Production of ^{166}Ho and ^{153}Sm using hot atom reactions in neutron irradiated tris(cyclopentadienyl) compounds

Lina Nassan,
Baida Achkar,
Taufik Yassine

Abstract. The behavior of a recoiled ^{166}Ho and ^{153}Sm resulting from the reactions ^{165}Ho(n,γ)^{166}Ho and ^{152}Sm(n,γ)^{153}Sm in the organometallic compounds tris(cyclopentadienyl)holmium $(C_5H_5)_3$Ho(III), and tris(cyclopentadienyl)samarium $(C_5H_5)_3$Sm(III) were investigated. Several chemical separation methods were developed for each compound to separate the recoil products from the irradiated compound. Retention value of $0.2 \pm 0.1\%$ was obtained for $(C_5H_5)_3$Ho(III) using sublimation. Another value of retention of $0.4 \pm 0.1\%$ resulted when column chromatography was used. Paper chromatography (using Whatman Chr. 1 and Whatman Chr. 4) gave different retention values of about $0.11 \pm 0.05\%$, and $0.4 \pm 0.1\%$, respectively. Similar behavior of ^{153}Sm in irradiated $(C_5H_5)_3$Sm(III) was found when paper chromatography was used for separation. The different retention values given by different methods of separation were discussed. An important improvement of the specific activity was achieved as compared with other published results in this field. The obtained results pointed out that tris(cyclopentadienyl)holmium and samarium could be used to produce high specific activity of ^{166}Ho and ^{153}Sm in the Syrian low flux miniature nuclear source reactor (MNSR), where the averaged achieved enrichment factor for holmium compound was found to be greater than 1.6×10^7.

Key words: hot atom reactions • holmium-166 • samarium-153 • miniature nuclear source reactor (MNSR)

L. Nassan✉
Nuclear Engineering Department,
Atomic Energy Commission of Syria,
P. O. Box 6091, Damascus, Syria,
Tel.: 00963 112 132 580, Fax: 00963 611 1926/7,
E-mail: pscientific@aec.org.sy (Lina Nassan)

B. Achkar
Department of Physics,
Damascus University,
Damascus, Syria

T. Yassine
Department of Chemistry,
Atomic Energy Commission of Syria,
P. O. Box 6091, Damascus, Syria

Introduction

The neutron rich ^{166}Ho and ^{153}Sm offer favorable nuclear characteristics for internal radiotherapy. The use of high specific activity (i.e., free of carrier or isotopic target material) radionuclides is desirable for radiotherapy involving receptor-targeting agents. Isotopes are typically produced in a reactor by neutron radiative capture, such as (n,γ) reactions. Normally, production by this route results in a low specific activity radionuclides [2]. Hot atom reactions can be used for increasing the specific activity of radionuclides using nuclear reactors [12].

Historically, nuclear recoil was observed in many nuclear reactions, and gave rise to numerous studies on enrichment of radioisotopes in different compounds like permanganates, chromates, iodates, alkyl halides, metal phthalocyanines, many coordination compounds of cobalt, and other compounds which have been extensively investigated since 1935, while organometallic compounds were less frequently studied. Study of the recoil chemistry of organometallic compounds, began in 1955 with the publication of a study by Maddock and Sutin on neutron activation of triphenylarsene [11]. Several metal phthalocyanine were used as target compounds for the preparation of radionuclides via recoil procedures, and an excellent high specific activity for ^{64}Cu preparations was obtained [3, 9]. However,

