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The Bio-Organometallic Chemistry of Technetium and Rhenium: Fundamental Concepts and Applications for the Design of Molecular Imaging and Therapy Agents

Continuing Education for Nuclear Pharmacists and
Nuclear Medicine Professionals

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STATEMENT OF OBJECTIVES

1. To gain an understanding of the concepts of oxidation states and coordination numbers in the context of the diversity of technetium chemistry

2. To acquire working knowledge of the chemistry involved in making isonitrile complexes of Tc(I). This includes a discussion of the differences in the chemistry of technetium and rhenium

3. To develop an appreciation for the chemistry involved in the preparation of the $[Tc(CO)_3]^+$ core including aspects associated with kit-based formulations

4. To acquire a working knowledge of the coordination chemistry of the $[M(CO)_3]^+$ core through the use of examples from the recent literature

5. To gain insight into the future applications of Tc and Re organometallic in molecular imaging and therapy

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Given its central position in the periodic table, it is not surprising that the chemistry of technetium, the most widely used element in diagnostic medicine, is so diverse. Compounds of technetium exist in oxidation states from -I to +VII consisting of ligands that are as simple as hydride (H^-) to more complex multidentate chelates.

The diversity of the chemistry of technetium is both a dilemma and an opportunity. The fact that the metal can readily change its oxidation and coordination numbers makes it difficult to develop high yielding reactions that result in the formation of only a single compound. This is made even more difficult in radiopharmaceutical chemistry where reactions are performed in water under highly dilute reaction conditions with a specific time limit. From an optimist's perspective however, one can harness the diverse chemistry of technetium and use it judiciously to design novel radiopharmaceuticals including those that can target specific proteins.

The following is a concise overview of the chemistry of technetium focusing on oxidation states that are relevant to nuclear medicine. Although examples of the structural diversity of technetium chemistry are presented, an emphasis is placed on Tc(I) as there is likely to be significant growth in the number of clinically approved compounds derived from this oxidation state in the near future.

INTRODUCTORY CONCEPTS

Oxidation State and Coordination Numbers

Before reviewing the chemistry of technetium it is important to properly define some key concepts. Oxidation state and coordination number are terms used to define the metal atom(s) in a complex. This information enables one to categorize analogous complexes, compare isoelectronic species and monitor the flow of electrons in oxidation and reduction reactions. Isoelectronic, in general terms,

refers to a group of atoms that have the same number of electrons as each other and similar connectivity of atoms.

The formal oxidation state is defined as the hypothetical charge that an atom would have if all bonds to atoms of different elements were completely ionic. The oxidation state does not correspond to the electric charge on the atom; it is simply a useful way to keep track of electrons. The oxidation number of an atom in a compound is determined by the following rules:

a. The oxidation number of an atom in the elemental form is zero

b. The oxidation number of an atom in a simple ionic compound is typically equal to the charge on that atom (with the appropriate sign)

c. The oxidation number of an atom in a covalent compound is equal to the formal charge which is determined by assigning pairs of bonding electrons to the most electronegative element then subtracting the formal number of valence electrons present on the atom of interest from the number of valence electrons that atom has in its elemental form.

The first two rules are simple while the last one requires knowledge of electronegativities and bonding. Conveniently, some elements almost always have the same oxidation state in their compounds which greatly simplifies matters. For instance, group 1 and 2 metals are almost always +1 and +2, respectively while the usual oxidation state for oxygen and hydrogen are normally -2 and +1, respectively. There are notable exceptions but these rules hold for the majority of compounds.

Coordination number is a much simpler concept. It is defined as the number of nearest neighbors to the given atom. For instance, in the complex $[TcCl_6]^{2-}$, the coordination number of technetium atom is 6 as that is the number of chloride ligands bound to the central technetium atom. This complex is therefore referred to as hexacoordinate. Note that the oxidation state of technetium in this complex is (+IV).

Another concept that is important in Tc radiopharmaceutical chemistry, is standard reduction potential. This is defined as the electrical potential necessary to effect a change in oxidation state. The value cited for a particular system is typically done relative to the normal hydrogen electrode under a specified set of experimental conditions (temperature, pressure and concentration). The more negative the value of the standard reduction potential the more easily the system loses electrons, and so the greater its reducing power. These values can be used to predict the course of reactions involving redox equilibria. In the case of technetium, it allows one to judiciously select an appropriate agent to reduce TcO_4^-.

Ligands

A ligand is defined as an atom, ion or molecule that donates electrons to a central atom. Ligands range from single electron donors to those that can donate six or more electrons. Ligands are important in Tc radiopharmaceutical chemistry because they determine the distribution of the tracer in the case of Tc-essential compounds and they make it possible to form strong covalent linkages between Tc and vectors in the case of targeted radiopharmaceuticals.

