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Radiopharmaceutical chemistry of technetium and rhenium

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Technetium-99m is the most widely used SPET radionuclide in Nuclear Medicine. It owes this favourable position to its low radiation dose (no particular radiation, short half-life of 6 h), ideal physical radiation characteristics (mono-energetic gamma-rays of 141 keV, well absorbed by the NaI(Tl) crystal of gamma cameras and by a few millimeters of lead for shielding purposes) and its continuous availability from ^{99}Mo-^{99m}Tc generators. Moreover, an intensive search for useful ^{99m}Tc labeled radiopharmaceuticals since the seventies has resulted in a good knowledge of technetium complexation chemistry.

A few inorganic ^{99m}Tc radiopharmaceuticals are or have been used in Nuclear Medicine. It concerns especially:
- heptavalent ^{99m}Tc in the form of pertechnetate and colloidal Tc_2S_7,
- tetravalent colloidal technetiumdioxide,
- (probably) metallic ^{99m}Tc in ultrafine form in the pseudogas Technegas.

Other ^{99m}Tc radiopharmaceuticals consist of complexes in which technetium has a lower oxidation state than +7. Starting from ^{99m}Tc-pertechnetate a reduction step is therefore required in the preparation of these ^{99m}Tc labelled agents. A stannous salt (Sn^{2+} ions) is mostly being used for this purpose. Depending on the chelating agent present, the reduction may lead to technetium in different oxidation states (such as +5, +4, and +1).

The exact nature of the ^{99m}Tc complexes in first-generation ^{99m}Tc radiopharmaceuticals (such as ^{99m}Tc-MDP and other bisphosphonate complexes, ^{99m}Tc-DTPA, ^{99m}Tc(III)DMSA, ^{99m}Tc-human serum albumin), is not or not well known. This is partially due to the presence of more than one ^{99m}Tc labeled species in the labeling reaction mixtures, even varying in nature and relative amounts as a function of time, but this does generally not interfere with the clinical usefulness of these diagnostic agents.

A large number of well characterized ^{99m}Tc complexes based on metal binding agents with strong donor atoms in an appropriate arrangement has been developed since the end of the seventies and these have resulted in a variety of useful radiopharmaceuticals. Some of them are prepared by a so-called direct labeling, just requiring combining ^{99m}Tc-pertechnetate with stannous ion and the complexing agent followed by incubation at room temperature. In other cases, reduced ^{99m}Tc is first bound to a weak chelating agent and the intermediary complex is converted to the final ^{99m}Tc chelate by a transmetalation reaction. This so-called exchange labelling is applied when the ligand cannot form rapidly the desired complex due to the presence of a protecting group (MAG3) or binding of the ligand to another metal (MIBI). Most success has been obtained with tracer agents characterized by the presence of a ^{99m}Tc(V)-oxo core bound to tetraligands such as a diamine dioxime (^{99m}Tc-d,l-HMPAO), a diamine dithiol (ECD, EC, TRODAT), a mercaptotriamide (MAG3), a tetrapeptide (tetraglycine), a monoamine monoamide dithiol (MAMA) or hydroxytriamide (HAG3). Examples of other ^{99m}Tc chelates are ^{99m}Tc(V) dioxo complexes with diphosphines (tetrofosmin) or tetraamines (demotate), Tc(I) complexes with six isonitrile ligands (MIBI), complexes of ^{99m}Tc with a combination of a hydrazinonicotinamide and a coligand such as tricine and still several other complex systems.

The most recent development in this field is a convenient synthesis of ^{99m}Tc(I)-tricarbonyl complexes via the reduction of $Na^{99m}TcO_4$ with sodium borohydride at pH 11 under an atmosphere of carbon monoxide or in the presence of potassium boranocarbonate to form a $Tc(I)(CO)_3(OH_2)_3$ precursor. This cationic species readily undergoes ligand exchange of coordinated water with a wide variety of donor ligands, of which the tridentate ligands such as histidine yield the most stable complexes. Interesting biologically active agents have been labeled as a ^{99m}Tc(I) tricarbonyl complex, e.g. octreotate and glucose. This exciting chemistry can be assumed to allow technetium-99m labeling of any appropriately designed recombinant protein, synthetic peptide and a wide variety of organic synthetic compounds and holds a

great potential for the development of a new generation of ^{99m}Tc-radiopharmaceuticals.

Rhenium is a chemical congener of technetium and two rhenium radionuclides may be useful for labelling of radiopharmaceuticals intended for radiotherapy, i.e. ^{186}Re and ^{188}Re. Because of the similarity between Tc and Re, radiorhenium radiopharmaceuticals have been designed based on ^{99m}Tc-labelled tracer agents. Technetium is more easily reduced than rhenium but, once formed, Tc- and Re-complexes are similar in terms of size, geometry and lipophilicity. On the other hand, Re-complexes show a higher in vivo instability, characterized by dissociation of the radiorhenium from the metal binding ligand. Ligands most used for the formation of radiorhenium complexes, e.g. with antibodies, are diaminodithiol, diamidedithiol and mercaptotriamide tetraligands, which form Re(V)oxo complexes. Also several Re(I)tricarbonyl chelates have been developed and tested. However, at this moment no radiorhenium radiopharmaceutical is commercially available yet.

References

1. Mahmood A, Jones AG. Technetium radiopharmaceuticals. In: Handbook of Radiopharmaceuticals. Radiochemistry and applications; Welch MJ, Redvanly CS, eds. Wiley, West Sussex, 2003, pp 323-362.
2. Schwochau K. Technetium. Chemistry and Radiopharmaceutical applications. Wiley-VCH, New York, 2000.
3. Alberto R, Schibli R, Egli A et al. A novel organometallic aqua complex of technetium for the labeling of biomolecules: Synthesis of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ from $[^{99m}TcO_4]^-$ in aqueous solution and its reaction with a bifunctional ligand. J Am Chem Soc 1998; 120:7987-7988.