Inorganic Bone-Imaging Agents

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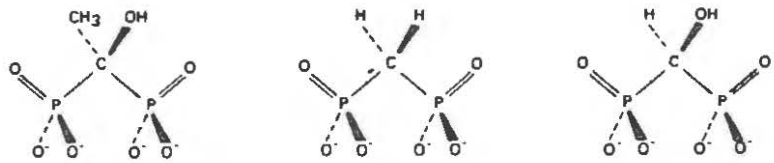
Inorganic radiopharmaceuticals [1] utilize complexes of chromium, iron, technetium, ruthenium, platinum, gallium, indium, and thallium. They possess chemical properties which allow localization at specific parts of the body. The resulting accumulations are traced by emitted radiation.

Technetium-99m(^{99m}Tc) is the primary isotope used in nuclear medicine [2] for two reasons. First, ^{99m}Tc has optimum nuclear properties for imaging, second the position of technetium in the periodic table ensures the possibility of generating wide ranges of complexes. An interesting application of ^{99m}Tc is in the area of bone-imaging radiopharmaceuticals. To image bone, ^{99m}Tc is most often chelated to a class of ligands known as diphosphonates:

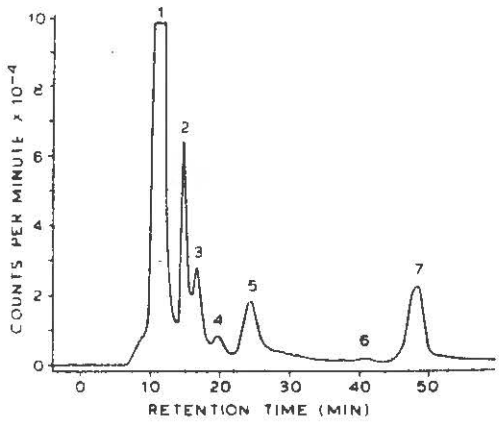


The preparation of Tc radiopharmaceuticals is based on the aqueous reduction of pertechnetate, TcO_4^-, in the presence of chelating agents which prevent the precipitation of TcO_2. The most commonly used reductant is stannous chloride. Evidence exists for a complicated reaction process which is dependent on reductant, ligand, pH, temperature, presence of oxygen, ligand-to-metal ratio, and reaction time.

Using stannous ion for reduction of TcO_4^- leads to several problems [3]. Since Sn(IV) and Tc(IV) have similar ionic radii, the incorporation of tin into the radiopharmaceutical may occur. For example, Deutsch et al. [4] have structurally characterized a bridged Tc-Sn-dimethylglyoxime complex. Also, the total amount of Sn(II) initially added to a radiopharmaceutical kit may not be in a usable form by the time $^{99}TcO_4^-$ is added [5]. Side reactions involving tin will have a direct outcome on the final Tc oxidation state(s).

Electroanalytical techniques have been applied, with much difficulty, to the determination of Tc oxidation states. For example, Russell and Cash [6] have combined normal polarography, pulse polarography, and amperometric titrations to determine Tc oxidation states in aqueous media containing pyrophosphate, MDP, or HEDP.

To investigate the structure of the Tc-diphosphonates, Pinkerton et al. [7] developed an anion-exchange HPLC technique. When applied to Tc($NaBH_4$)-HEDP and Tc($NaBH_4$)-MDP preparations, at least seven components have been shown to be present [8,12]:



They concluded, based on the polymeric structure of $[Tc(OH)(MDP)^{-}]_n$ [9], that the components represented various oligomers. It was also shown, both for HEDP [8] and MDP [10], that each separated component had different biodistributions.

Jurrison et al. [11] have conducted in vitro experiments on the calcium affinity of coordinated diphosphonate ligands. A series of diphosphonate-cobalt complexes were titrated with calcium. The results from these experiments provided evidence for a relationship between structure and function of the ligands. They demonstrated that the nature of the groups attached to the carbon in the P-C-P backbone play an important role in calcium affinity.

References

1. Deutsch, E., "Inorganic Radiopharmaceuticals", In "Radiopharmaceuticals II", Society of Nuclear Medicine: New York, 1979; pp 129-46.

