{99m}Tc radiopharmaceuticals involves the synthesis and characterization of new technetium complexes using macroscopic amounts of ^{99}Tc, followed by the translation of this chemistry from the macroscopic ^{99}Tc world of inorganic chemistry to the microscopic ^{99m}Tc milieu of nuclear medicine. More specifically, this bridging of inorganic chemistry to nuclear medicine requires translating preparative chemistry performed at technitium concentrations of 10^{-4}–10^{-2} M to the 10^{-8}–10^{-6} M concentration level encountered in generator eluants.

The ease with which preparative chemistry performed using macroscopic amounts of ^{99}Tc can be translated to the no carrier added ^{99m}Tc level depends on the kinetics and mechanism of the reaction steps that control product formation. In the simplest case, if the crucial step in generating a technetium complex is zero-order in technetium concentration, then the rate at which product is formed will be independent of technetium under all conditions and translation will be trivial. However, it is much more likely for the crucial step to be first-order in technetium concentration. In this case, as long as the concentrations of the other reagents that are necessary for the crucial step are all much greater than the concentration of technetium, a pseudo first-order situation obtains and the product complex will appear by first-order kinetics:

$$\frac{d(\text{Product})}{dt} = \frac{-d(\text{Tc})}{dt} = k(\text{Tc}) .$$

Simple integration gives the time necessary for 99% of reaction to occur (t_{99}) as

$$t_{99} = \frac{4.6}{k} ,$$

which is independent of technetium concentration. Thus, when other reagents are present in great excess, if the crucial product forming step is first-order in technetium concentration then macroscopic ^{99}Tc chemistry should readily translate to the no carrier added ^{99m}Tc level. A more difficult situation occurs if the crucial step in product formation is second-order (or higher order) in technetium concentration.

This can arise if the crucial step involves dimer (or polymer) formation, or disproportionation of an unstable oxidation state. Given a rate low of the form

$$\frac{d(\text{Product})}{dt} = \frac{-d(\text{Tc})}{dt} = k'(\text{Tc})^2 ,$$

simple integration leads to

$$t_{99} = \frac{99}{k'(\text{Tc})} .$$

In this case the time required for 99% of reaction to occur *is* a function of technetium concentration, and chemistry developed at the 10^{-4}–10^{-2} M level with ^{99}Tc is not expected to translate readily to the 10^{-8}–10^{-6} M level encountered with no carrier added ^{99m}Tc solutions. For example, when a bimolecular, second-order process competes with a pseudo first-order process the bimolecular process will be favored at high technetium concentrations and will be less competitive at low technetium concentrations. To illustrate this point, assume that during the synthesis of a technetium radiopharmaceutical, initial reduction of pertechnetate leads rapidly to the technetium(VI) intermediate $[TcO_4]^{2-}$. Technetium(VI) is unstable with respect to disproportionation to pertechnetate and insoluble TcO_2; the second-order rate constant governing bimolecular decay of technetium(VI) in neutral aqueous solution has recently been determined[7] to be 10^8 $M^{-1}s^{-1}$. Further assume that this undesired disproportionation of technetium(VI) competes with heteronuclear reduction of technetium(VI) to yield the radiopharmaceutical product this desired reduction being affected by a reagent present at 0.10 M concentration reacting at a specific rate of 50 $M^{-1}s^{-1}$. Under these conditions t_{99} for production of the radiopharmaceutical is always 1 s, whereas t_{99} for disproportionation varies with technetium concentration. At [Tc] $= 10^{-8}$ M, t_{99} for disproportionation is 100 s and thus about 99% of the reaction proceeds to yield the desired radiopharmaceutical. At [Tc] $= 10^{-6}$ M, t_{99} for disproportionation is 1 s and thus only about 50% of the reaction yields the desired product. If [Tc] is raised to 10^{-4} M by addition of ^{99}Tc, only about 1% of the reaction proceeds along the desired path and about 99% of the reaction proceeds by

disproportionation. Thus, in this hypothetical situation it would be impossible to mimic the ^{99m}Tc chemistry conducted at 10^{-8} M by using ^{99}Tc at 10^{-4} M. Also, interestingly, from this example it is seen that the range of technetium concentrations encountered in ^{99}Mo/^{99m}Tc generator eluants (i.e., 10^{-8}–10^{-6} M) is sufficiently large so that in second-order situations significant rate effects can be expected to result from natural variations in technetium concentration. Such effects are indeed observed in the ^{99m}Tc-diphosphonate bone imaging agents.