Table 1. Some activation characteristic and nuclear reactions of Ho and Sm

Target nuclide	Natural abundance (%)	Activation integral resonance (b)	Absorption integral resonance (b)	$\sigma(b)$ for (n,γ) reaction	Product radionuclide
^{165}Ho	100	650 ± 22	700 ± 20	64 ± 3	^{165}Ho$(n,\gamma)^{166}$Ho(26.8 h) → ^{166}Er
^{165}Ho	100	–	–	–	^{165}Ho$(n,\gamma)^{166m}$Ho(1200 y) → ^{166}Er
^{152}Sm	26.738	2970 ± 100	3020 ± 170	219 ± 8	^{152}Sm$(n,\gamma)^{153}$Sm(46.7 h) → ^{153}Eu
^{144}Sm	3.10	–	–	0.7	^{144}Sm$(n,\gamma)^{145}$Sm(340 d) → ^{145}Pm(17.7 y) → ^{145}Nd
^{150}Sm	7.40	–	255 ± 25	102 ± 9	^{150}Sm$(n,\gamma)^{151}$Sm(90 y) → ^{151}Eu
^{154}Sm	22.70	32 ± 6	–	–	^{154}Sm$(n,\gamma)^{155}$Sm(22.3 m) → ^{155}Eu(4.68 y) → ^{155}Gd

relatively low enrichment and specific activities resulted from production scale experiments with other metal phthalocyanines [3]. Chromium-51 of high specific activity was prepared by recoil enrichment, using pure crystalline potassium chromate as a target [5, 6]. Szilard--Chalmers process used to improve the specific activity of reactor produced ^{117m}Sn using tetraphenyl tin $(C_6H_5)_4$Sn [7]. Table 1 lists the isotopic abundance of natural Ho and Sm, cross sections, in addition to the all possible (n,γ) activation products [8].

Specific activity could be further enhanced considerably by using an enriched target (for ^{153}Sm), carrying out irradiation in high flux reactors, as well as by optimizing the duration of irradiation. On the other hand, using enriched targets have no sense in a low flux research reactor of the order of 10^{12} n·cm^{-2}·s^{-1} with restricted period of operation. The only way to improve the specific activity in this case is achieved by using the nuclear recoil effect. The aim of the present work is to investigate the nuclear recoil of ^{166}Ho and ^{153}Sm at a low thermal neutron flux reactor for improving their specific activity to be adequate for therapeutic applications.

Experimental

Materials

Organometallic compounds tris(cyclopentadienyl) holmium $(C_5H_5)_3$Ho(III), and tris(cyclopentadienyl) samarium $(C_5H_5)_3$Sm(III) were obtained from Alfa company and used without further purification. All chemical solvents, silica gel for column chromatography were of analytical reagent grade. Solvents were dried before using by MgSO$_4$ to prevent any scavenger action as a result of presence of moisture in solvents, in addition to the fact that the compounds under investigation are themselves moisture sensitive. Whatman Chr. 1 and Whatman Chr. 4 chromatographic paper were used for paper chromatography. Furthermore, thin-layer aluminum plates/silica gel (SG) were used for thin--layer chromatography (TLC).

Irradiation

A weighed amount of 5 mg was irradiated in the Syrian MNSR low power tank in a pool research reactor for 2 h at a thermal neutron flux of 10^{12} n·cm^{-2}·s^{-1} and at a temperature of approximately 50°C. The inner polyethylene capsule was encapsulated into the outer polyethylene capsule. Both of them were closed by thermal welding. The tightness of the inner capsules was examined by putting them in a hot water bath. At the end of bombardment, targets were cooled for 24 h to allow sodium and other short-lived isotopes to decay before chemical processing. $(C_5H_5)_3$Ho(III) and $(C_5H_5)_3$Sm(III), which are oxygen sensitive, were encapsulated in an inert dry atmosphere of nitrogen (99.999%) using a glove box.

Separation procedure

Separation methods of organic species from inorganic recoil species were chosen for both compounds according to their physical and chemical properties. Irradiated $(C_5H_5)_3$Ho(III) target was separated from inorganic recoil species by the following different four methods:

1. Sublimation was carried out at 230°C under vacuum. Thermostated glycerol bath was used for heating, and water for cooling. The sublimate was collected on a cold finger and dissolved in tetrahydrofuran (THF), while the inorganic species were dissolved in HNO$_3$ (65%). The two fractions were then counted.
2. Column chromatography was carried out. The irradiated target was dissolved in THF and chromatographed through $(1 \times 10$ cm) glass columns, which were packed with SG and conditioned with THF. THF was used as well for organic species elution. Inorganic recoil species, which remained concentrated at the top of the column, were eluted by HCl (1 M). The two fractions were then counted.
3. Paper chromatography using two different types of paper Whatman Chr. 1, and Whatman Chr. 4 with dimensions of $(1.5 \times 10$ cm) was carried out. THF was used as a solvent and a developer. Dividing chromatogram sheet into 10 equal pieces, each one of 1 cm length, and counting each one separately led to the conclusion that organic species moved 6 cm, while inorganic species remained almost at the point of spotting. Chromatographic papers were divided exactly in the middle to separate inorganic and organic parts. This choice was proved using beta scanner.
4. Thin-layer chromatography/silica gel (TLC/SG) using THF as a solvent, and both toluene and THF were used separately as developers.