2. Recent reviews:
   a) Burns, H. D.; Worley, P.; Wagner, H. N., Jr., "Design of Technetium Radiopharmaceuticals", In "The Chemistry of Radiopharmaceuticals", Masson: New York, 1978; pp 269-89.
   b) Marzilli, L. G.; Dannals, A. F.; Burns, H. D., "Technetium-99m Radiopharmaceuticals", In "Inorganic Chemistry in Biology and Medicine", A. E. Martell, Ed.; ACS: Washington, D.C.; ACS Symp. Ser. No. 140, pp 91-101.
   c) Deutsch, E.; Barnett, B. L., "Synthetic and Structural Aspects of Technetium Chemistry as Related to Nuclear Medicine", In "Inorganic Chemistry in Biology and Medicine", A. E. Martell, Ed.; ACS: Washington, D.C.; ACS Symp. Ser. No. 140, pp 103-19.
   d) Clarke, M. J.; Fackler, P. F., "The Chemistry of Technetium: Toward Improved Diagnostic Agents", Structure and Bonding 1982, 50, 57-78.
   e) Deutsch, E.; Libson, K.; Jurisson, S.; Lindoy, L. F., "Technetium Chemistry and Technetium Radiopharmaceuticals", Prog. Inorg. Chem. 1983, 30, 75-139.

3. Francis, M. D.; Tofe, A. J.; Hiles, R. A.; Birch, C. G.; Bevan, J. A.; Grabenstetler, R. J., "Inorganic Tin Chemistry, Disposition, and Role in Nuclear Medicine Diagnostic Skeletal Imaging Agents", Int. J. Nucl. Med. Biol. 1981, 8, 145-52.

4. Deutsch, E.; Elder, R. C.; Lange, B. A.; Vaal, M. J.; Lay, D. G., "Structural Characterization of a Bridged ^{99}Tc-Sn-dimethylglyoxime Complex", Proc. Natl. Acad. Sci. U.S.A. 1976, 73, 4287.

5. Srivastava, S. C.; Meinken, G.; Smith, T. D.; Richards, P., "Problems Associated with Stannous ^{99m}Tc-radiopharmaceuticals", Int. J. Appl. Radiot. Isot. 1977, 28, 83-95.

6. a) Russell, C. D.; Cash, A. G., "Complexes of Technetium with Pyrophosphate, Etidronate, and Medronate", J. Nucl. Med. 1979, 20, 532.
   b) Russell, C. D.; Cash, A. G., "Oxidation State of Technetium in Bone Scanning Agents as Determined at Carrier Concentration by Amperometric Titration", Int. J. Appl. Radiat. Isot. 1979, 30, 485.

7. Pinkerton, T. C.; Heineman, W. R.; Deutsch, E., "Separation of Technetium Hydroxyethylidene Diphosphonate Complexes by Anion-Exchange HPLC", Anal. Chem. 1980, 52, 1106.

8. Pinkerton, T. C.; Ferguson, D. L.; Deutsch, E.; Heineman, W. R.; Libson, K. "In vivo Distribution of Some Component Fractions of Tc($NaBH_4$)-HEDP Mixtures Separated by Anion-Exchange HPLC", Int. J. Appl. Radiat. Isot. 1982, 33, 907.

9. Libson, K.; Deutsch, E.; Barnett, B. L., "Structural Characterization of a ^{99}Tc-diphosphonate Complex", J. Am. Chem. Soc. 1980, 102, 2476.

10. Tanabe, S.; Zodda, J. P.; Libson, K.; Deutsch, E.; Heineman, W. R., "The Biological Distributions of Some Technetium-MDP Components", Int. J. Appl. Radiat. Isot. 1983, 34, 1585.

11. Jurisson, S. S.; Benedict, J. J.; Elder, R. C.; Whittle, R.; Deutsch, E., "Calcium Affinity of Coordinated Diphosphonate Ligands", Inorg. Chem. 1983, 22, 1332.

12. Tanabe, S.; Zodda, J. P.; Deutsch, E.; Heineman, W. R. "Effect of pH on the Formation of Tc($NaBH_4$)-MDP Radiopharmaceutical Analogues", Int. J. Appl. Radiat. Isot. 1983, 34, 1577.