SELECTED CHEMICAL SYSTEMS

During the past five years the inorganic chemistry of several technetium systems has been investigated in some detail with the goal of developing new or improving old ^{99m}Tc radiopharmaceuticals. Several of these systems are discussed here in the context of bridging inorganic chemistry and nuclear medicine by translating chemistries conducted in disparate concentration regimes.

Heart Imaging Agents

The development of a ^{99m}Tc heart imaging agent has been a long standing goal of diagnostic nuclear medicine. On the basis of the known heart uptake of both inorganic or organic cations, it was proposed that cationic complexes of ^{99m}Tc might accumulate in the heart to an extent sufficient to provide gamma ray images.[8-10] In 1981 it was first demonstrated that the robust, cationic technetium(III) complexes *trans*$[Tc(diars)_2Cl_2]^+$, *trans*$[Tc(diars)_2Br_2]^+$ and *trans*$[Tc(dmpe)_2Cl_2]^+$ [where diars represents *o*-phenylenebis(dimethylarsine) and dmpe represents 1,2-bis(dimethylphosphino)ethane] all provide acceptable heart images in mongrel dogs.[6-8] These demonstrations involved first the synthesis and characterization of the complexes using macroscopic amounts of ^{99}Tc, employing single crystal x-ray structural analysis as the definitive characterization technique, followed by translation of the preparative chemistry to the no carrier added ^{99m}Tc level. This translation proved to be very direct for the synthesis of the diars complexes, providing a prime example of a synthetic system controlled by a first-order reaction. For example, when pertechnetate is added to excess diars ligand in HBr, the

trans$[Tc(diars)_2Br_2]^+$ complex is generated in greater than 95% yield under no carrier added conditions where the total pertechnetate concentration is less than 10^{-8} M, and under carrier added conditions where the total pertechnetate concentration is greater than 10^{-1} M. Thus, as long as the diars ligand and the HBr are present in great excess a variation of more than 10^7 in pertechnetate concentration does not affect the rate or yield of the synthetic eaction.

Translation of the synthesis of the dmpe complex *trans*$[Tc(dmpe)_2Cl_2]^+$ was not as direct as the translation for the diars complexes, but once the chemistry of the dmpe system was clarified, all the crucial reaction steps proved again to be first-order. Starting with an aqueous solution of pertechnetate, reaction with excess dmpe under carefully controlled conditions allows generation of any one of three different cationic complexes, each complex being attainable in greater than 95% yield under either carrier added or no carrier added conditions.[11,12]

$$TcO_4^- + \text{dmpe} \xrightarrow[\text{NaOH}]{25°C} \textit{trans}Tc^{V}(\text{dmpe})_2O_2^+ ,$$

$$TcO_4^- + \text{dmpe} \xrightarrow[\text{HCl}]{120°C} \textit{trans}Tc^{III}(\text{dmpe})_2Cl_2^+ ,$$

$$TcO_4^- + \text{dmpe} \xrightarrow[\text{NaOH}]{140°C} Tc^{I}(\text{dmpe})_3^+ .$$

These three complexes can also be prepared successively, starting with Tc(VII), proceeding through the Tc(V) and Tc(III) intermediates and finally yielding the Tc(I) species. This Tc(VII) → Tc(V) → Tc(III) → Tc(I) series nicely illustrates the variety of oxidation states available to technetium and their successive generation by the action of a two-equivalent reductant (dmpe).