A review of all the ligands used to prepare Tc complexes is beyond the scope of this paper as it is an enormous field. However, common moieties are often employed and include thiols (RSH), thioethers (RSR, RSR'), amides (RC(O)NHR'), amines (R-NH_2, R-NHR', R-NR'R''), thioureas (RNH(S)NHR), phosphines (R_3P), and carboxylic acids (RCO_2H). Combinations of these functional groups are used to design chelates (i.e. multidentate donors) for Tc. In the case of bifunctional chelates, a combination of donor groups are used to bind the metal and an additional functional group (usually a carboxylic acid) which does not coordinate to the metal is used as a site to attach a targeting vector.

Isonitriles are a special class of ligands that are frequently used to prepare organometallic complexes. Isonitriles have the general formula RNC where the carbon atom is the entity that donates an electron pair to the metal. Isonitriles are isoelectronic with carbon monoxide (CO) but are stronger σ-donors. It is important to note that isonitriles (also known as isocyanides) are fairly reactive species that are susceptible to insertion reactions and be attacked by nucleophiles (i.e. they are not infinitely stable).

TECHNETIUM CHEMISTRY

To form technetium coordination complexes in nuclear medicine, pertechnetate (TcO_4^-) is treated with a reducing agent in the presence of a coordinating ligand. A wide range of different reducing agents have been investigated with $SnCl_2$ being the most widely employed for preparing complexes of Tc(V) and Tc(I), while boron-hydrides are used to prepare organometallic Tc(I) complexes (*vide infra*). The reduction potential of TcO_4^- to TcO_2 in acidic aqueous solutions is +0.738 V, which is comparable to the standard reduction potential for Fe^{3+}/Fe^{2+} (+0.771 V).[1] It is the combination of the reducing power of the reductant (which is highly pH dependent) and the nature of the ligand that determine the ultimate oxidation number and structure of the product. The two oxidation states that are most relevant to nuclear medicine are Tc(V) and Tc(I) and these are reviewed here.

Tc(V*)*

The radiopharmaceutical chemistry of Tc(V) is dominated by the $\{TcO\}^{3+}$ core, which appears in numerous approved radiopharmaceuticals. Ceretec™, for example, is a Tc(V) complex where the hexamethylpropyleneamineoxime (HMPAO) ligand forms a neutral square pyramidal complex with the $\{TcO\}^{3+}$ core (**Figure 1-A**).[2] Neurolite™ consists of a chelate (ECD) which is made up of two cysteine ethyl ester units that form a neutral complex with the same core (**Figure 1-B**).[3] The square pyramidal complex freely crosses the blood-brain-barrier whereupon an ester group of one of the isomers of Tc-ECD is hydrolyzed by an esterase, which in turn prevents premature efflux of the imaging agent from the brain. The ^{99m}Tc complex of mercaptoacetyltriglycine (MAG_3) (**Figure 1-C**) also forms a square pyramidal complex with Tc(V) with the basal plane consisting of the three nitrogen and one sulfur donor atoms. The carboxylic acid group, which can be used as a site to link targeting agents, does not coordinate to the metal center and is believed to help facilitating excretion via the kidneys.

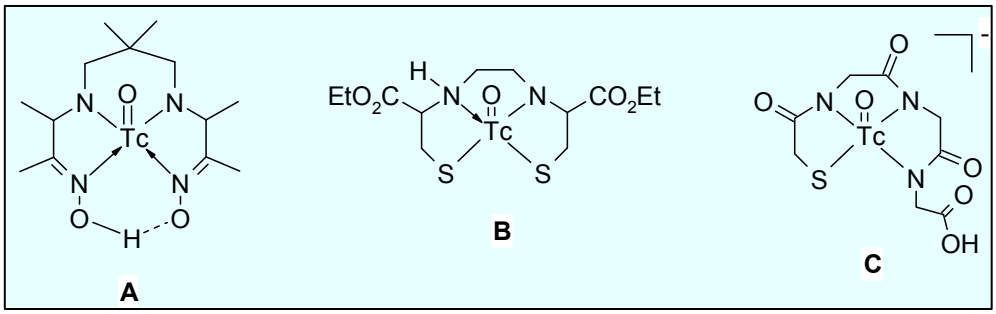

Figure 1

The $\{TcO\}^{3+}$ core is stabilized by a wide range of donors but has a preference for thiolate, amido, and

