MACROCYCLIC COMPLEXES OF $^{44/47}$Sc AS PRECURSORS OF RADIOPHARMACEUTICALS

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Two isotopes of scandium, ^{47}Sc and ^{44}Sc, are perspective radinuclides for radiotherapy and diagnostic imaging. ^{47}Sc decays with a half-life of 3.35 days and a maximum β^- energy of 600 keV. It also emits low-energy gamma radiation (E_γ=159 keV) suitable for simultaneous imaging. The other scandium radionuclide – ^{44}Sc ($T_{1/2}$=3.92 h) is an ideal β^+ emitter for PET diagnosis. It can be produced by the ^{44}Ca(p,n)^{44}Sc nuclear reaction in small cyclotrons or as a daughter of long-lived ^{44}Ti ($T_{1/2}$=60.4 y) from a ^{44}Ti/^{44}Sc generator. For reasons of availability, we used in our experiments the ^{46}Sc ($T_{1/2}$=83.8 d) – carrier added nuclide instead of ^{47}Sc and ^{44}Sc.

The goal of our work was to find the best ligands for attaching scandium radionuclides with biomolecules. Due to the formation of thermodynamically stable and kinetically inert complexes macrocyclic ligands were choosen.

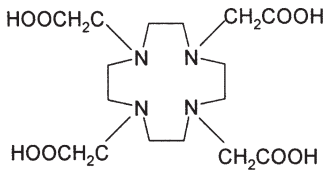
The ionic radius of Sc^{3+} is 74.5 pm (CN=6), the ion is chemically similar to Ga^{3+}, In^{3+}, Y^{3+} and to the heaviest lanthanides. Ligands developed for these cations should also be suitable for chelating ^{47}Sc, ^{44}Sc. Since the complexation ability of macrocyclic ligands depends on the ionic radius of the cation, we expected that Sc^{3+} would form strong complexes with the ligands having a cavity size similar to the ionic radius of Sc^{3+}: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), 1,4,7-triazacyclononane-1,4,7 triacetic acid (NOTA), 1,4,7-triazacyclodecane-1,4,7 triacetic acid and 1,4,7-triazacycloundecane triacetic acid and analogs of NOTA with 10, 11 and 12 atoms of carbon in the ring (Fig.1).

DOTA was obtained from Macrocyclic Company, the other ligands were synthesized by a reaction of triaza rings with bromoacetic acid according to the reported method [1]. All the compounds were characterized by NMR spectroscopy and MS spectrometry.

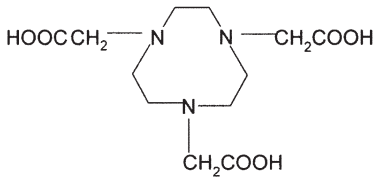
Stability constants of scandium complexes were determined using the HPLC method. Sc complexes were prepared by reacting macrocyclic ligands of 0.01 M concentration, respectively, with $^{46}ScCl_3$ in ammonium acetate buffer at pH=6.0. The samples were heated at 70°C. When the reactions reached equilibrium (8 days), small samples of the solution were injected into an HPLC loop to determine the concentrations of the complex and free Sc^{3+}. The HPLC data were collected using a Shimadzu Coulter device coupled with a radiometric detector. This method used a Supelco C_{18} column and a mobile phase gradient starting from 100% solvent A (0.01 M EDTA) to 100% solvent B (0.01 M EDTA in acetonitrile) for 26 min at a flow rate of 1 ml/min.

The stability constants were calculated from the ratio of Sc-L complex to free Sc peaks measured with the gamma detector. Taking into account stepwise protonation constants of the ligands, the stability constants were determined. For comparison, in the same way stability constants of ^{177}Lu complexes were calculated. The results are presented in Table.

As shown in Table, Sc^{3+} forms more stable complexes with a DOTA ligand than Lu^{3+}. Also complexes of Sc with DOTA are stronger by a few orders of magnitude than the complexes with NOTA and [10]ane ligands. The radiochemical yield of

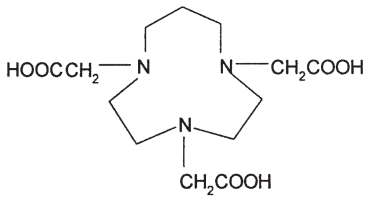


DOTA

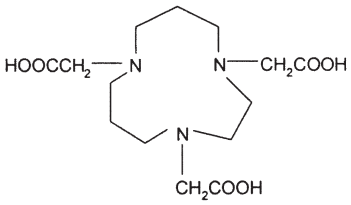


NOTA

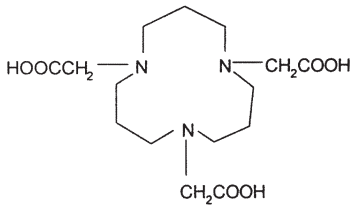
analogs of NOTA



[10]ane



[11]ane



[12]ane

Fig.1. Macrocyclic ligands used for Sc^{3+} complexation.

labelling (5.5 nmol of Sc^{3+} and 55 nmol of ligands) for Sc-DOTA is about 99% and it is much higher than that for the Sc-NOTA complex (80%).