Using macroscopic amounts of ^{99}Tc, the Tc(V) complex *trans*$[Tc(dmpe)_2O_2]^+$ and the Tc(III) complex *trans*$[Tc(dmpe)_2Cl_2]^+$ have been characterized by single crystal x-ray structural analyses, while the Tc(I) complex $[Tc(dmpe)_3]^+$ has been characterized by a combination of ^{31}P-NMR, ^{99}Tc NMR, and ^{99}Tc-EXAFS (Extended X-Ray Absorption Fine Structure) experiments.[9,12] Using no carrier added ^{99m}Tc, the Tc(III) and Tc(I) complexes have been shown to image the heart of a variety of animal species, while the Tc(V) complex

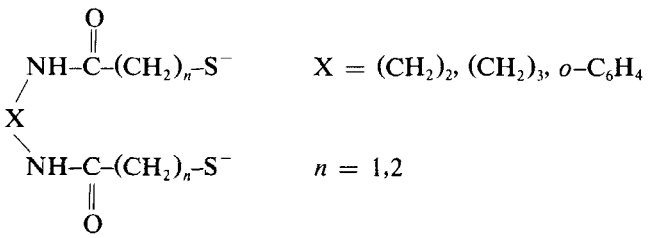
does not exhibit heart uptake in any species investigated.[13,14] The no carrier added Tc(III) and Tc(I) complexes have also been evaluated as heart imaging agents in humans, but while the human heart is indeed visualized by these species, the results are not yet of clinical utility. Further progress in this area will depend upon the development of animal models and *in vitro* tests which accurately predict the biodistributions of new agents in humans.

In an analogous system, Davison and co-workers[15,16] have used dithionite to reduce pertechnetate in the presence of isonitrile ligands to yield the cationic Tc(I) complexes $[Tc(CNR)_6]^+$. This reaction can be accomplished on both the carrier added and no carrier added levels, and thus again the crucial step in the synthesis appears to be a first-order process. Using macroscopic amounts of ^{99}Tc, these complexes have been characterized by a variety of techniques including field desorption mass spectrometry. Using no carrier added ^{99m}Tc, many of these isonitrile complexes provide good images of dog hearts, the best images being obtained with R = *sec*-butyl. No evaluation of these complexes as heart imaging agents in humans has yet been reported.

These recent studies on ^{99m}Tc heart imaging agents provide an elegant example of how inorganic chemistry can be bridged to nuclear medicine. It is very rare in the annals of nuclear medicine for even the composition of potential ^{99m}Tc radiopharmaceuticals to be known with certainty, but in this area of research both the compositions and exact structures of the cationic complexes providing the gamma ray images are known definitively. The field has now progressed to the point where ORTEP drawings of specific ^{99}Tc complexes and the gamma ray images resulting from injection of these complexes when prepared with no carrier added ^{99m}Tc can be displayed side by side. With this sort of detailed structure-activity data being rapidly accumulated, it is only a matter of time until a clinically useful cationic ^{99m}Tc complex will be developed for heart imaging.

It is also intriguing to note that the technetium(III) and technetium(I) complexes currently being investigated as heart imaging agents are essentially organometallic species. Given that nuclear medicine requires agents that are compatible with aqueous media and that ^{99m}Tc radiopharmaceuticals have historically been thought to contain technetium in higher oxidation states, it would have been hard to predict even three years ago that the organometallic chemistry of low-valence technetium centers would be successfully applied to the search for a ^{99m}Tc heart imaging agent.

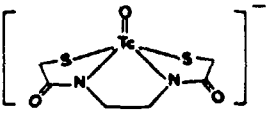
Davison and co-workers have recently reported[17] on another system in which well characterized ^{99}Tc complexes have been translated into ^{99m}Tc radiopharmaceuticals for evaluation in humans. In 1981 these researchers reported[18] the synthesis of a series of tetradentate, dimercaptoamide ligands specifically designed to chelate to the technetium(V) TcO^{3+} core. A schematic representation of these ligands is shown below:



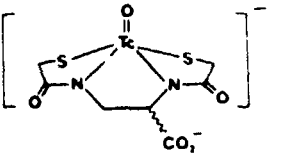
The prototype complex with $X = (CH_2)_2$ and $n = 1$ has been given the acronym Tc-DADS.[19] The acronym DADS is also used to refer to all the DiAmidoDiSulfur ligands of the original series, resulting in occasional confusion. The technetium(V)-DADS system was chosen for three main reasons: (a) Synthetic routes to technetium(V) complexes were already available on both the macroscopic ^{99}Tc and no carrier added ^{99m}Tc levels[1,20] and the resulting coordination compounds were both reasonably robust and well characterized. (b) It was likely that these tetradentate N_2S_2 ligands would form kinetically inert complexes of sufficient *in vivo* stability for use as radiopharmaceuticals. (c) Since the DADS ligand system is amenable to variations in both the size of the chelate rings and in the nature of the substituents attached to these chelate rings, systematic structure–activity relationships should be readily determinable.