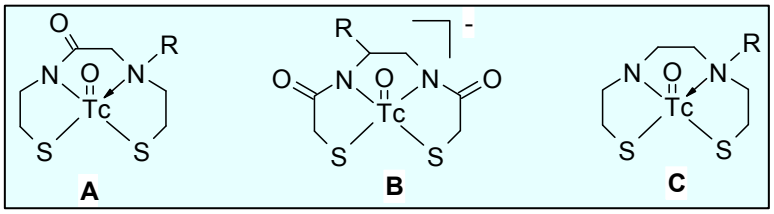

Figure 3

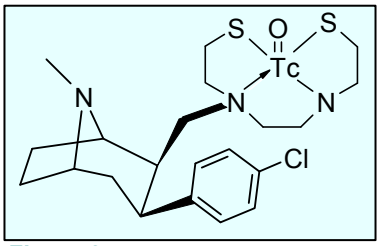

Figure 2

alkoxide ligands, which helps satisfy the high formal charge at the metal center. Chelates designed to bind Tc(V) are typically tetradentate (i.e. they contain sets of four donor atoms) and form complexes having square pyramidal geometries. These include ligands that contain all nitrogen donors, like the N_4 propylene diamine dioxime (PnAO) type ligands and the often employed mixed nitrogen-sulfur ligands. Examples of the latter are triamidomonothiol (N_3S), monoamine monoamide (N_2S_2) (**Figure**

2-A)[4,5], diamidodithiols (**Figure 2-B**)[6] and diaminodithiol ligands (**Figure 2-C**).[7] These have been used to prepare targeted radiopharmaceuticals including ^{99m}Tc TRODAT-1 (**Figure 3**),[8] which is a tropane analogue containing a diaminodithiol ligand. TRODAT-1 has been used for imaging CNS dopamine transporters (DAT) which is particularly useful for studying patients with Parkinson's disease.[9]

An important consideration when preparing complexes of Tc(V) is the formation of stereoisomers. Stereoisomers are defined as two or more compounds that have the same chemical formula but a different arrangement of atoms in space. Although stereoisomers can have similar chemical properties (or identical chemical properties in the case of enantiomers) they can have very different biological properties. As a result, when designing radiopharmaceuticals it is desirable to preclude the formation of stereoisomers.

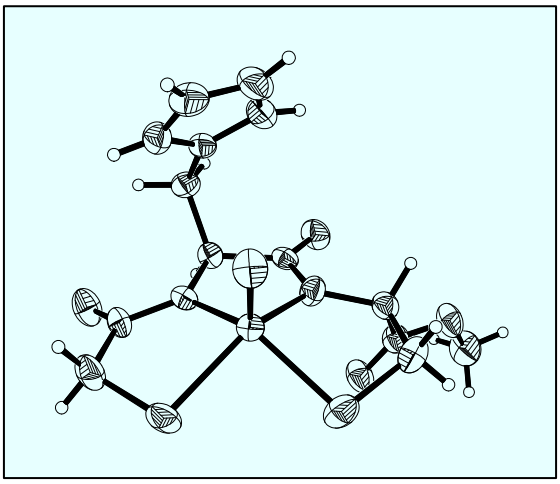

Figure 4. X-ray structure of a single stereoisomer of a Tc chelate complex derived from the amino acid histidine. Note that the amino acid ring and the oxygen bound to the Tc are *syn*.

As an example, complications due to the presence of stereoisomers arose during the synthesis of Tc(V) chelate complexes of ligands prepared from amino acids. The presence of the stereogenic center in the backbone of the ligands resulted in the formation of a mixture of isomers upon complexation with Tc.[10] The stereoisomers are a result of the fact that the substituents of the stereogenic center can be located *syn* (same side) (**Figure 4**) or *anti* (opposite side) to the Tc-oxo bond. These compounds are diastereomers, which are defined as isomeric compounds that are non-superimposable non-mirror images of one another. They have different chemical and physical properties (melting point, boiling point, solubility etc.). For substituted PnAO[11] and certain amino acid based monoamide monamino Tc(V) complexes,[12] when the isomers were separated they were shown to interconvert in solution.

Organometallic Chemistry of Technetium (Tc(I))

Organometallic compounds are defined as species that contain direct metal-carbon bonds. These types of compounds are traditionally prepared under strictly anhydrous (i.e. no moisture) conditions making them completely unsuitable for use as radiopharmaceuticals. However, as a result of some innovative thinking and creative chemistry, organometallic complexes of technetium can now be prepared in water and play a significant role in nuclear medicine. The field of Tc-organometallic chemistry is

growing rapidly and is expected to produce the next generation of targeted Tc and rhenium (Re) radiopharmaceuticals.

