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Structural determination of ^{99}Tc radiopharmaceuticals and compounds using X-ray absorption spectroscopy

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^{99m}Tc compounds play a very important role in modern medicine. These compounds are among the most widely used radiopharmaceuticals. Unfortunately, due to the necessity of working with small quantities of materials, the chemistry of these materials is not completely understood. Currently, the structure of the ^{99m}Tc-DTPA (a common renal imaging agent) is unknown. In this paper, we show that X-ray absorption spectroscopy (XAS) can be used to determine the structure of Tc compounds by comparing XAS results to those from X-ray diffraction (XRD). Specifically, XAS data and fits for $TcCl_6^{2-}$, $TcOCl_4^-$, and $TcNCl_4^-$ were found to be in excellent agreement with the known structures from XRD. Finally, we show the XAS spectrum from a 77 ng sample of ^{99}Tc-DTPA. To our knowledge this is the first XAS spectrum taken from this material. The near-edge region (XANES) was visible after a single scan on this material. This clearly indicates that we will be able to determine the local atomic structure of this material.

Introduction

At the present time, more than seventy-five percent of routine nuclear medicine diagnostic procedures use ^{99m}Tc.[1] This isotope is an ideal imaging agent in that it decays with a half-life of 6.03 hours to ^{99}Tc primarily by the emission of a 140 keV gamma-ray. The gamma-ray is high enough in energy to readily penetrate (escape) tissue but low enough in energy to be absorbed with very high efficiency by the thin thallium-doped, sodium iodide, single-crystal slabs used in the various nuclear medicine imaging cameras. Although, other radioisotope generator systems offer some real advantages over the ^{99}Mo–^{99m}Tc generator, the use of ^{99m}Tc is still increasing.

Much of the chemistry of ^{99m}Tc in radiopharmaceuticals remains unknown.[2] Technetium is a second-row transition metal and can assume any oxidation state from +7 to 0. It resembles manganese to a limited extent and rhenium to a much greater extent. In its compounds, it exhibits coordination numbers from 4 to 9 and their crystal structures show great variety. Complexities in the chemistry, especially in aqueous solution, make it difficult to assign an overall role to its behavior in medically useful radiopharmaceuticals as one might do in the case of much better understood elements like nickel and cobalt. Compounding this complexity, ^{99m}Tc is available at tracer levels, which does not permit the characterization of its compounds by routine spectroscopic and analytical methods. Hence, studies are performed by using either the long-lived radionuclide ^{99g}Tc ($T_{1/2} = 2.1\cdot 10^5$ y) or its stable congener, rhenium. In many cases though, different products are formed at the macroscopic (^{99g}Tc or Re) and tracer (^{99m}Tc) levels, primarily due to the different reaction conditions (metal: ligand ratio, solvent, etc.), in addition to the fact that many of technetium compounds in water hydrolyze, polymerize or form colloids.

The physical structure of the three most widely utilized ^{99m}Tc radiopharmaceuticals are not known: ^{99m}Tc Pentetate (^{99m}Tc DTPA) used for kidney and brain imaging and assessment of renal perfusion; ^{99m}Tc Medronate used as a bone imaging agent to delineate areas of altered osteogenesis; and ^{99m}Tc sodium phosphates used both for bone and myocardial imaging and blood pool and gastrointestinal imaging. This is problematic, as the FDA now requires structural information prior to the approval for general usage of new pharmaceutical compounds.[3] It is with this problem in mind that we initiated this work.

It is difficult to determine the structure of materials that cannot be crystallized because one of the principal techniques of structural determination, X-ray diffraction, cannot be used.[4] X-ray absorption spectroscopy (XAS), specifically, the extended X-ray absorption fine structure (EXAFS) region, has a long history of being used for local structure determination in systems where crystallization is difficult or impossible.[5] X-ray absorption spectroscopy measures X-ray induced transitions from core electron states of an atom to either bound, unoccupied states or free-electron-like states. In general, XAS measurements allow one to determine the oxidation state of an element, its atomic coordination (i.e., the number of neighboring atoms), and the distance between the neighboring atoms.

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