Using macroscopic amounts of ^{99}Tc, the prototype complex ^{99}Tc-DADS was prepared and characterized by single crystal x-ray structural analysis, as well as by field desorption mass spectrometry.[17] As expected, the four donor atoms of the tetradentate ligand occupy the basal plane of a square pyramid, the yl oxygen atom of the TcO^{3+} core comprising the apex of this pyramid. Dithionite reduction of pertechnetate in the presence of excess ligand quantitatively yields the Tc-DADS complex whether the pertechnetate is present as 10^{-5} M $^{99}TcO_4^-$ or as no carrier added $^{99m}TcO_4^-$. Thus, the crucial step in this synthesis again appears to be a first-order process.

Routine biological screening of the various ^{99m}Tc complexes of the DADS ligand series showed that, not surprisingly, ^{99m}Tc-DADS is excreted predominantly through the renal system. ^{99m}Tc-DADS and the carboxylate derivative ^{99m}Tc-CO_2-DADS have been evaluated as potential renal agents in both animal models and humans.[19–21]



Tc-DADS

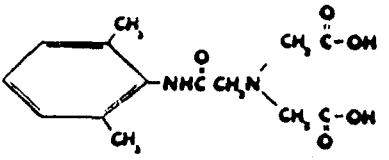


Tc-CO_2-DADS

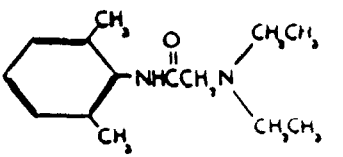
One of the epimers of the carboxylate derivative appears to have superior characteristics for this type of imaging study but the other has inferior biological properties. Current research is being directed towards modifying either the ligand or the synthetic conditions to produce only the efficacious epimer.

Hepatobiliary Imaging Agents

A less well defined system that has received recent attention involves the dimethyl-HIDA ligand originally developed by Loberg and co-workers[22,23] as a lidocaine analog.



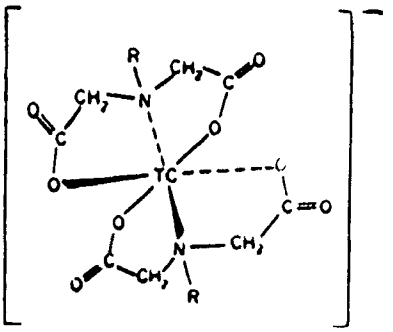
Dimethyl-HIDA



Lidocaine

However, not surprisingly, after complexation to technetium the resulting ^{99m}Tc-HIDA agent does not accumulate in the heart as does lidocaine but rather is rapidly excreted through the hepatobiliary system. This serendipitous discovery has led to a new generation of HIDA derivatives which are currently being marketed and clinically used as efficacious hepatobiliary imaging agents.

Despite the widespread use of these agents there is still considerable debate as to the exact chemical structure of the Tc-HIDA complexes. Loberg and Fields[23] originally formulated Tc-dimethyl-HIDA as an anionic, bis(chelate), complex of Tc(III), i.e.,



and this formulation is supported by recent FABMS (Fast Atom Bombardment Mass Spectrometry) evidence obtained by Davison and co-workers.[24] However, this formulation is unlikely on the basis that the aminodiacetate ligands do not have sufficient backbonding character to stabilize the Tc(III) oxidation state, and has been further thrown into doubt by recent HPLC (High Performance Liquid Chromatography) analyses. Fritzberg and Lewis[25] have shown that contrary to the original report, [24] ^{99m}Tc-dimethyl-HIDA consists of two components which can be separated by HPLC and that these components can be interconverted by variations in pH and chloride concentration. Moreover, HPLC studies on a variety of 2,6-disubstituted HIDA systems[26] show that the preparative chemistry and product distributions of these ^{99m}Tc-HIDA agents become increasingly complex as the size of the ortho substituents increases. These observations strongly imply the presence of a labile coordination site on the technetium center and indicate that the single complex formulation proposed by Loberg and Fields[24] is not sufficient to completely describe the chemistry of the Tc-HIDA systems.