Tc-Isonitrile Complexes

Technetium isonitrile complexes of the type $[Tc(CNR)_6]^+$ are widely used to assess cardiac function.[13] The hexakis-((2-methoxy-2-methyl-1-propyl) isonitrile) complex of Tc(I) (**Figure 5**, Tc-Sestamibi, Tc-MIBI or Cardiolite™) is used for myocardial perfusion imaging studies and breast cancer imaging (under the name Miraluma™).[14] The preparation of Tc-isonitrile complexes in water[15] often gets special attention as it is recognized as a milestone in Tc chemistry.

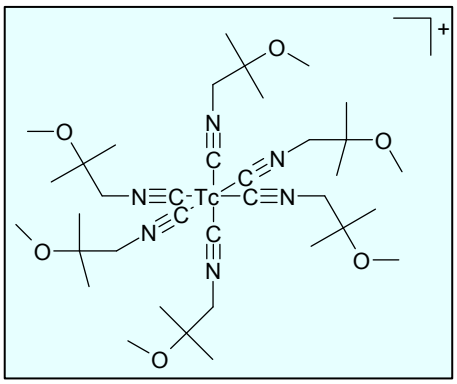

Figure 5

$[Tc(CNR)_6]^+$ complexes, unlike most organometallic compounds, can be prepared in high yield in aqueous solutions. Tc-Sestamibi is currently prepared using a kit which consists of, amongst other components, a tetrakis(isonitrile) Cu(I) complex as the source of the isonitrile ligands and stannous chloride as the reducing agent. One of the reasons for using the copper complex is to prevent premature degradation of the reactive isonitrile ligands.

The Tc(I) isonitrile complexes on which Cardiolite™ is based are inert owing in part to their low-spin d^6 electronic configuration of the metal center. Tc(I) complexes would therefore appear to be ideal compounds from which to prepare radiopharmaceuticals that target other organs or disease states. Unfortunately the poly-substituted isonitrile complexes are unreactive making them unsuitable starting materials from which to prepare Tc-tagged radiopharmaceuticals and furthermore isonitriles are notoriously difficult to work with.

Tc-Tricarbonyl Core, $[Tc(CO)_3]^+$

A renaissance in technetium chemistry has occurred recently as a result of a discovery of a new and highly adaptable Tc core that makes it possible to prepare organometallic complexes in aqueous solution. Alberto and co-workers showed that by treating TcO_4^- with borohydride in the presence of CO gas (**Figure 6**) they could produce the reactive Tc(I) species $[Tc(CO)_3(OH_2)_3]^+$.[16] In this complex, the three facially oriented water molecules are sufficiently labile that they can be readily displaced by a variety of mono-, bi- and tridentate ligands.

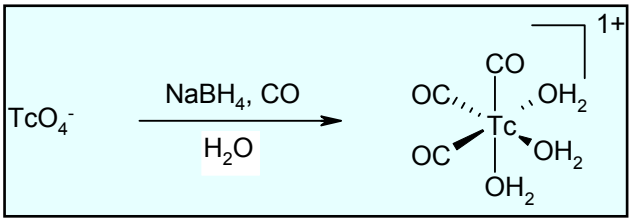

Figure 6

Working with gaseous carbon monoxide is not desirable, consequently a kit for the preparation of $[^{99m}Tc(CO)_3(OH_2)_3]^+$ was developed. The technology is based on the use of a solid reagent, potassium boranocarbonate ($K_2H_3BCO_2$). This unique species acts as both a reducing agent and a source of CO.[17] The kit is available from Mallinckrodt (Tyco) Medical under the trade name Isolink.

The $[Tc(CO)_3]^+$ core interacts with a broad range of different ligands including thioureas, isonitriles, and phosphines. The resulting complexes are for the most part octahedral, d^6-low spin and are therefore typically inert, which is ideal for radiopharmaceutical applications. Aliphatic amines and carboxylates coordinate rapidly to $[Tc(CO)_3]^+$, however, the resulting complexes are more reactive than complexes containing "soft" donors. Thioethers, for example, form inert complexes but do so at a very slow rate. A compromise between the rapid coordination of hard donors and the inertness of complexes containing soft donors can be achieved using ligands that contain aromatic amines, including substituted pyridines and imidazoles.[18]

Access to $[Tc(CO)_3(OH_2)_3]^+$ is transforming Tc-radiopharmaceutical chemistry because it provides a means to append inert and low molecular weight Tc-complexes to targeting vectors.[19,20] There are a number of bifunctional Tc(I) ligands that are now available for preparing bioconjugates. These include N_2O, N_3, and NSN type ligands which form neutral or cationic complexes with the $[Tc(CO)_3]^+$ core.[21,22]