Table. Stability constants determined by the HPLC method.

Metal cation	DOTA	NOTA	[10]ane
Sc^{3+}	27.5	17.6	14.8
Lu^{3+}	26.7	15.8	12.7

The charges of Sc complexes were determined by paper electrophoresis.

The Sc-DOTA complex migrates towards the anode, so the charge is negative. The Sc-NOTA complex stays at the start, therefore the charge is neutral. The charges of the complexes were confirmed by the adsorption studies on cation and anion exchangers.

The kinetics of Sc-DOTA and Sc-NOTA complexes were measured at pH=6.0. Complex formation was determined by the instant thin layer chromatography method using ITLC-SG strips developed with the mobile phase: H_2O/NH_3 (25/1). The formation of the Sc-NOTA complex under these conditions is faster than for the Sc-DOTA complex. After 10 min, the equilibrium for Sc-NOTA was reached, while for Sc-DOTA 30 min is needed for attaining equilibrium.

Sc-DOTA and Sc-NOTA complexes exhibit high stability in human serum and PBS buffer at 37°C. After 120 h of incubation in the serum and PBS, more than 97% of Sc-DOTA and Sc-NOTA remains in solution.

Since radiolabelled compounds should be easy cleared from the blood *via* the kidneys, lipophilicity is very important feature of the radiopharmaceuticals. It was found by the HPLC method that Sc-DOTA complex is more hydrophilic than Lu-DOTA and Sc-NOTA, suggesting different coordination spheres in these complexes (Fig.2). The

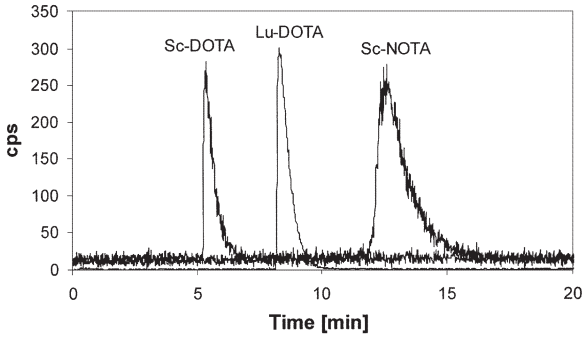


Fig.2. Comparison of lipophilicity of DOTA and NOTA complexes.

cation of Sc is smaller than Lu, so the peak of more hydrated Sc-DOTA complex appears before the peak of Lu-DOTA complex.

The presented results show that the macrocyclic complexes of ^{44}Sc and ^{47}Sc radionuclides are attractive precursors for diagnostic and therapeutic radiopharmaceuticals.

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References

[1]. Bevilacqua A., Gelby R.I., Hebard W.B., Zompa L.J.: Inorg. Chem., 26, 2699-2706 (1987).

THE SUBSTITUTION OF CHLORIDES IN A RHODIUM-BASED DRUG PRECURSOR BY HUMAN PLASMA THIOLS

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Complexes of rhodium-105 are promising precursors for radiopharmaceuticals for anti-tumor therapy utilizing the radiation in the destruction of cancerous tissues. The ^{105}Rh demonstrates a number of desirable nuclear characteristics like high specific activity, low gamma emission (0.320 MeV), a decay half-life 35.4 h, high linear energy transfer and emission of soft β^--particles (0.567 MeV – 70%, 0.247 MeV – 30%) [1]. Moreover, rhodium at +3 oxidation number forms d^6 low-spin electronic complexes considered as ones of the most inert. To date, several authors have evaluated the number of tetradent thioether S_4- or NS_3-structured ligands to be complexed with ^{105}Rh and selected ^{105}Rh[1,5,9,13-tetrathiacyclohexadecane-3,11-diol] as the most suitable drug precursor for radiopharmacy. When studying the pharmacokinetic mechanisms that determinate the fate of drug administered externally to a living organism, the identification of the possible chemical modifications of the substance in the body might be an essential step prior to investigating the distribution, stability and metabolism under physiological conditions.

In our studies the properties of Rh[1,5,9,13-tetrathiacyclohexadecane-3,11-diol]Cl_2^+ (Rh[S_4diol]Cl_2^+) (Fig.1) complex in the presence of two key organic thiol antioxidants: glutathione (GSH) and cysteine has been evaluated, prefacing the future experiments with radioactive rhodium. Both thiols are present in biological fluids in milimolar concen-

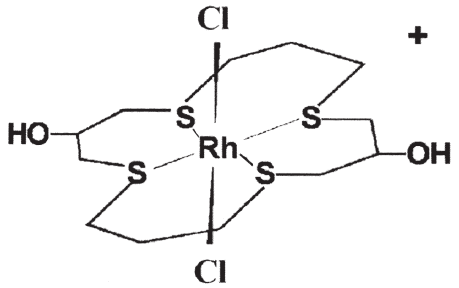

Fig.1. Structure of Rh[1,5,9,13-tetrathiacyclohexadecane-3,11-diol]Cl_2^+.