The Tc-HIDA radiopharmaceuticals are synthesized by stannous ion reduction of pertechnetate in the presence of excess HIDA ligand. HPLC analyses of no carrier added ^{99m}Tc-HIDA preparations and carrier added ^{99}Tc-HIDA preparations show that the total concentration of technetium strongly affects the number and distribution of product complexes,[24,27] implying the presence of dimeric or oligomeric species in the radiopharmaceutical mixture. Thus, in this system it appears that the synthetic reaction is *not* controlled solely by a single, first-order process, but rather that higher order processes contribute to the product distribution.

Bone Imaging Agents

The least defined system to be discussed in this section is comprised of skeletal imaging agents which are prepared by reduction of pertechnetate in the presence of excess diphosphonate ligand. As shown below, the disphosphonates are structurally related to pyrophosphate, a central carbon atom joining two $-PO_3^{2-}$ groups.

$O_3P-O-PO_3^{4-}$	$O_3P-CH_2-PO_3^{4-}$	$O_3P-C(CH_3)(OH)-PO_3^{4-}$
	MDP	HEDP
pyrophosphate	methylene diphosphonate	1-hydroxyethylidene diphosphonate

These ^{99m}Tc skeletal imaging agents are very widely used, over one million patient doses being administered each year primarily for the early diagnosis of metastatic cancer to bone. However, almost nothing at all is known about the composition or nature of these agents.

The inorganic chemistry of the skeletal imaging agents ultimately resides in (a) the ability of the diphosphonate ligands to bridge metal ions, and (b) the high affinity of the diphosphonate ligands for calcium even after they are coordinated to a metal center such as technetium.[28] Point (a) is nicely illustrated by Figure 1 which shows how MDP functions as a bridge between two technetium centers in the $[Tc(MDP)(OH)^-]_n$ polymer.[29] Point (b) has been amply documented by recent measurements[28] on the model system

$$(en)_2Co(DiP) + Ca^{2+} = (en)_2Co(DiP)Ca^+ ,$$

where DiP represents a bidentate, chelated, diphosphonate ligand. The equilibrium constants governing this reaction are very large, ranging from 10^3–10^6 M^{-1} (25°C, pH 10, I = 0.10 M), the exact value being dependent on the nature of the diphosphonate ligand. These observations strongly support the obvious mechanism of action of skeletal imaging agents, i.e., the technetium-diphosphonate complexes accumulate on bone via binding of the coordinated diphosphonate to calcium in the bone matrix.

The ability of diphosphonate ligands to bridge metal centers is the basis for the tendency of these ligands to form polymeric metal complexes. In turn, the polymeric nature of diphosphonate complexes

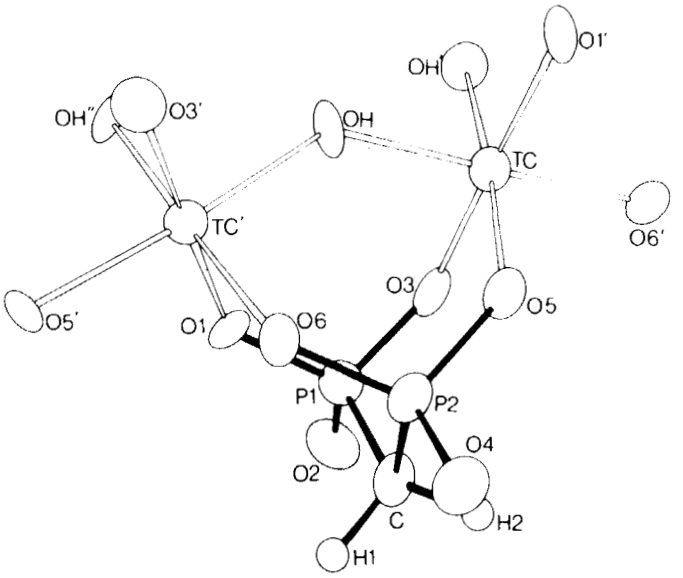


FIGURE 1 Perspective view of a portion of the $[Tc(MDP)(OH)^-]_n$ polymer showing a MDP ligand bridging two technetium centers. Reproduced from Ref. 29 with permission.

