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TRICARBONYL TECHNETIUM(I) COMPLEXES WITH DIFFERENT PHOSPHATE LIGANDS

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Abstract

The possibilities for labelling of different phosphate ligands with technetium-99m through $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ precursor were investigated. The HPLC results have shown that hydrophilic organometallic $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ precursor allows forming of Tc (I) complexes with different phosphate ligands, based on the tricarbonyltechnetium (I) core.

Introduction

In everyday nuclear medicine practice there are different phosphate ligands labeled with technetium pertechnetate ($^{99m}\text{TcO}_4^-$) eluted from $^{99}\text{Mo}/^{99m}\text{Tc}$ generator, where oxidation state of technetium in complexes isn't determined [1]. Tricarbonyl agent $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$, with oxidation state of technetium +1, has proved as an excellent agent for labeling different kind of ligands [2,3]. $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ precursor could be formed in high yield directly from $^{99m}\text{TcO}_4^-$. As the coordination of three water molecules are labile, they could be exchanged readily with a variety of mono-, bi- and tridentate ligands forming complexes. Phosphate ligands used in this study were: 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD), imido-diphosphate (IDP), pyrophosphate (PyP) and 1-hydroxyetan-1,1-diphosphonic acid (HEDP).

Experimental

$[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ was prepared from carbonyl labelling agent Isolink™ (Mallinckrodt Medical B.V.) or carbonyl precursor prepared in NCRS "Democritos", according the instructions for use. Before use the basic solution was neutralised. At first, phosphate solutions DPD, IDP, PYP and HEDP with concentration 10^{-3} mol dm⁻³ were prepared. Each of these solutions were distributed into three equal portions and pH was adjusted to 2.5, 5.5 or 7.5. Neutralised precursor was added to the solution in volumetric ratio: phosphate (DPD, IDP, PYP or HEDP): $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ =1:1; 1:2; 1:5 or 1:9. All mixtures were heated at 75°C for 30 minutes, because there was no reaction between phosphate ligands and Tc(I)-carbonyl without heating.

Reaction products, prepared from different solutions of ligand and Tc-carbonyl, were analysed by Liquid Chromatograph, Hewlett Packard 1050 S/N with UV and Raytest gamma flow detector RP and Alltech C18 column (250x4.6 mm). Flow was 0.7 ml/min. Runs were isocratic. Mobile phase was 90 % 0.05 mol dm⁻³ TEAP:9 % water:1 % methanol.

Results and Discussion

A great number of ^{99m}Tc -phosphate compounds, made by adding $^{99m}\text{TcO}_4^-$ to a kit, have been applied for bone imaging. There are a lot of literature data about forming mixed-metal complexes containing Tc(III), Tc(IV), Tc(V) and Sn(II) in undetermined proportions. The subject of this paper was labelling of some phosphate ligands with $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$, where oxidation state of technetium was +1.

The HPLC results performed by isocratic HPLC, pointed at complexation of phosphate ligands with $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$. The influence of molar ratio on labelling yield was presented in Fig.1. as HPLC chromatograms for Tc-carbonyl coordinated DPD, for three different ratios. These results pointed at the highest labelling yeald for ration: DPD: $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+=1:9$.

The quality control results of ^{99m}Tc -carbonyl tagged phosphate ligands, obtained with hitting of the samples ($75\text{ }^\circ\text{C}$) and for $\text{pH}\cong 7.5$, were presented as HPLC chromatograms in Fig. 2.

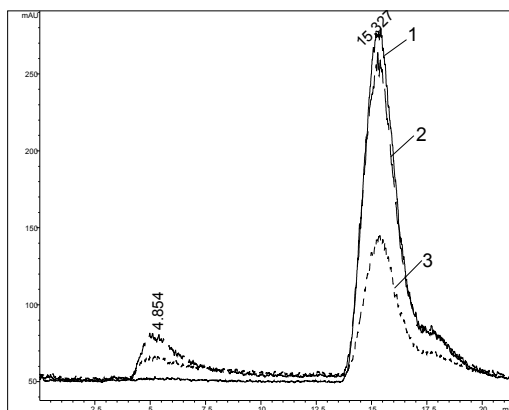


Fig. 1. HPLC radiochromatograms of $^{99m}\text{Tc}(\text{CO})_3$ -DPD, with different DPD : $[\text{}^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ ratios: 1:9 (1); 1:5 (2) and 1:2 (3) ($\text{pH}=7.5$, with heating)

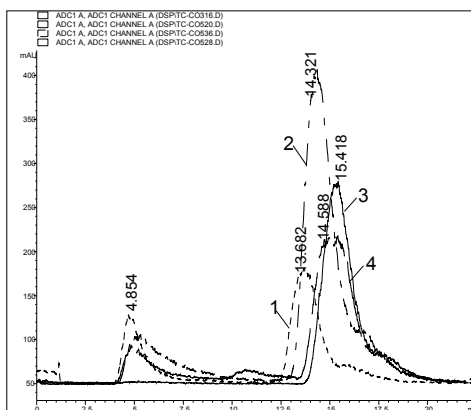


Fig. 2. HPLC radiochromatograms of different phosphate ligands labelled with $^{99m}\text{Tc}(\text{CO})_3$, at $\text{pH}=7.5$: IDP (1), PYP (2), DPD (3), HEDP (4)

The values of retention times, together with the labelling yield for each of Tc-carbonyl coordinated phosphate ligands, were presented in Table 1. Phosphate ligands have shown different bonding to tricarbonyl Tc(I) precursor, so obtained phosphate complexes have different retention times.

Table 1. Dependence of retention times and labelling yield for phosphate ligands coordinated to $^{99m}\text{Tc}(\text{CO})_3^+$ on pH

Ligand (L)	pH	5.5		7.5		
		^{99m}Tc -species	t_r (min)	Yield (%)	t_r (min)	Yield (%)
DPD	$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$		4.8	31.7	4.8	0
	$^{99m}\text{Tc}(\text{CO})_3\text{-L}$		15.4	68.3	15.3	100
	$^{99m}\text{TcO}_4^-$		10.7	0	10.7	0
IDP	$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$		4.7	58.8	4.7	31.0
	$^{99m}\text{Tc}(\text{CO})_3\text{-L}$		13.7	41.2	13.6	69.0
	$^{99m}\text{TcO}_4^-$		10.7	0	10.7	0
HEDP	$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$		4.8	19.6	4.8	16.0
	$^{99m}\text{Tc}(\text{CO})_3\text{-L}$		14.7	39.5	14.6	42.0
			15.4	21.0	15.4	36.2
	$^{99m}\text{TcO}_4^-$		10.7	19.9	10.7	5.8
PYP	$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$		4.8	64.1	4.8	15.4
	$^{99m}\text{Tc}(\text{CO})_3\text{-L}$		14.5	35.9	14.3	84.6
	$^{99m}\text{TcO}_4^-$		10.7	0	10.7	0

Conclusion

These investigations have shown that complexation of phosphate ligands with $^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ precursor were depended on labelling conditions like volumetric ratio, pH of solution or heating of samples. It was not possible without heating. If the samples of phosphate ligands together with $^{99m}\text{Tc}(\text{I})$ precursor were heated in water boiling bath for thirty minutes, higher labelling yield was obtained at pH=7.5 than at pH=5.5, but there was no labelling at pH=2.5. The best results were obtained for molar ratio 1:9. Among investigated phosphate compounds, DPD was the best labelled ligand.

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$^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3^+$ precursor (IsoLinkTM) was obtained from Tyco Healthcare, Mallinckrodt Medical B.V., The Netherlands.

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