Schibli and coworkers investigated the reaction of the $[Tc(CO)_3]^+$ core with a variety of these bi- and tridentate ligands to gain insight into the optimal chelate type and "denticity" for radiopharmaceutical development.[23] Their study revealed that both bidentate and tridentate chelates bind rapidly to the $[Tc(CO)_3]^+$ core on a macroscopic scale and at the tracer level. The tridentate systems were shown to be superior for developing Tc-tagged compounds because they demonstrated enhanced stability in ligand challenge experiments, and the complexes remained in tact *in vivo*. The bidentate analogues, in contrast, decomposed after being incubated with histidine and cysteine for 24 hours, and showed significant binding to plasma after one hour of incubation in human blood.

A COMPARISON OF THE CHEMISTRY OF RE AND TC

Determining the structures of ^{99m}Tc complexes unambiguously is complicated by the miniscule amounts of the isotope that is present at the tracer level (10^{-7} to 10^{-10} M), which is below the detection limits of standard structural characterization techniques. This problem is overcome by using the long-lived isotope ^{99}Tc, which can be handled safely in large quantities (typically 10-250 mg per reaction) with only nominal shielding. Reactions with ^{99}Tc provide sufficient material to characterize new Tc complexes, which in turn serve as (HPLC) reference standards for the analogous compounds produced at the tracer level.

In the absence of a license to handle the long-lived ^{99}Tc isotope, which is considered a disposal problem, researchers can use Re to prepare well-characterized reference standards. This latter approach must be done cautiously because there are numerous examples in which the chemistry of the two congeners differs significantly. This is a particularly important issue as there is growing interest in using ^{186}Re and ^{188}Re for therapeutic applications.

An example of the differences between Tc and Re is evident in the chemistry of the $[M(CO)_3]^+$ core (M = Tc, Re). The synthesis of $[^{99m}Tc(CO)_3(OH_2)_3]^+$ occurs readily from $^{99m}TcO_4^-$ using boranocarbonate in a basic solution. If the same reaction is performed using $^{186}ReO_4^-$, the reaction is slow and the major product is unreacted starting material. To get good yields of $[^{186}Re(CO)_3(OH_2)_3]^+$ it is necessary to acidify the solution of $^{186}ReO_4^-$ with strong acid prior to carrying out the reduction using a strong reducing agent (BH_3-NH_3) in place of only boranocarbonate. A two stage kit to perform such a reaction is now available.

SUMMARY

The chemistry of technetium is diverse and can be used to develop radiopharmaceuticals for a wide range of applications. By understanding key fundamental concepts in inorganic chemistry, high yields of novel radiopharmaceuticals derived from Tc and Re can be achieved. The future of Tc and Re radiopharmaceutical chemistry lies in the development of targeted agents. This will depend upon new advances in fundamental chemistry, the application of new technologies, and the utilization of novel metal cores like $[Tc(CO)_3(OH_2)_3]^+$.

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ASSESSMENT QUESTIONS

1. Chelates designed to bind Tc(V) are typically

    a. tetradentate
    b. hexacoordinate
    c. bifunctional
    d. isoelectronic

2. Numerous approved radiopharmaceuticals are a Tc(v) complex where the ligand forms a neutral square pyramidal complex with the core of

    a. $\{TcO\}^{3+}$
    b. $[Tc(CO)_3]^{+}$
    c. $[TcO4]^{-}$
    d. (Tc(I))

3. Detecting the structures of $^{99m}_{Tc}$ complexes is complicated since the minute amounts of isotope present are below the detection limits of characterization techniques. This problem can be overcome by

    a. using large amounts of 99Tc to investigate reactions.
    b. substituting Re since the chemistry is identical.
    c. substituting M since the chemistry is identical.
    d. substituting acidic Re solution with a strong reducing agent.

4. The standard reduction potential is defined as the potential measured for a system relative to the normal hydrogen electrode under specific conditions. The more negative the standard reduction potential the more easily the system loses electrons. This loss of electron is correlated with

    a. An increase in reducing power.
    b. A decrease in oxidizing power.
    c. A decrease in reducing power.
    d. An increase in oxidizing power.

5. Ligands are important in technetium radiopharmaceutical chemistry since they

    a. form strong coordinate linkages in targeted radiopharmaceuticals
    b. determine the tracer properties in Tc-essential compounds.
    c. are used to design chelates for greater stability.
    d. are a well-established impurity in isonitrile preparations.