severely complicates the synthetic chemistry of technetium-diphosphonate radiopharmaceuticals. For example, Figure 2 shows an HPLC analysis of a ^{99m}Tc-HEDP radiopharmaceutical prepared by $NaBH_4$ reduction of no carrier added $[^{99m}TcO_4]^-$ in the presence of excess HEDP while Figure 3 shows the corresponding chromatogram resulting from an analogous preparation using 3 mM $[^{99}TcO_4]^-$. Comparison of these figures dramatically illustrates that this synthesis is very sensitive to technetium concentration, the numbers and distributions of product complexes increasing drastically as ^{99}Tc carrier is added.[30] Thus, this synthetic reaction appears to be governed by a second or higher order process, and for skeletal imaging agents no carrier added chemistry *cannot* be readily translated to carrier added chemistry.

The effects of total technetium concentration on ^{99m}Tc-diphosphonate radiopharmaceuticals can even be observed within the 10^{-8}–10^{-6}M range of technetium concentrations encountered in the eluants of ^{99}Mo/^{99m}Tc generators. In both clinical studies and controlled animal studies it has been shown that a 16-fold variation in tech-

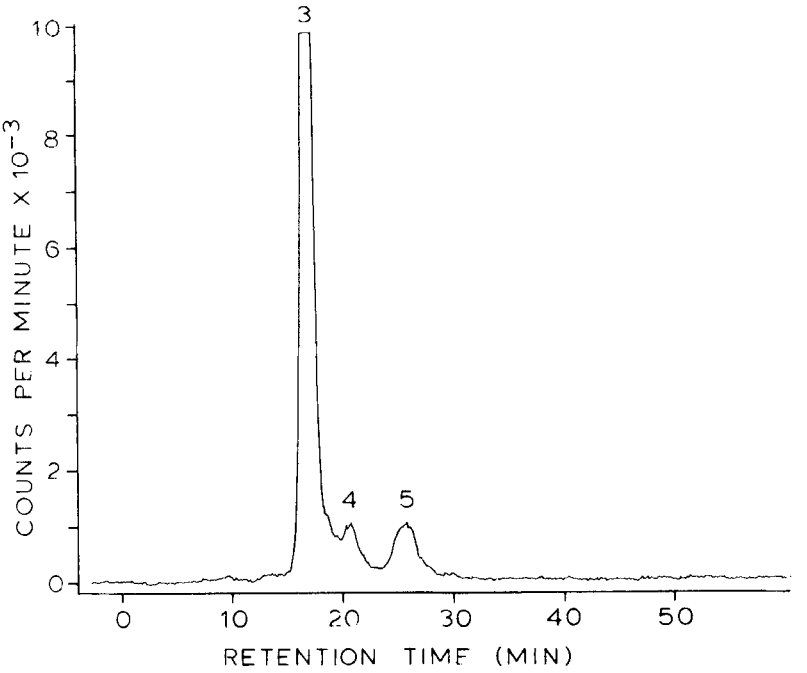


FIGURE 2 HPLC analysis of no carrier added ^{99m}Tc-HEDP complex prepared by $NaBH_4$ reduction of $[^{99m}TcO_4]^-$ in the presence of excess HEDP ligand. Radiometric detection of ^{99m}Tc is shown on the *y* axis. Reproduced from Ref. 30 with permission.

netium concentration in no carrier added ^{99m}Tc-diphosphonate radiopharmaceuticals dramatically affects the biodistributions and the resulting gamma ray images of these agents.[31]

Ligand Exchange Syntheses

All ^{99m}Tc radiopharmaceuticals except pertechnetate itself are generated by reduction of $[^{99m}TcO_4]^-$ in the presence of excess ligand. The mechanisms of these redox syntheses are still totally obscure. However, there have very recently appeared reports of syntheses effected by substitution rather than redox reactions; these routes appear more amenable to mechanistic analysis and eventual control. For example, Volkert *et al.*[32] report that reaction of 10^{-4} M cyclam with the no carrier added technetium(V) complex ^{99m}Tc-DTPA (cyclam = 1,4,8,11-tetraazacyclotetradecane; DTPA = diethylenetria-

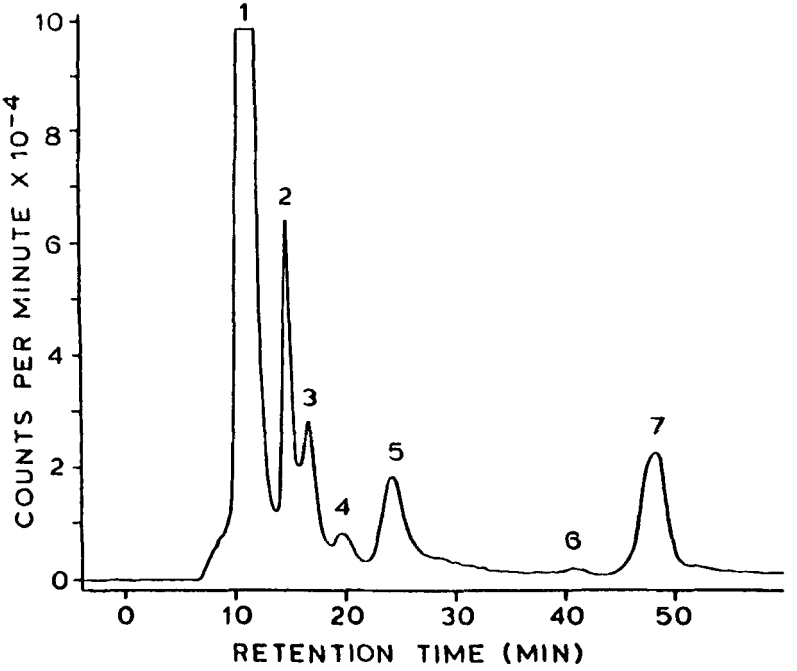
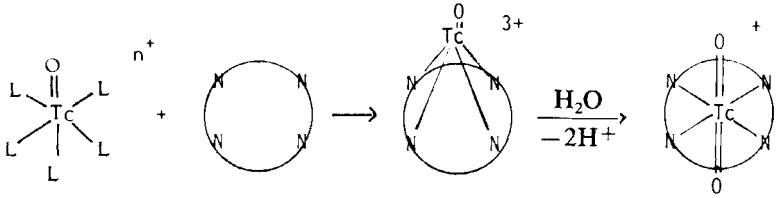


FIGURE 3 HPLC analysis of carrier added ^{99m}Tc-HEDP complex prepared as described in Figure 1 except with the addition of 3 mM $[^{99}TcO_4]^-$. Reproduced from Ref. 30 with ermission.

minepentaacetic acid) quantitatively yields the structurally characterized[33] technetium(V) complex *trans*$[Tc(O)_2(cyclam)]^+$ in less than 30 minutes. From the equations presented earlier for a pseudo first-order process, since t_{99} is less than 30 minutes, the second-order rate constant governing insertion of Tc(V) into the cyclam ring must be greater than 20 $M^{-1}s^{-1}$ at ambient temperature. This is a remarkably rapid specific rate for a reaction involving exchange of polydentate ligands coupled with insertion of a metal center into a macrocyclic ligand. While the detailed mechanism of this reaction is still unclear, the facility of the overall process can be explained on the basis of the recently elucidated structural chemistry of technetium(V) cores.[34] Several complexes containing the dioxo *trans*TcO_2^+ and the monooxo TcO^{3+} technetium(V) cores have been structurally characterized,[16,34] and recently reported crystal structures document the existence of the intermediate oxo(hydroxo) *trans*$Tc(O)(OH)^{2+}$

and oxo(aquo) *trans*$Tc(O)(OH_2)^{3+}$ cores.[12,35] Thus, interconversion of the *trans*TcO_2^+ and TcO^{3+} cores is seen to require nothing more than facile aquation of the *trans*-labilized TcO^{3+} core, followed by rapid deprotonation of the coordinated water molecule. This interconversion provides a ready route for insertion of six-coordinate Tc(V) into a macrocyclic ring via a five-coordinate TcO^{3+} "sitting atop" intermediate.



The sitting atop intermediate can be readily formed from almost any technetium(V) starting material since all of the oxo-Tc(V) cores have a spin-paired, d^2 electronic configuration[16,34] and thus are essentially closed shell systems with no ligand field barrier to substitution in the equatorial coordination sites.

In sum, the technetium(V) oxo cores provide remarkably labile, readily interconvertible centers which can be used to prepare ^{99m}Tc complexes by substitution rather than redox reactions. These substitution routes promise to expand considerably the range of well defined technetium species available for evaluation as radiopharmaceuticals.

SELECTED TECHNIQUES

Many extant ^{99m}Tc radiopharmaceuticals have been prepared and developed by researchers in nuclear medicine using only the very dilute solutions of technetium derived from $^{99}Mo/^{99m}Tc$ generators. The chemistry, structure and even composition of these agents are therefore almost totally unknown. Thus, another aspect of bridging inorganic chemistry and nuclear medicine involves the development and application of experimental techniques that will yield chemical information when applied to 10^{-8}–10^{-6} M solutions of technetium complexes. By the use of such techniques it may be possible to determine the identity and nature of existing ^{99m}Tc radiopharma-

ceuticals, thereby better understanding their mode of action and eventually leading to the development of more efficacious replacements.

The classic technique used to bridge macroscopic ^{99}Tc chemistry to the no carrier added ^{99m}Tc level is chromatography. Several types of chromatographic separations can be effectively employed with both 10^{-4}–10^{-2} M solutions of ^{99}Tc complexes (using a variety of detection modes) and with 10^{-8}–10^{-6} M solutions of no carrier added ^{99m}Tc complexes (using radiometric detection). In a typical application, the chemistry, properties and especially the chromatographic profile of a new technetium complex are first established using milligram amounts of ^{99m}Tc; transfer of the preparative chemistry from the ^{99}Tc level to the ^{99m}Tc level is then assessed chromatographically; finally, preparation of the no carrier added ^{99m}Tc analog is confirmed by concurrence of the chromatographic characteristics of the ^{99}Tc and ^{99m}Tc forms. Using HPLC as the chromatographic technique, this approach has been successfully employed in several systems to rationally transfer inorganic chemistry developed on the macroscopic scale to the microscopic scale of nuclear medicine. Even if a well characterized ^{99}Tc standard complex is not available, chromatography can often yield useful information (e.g., relative lipophilicities or relative formal charges) about no carrier added ^{99m}Tc complexes.

While chromatography can *indirectly* yield structural and chemical information about no carrier added ^{99m}Tc complexes (via analogy to characterized ^{99}Tc complexes) there are at least three other techniques which have the potential of *directly* yielding structural and chemical information on 10^{-8}–10^{-6} M solutions of technetium complexes: mass spectrometry (especially fast atom bombardment and field desorption[17,24]), ^{99}Tc-NMR[36] and electrochemistry.[4] To our knowledge mass spectrometry has not yet been applied to no carrier added ^{99m}Tc solutions, and ^{99}Tc-NMR has only been successfully applied to no carrier added $[^{99m}TcO_4]^-$[37]; however, both techniques have yielded useful results on very dilute carrier added analogs. Electrochemistry, especially when coupled to HPLC, can yield chemical information on solutions as dilute as 10^{-8} M[38]; one report of electrochemical measurements on no carrier added $[^{99m}TcO_4]^-$ has appeared.[4] It is not unreasonable to expect that applications of these three techniques to no carrier added ^{99m}Tc radiopharmaceuticals, both before and after injection, will add greatly to our understanding of the chemistry and biology of these agents.

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