Irradiated $(C_5H_5)_3$Sm(III) target could not be practically separated from inorganic recoil species by sublimation. In the literature only Burgess [1] mentioned that the sublimation temperature of $(C_5H_5)_3$Sm(III) was

possible within the range 200–250°C under vacuum. In other publications the sublimation temperature was not mentioned. Unfortunately, this different behavior could not be interpreted using different physical analytical methods: ultraviolet (UV), nuclear magnetic resonance (NMR), infrared (IR) spectroscopy for the compounds under investigation. So, in this work the separation for irradiated $(C_5H_5)_3$Sm(III) was not carried out by sublimation, but with two other methods: paper chromatography, and TLC using the same procedure as used in dealing with $(C_5H_5)_3$Ho(III).

After the decay of ^{166}Ho, the content of Ho carrier was analyzed by inductively coupled plasma mass spectroscopy (ICP-MS). It was found that the content of Ho carrier is beyond the detection limit of the used ICP-MS spectrometry (10 ppt). The enrichment factor for $(C_5H_5)_3$Ho(III) using sublimation, as a method of separation, was calculated using the value of the detection limit. The enrichment factor for $(C_5H_5)_3$Sm(III) could be calculated in a similar way.

Counting procedure

The activity of ^{166}Ho was measured by high resolution γ-spectrometry using an high purity germanium (HPGe) detector with a relative efficiency of 60%, where the efficiency was calibrated using multigammas standard source. Beta scanner was also used in some experiments for β$^-$ counting using paper chromatography as a method of separation. Liquid scintillation was used in some experiments of paper chromatography and TLC by measuring Cherenkov-photons using plastic vials as a converting media. Doing this, all the chemical and physical variations of the medium causing instabilities and insufficient reproducibilities by affecting the generation and transmission of the photons were eliminated. The last two methods of determining activities were used either for comparison with γ-spectrometry or obligatory when the activity was low (for ^{166}Ho) mea-
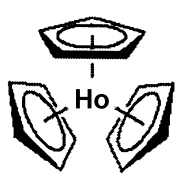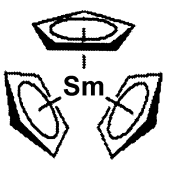
surement. On the other hand, measuring Cherenkov--photons or β$^-$ radiation could not be used for ^{153}Sm activity measurement because $(C_5H_5)_3$Sm(III) was of natural abundance. When sublimation and column chromatography were used, all samples were counted using equal volumes in reproducibly positioned identical vials to avoid error resulting from variations in counting geometry. The fixed counting geometry was taken into consideration using chromatography as well. The activity of ^{153}Sm was ascertained by only the previous high resolution γ-spectrometry. Finally, all the counting data were corrected for the dead time.

Results and discussion

The obtained results of the retention or parent yield, which is defined as $R = (A_{organic}/(A_{organic} + A_{inorganic}))$, where: $A_{organic}$ is the activity of organic species, and $A_{inorganic}$ is the activity of inorganic species, using different methods of separation are shown in Table 2. Extracted ^{166}Ho and ^{153}Sm yields, based on the total ^{166}Ho and ^{153}Sm radioactivities for each method of separation were listed in Table 2 as well. The values, in all cases, were averaged over several independent experiments.

With respect to $(C_5H_5)_3$Ho, a retention value of $0.2 \pm 0.1\%$ was obtained using sublimation. Another close value of retention of $0.4 \pm 0.1\%$ resulted using column chromatography as a method of separation. Corrections of the decay time and the distance from the detector for inorganic separated activity were made for the previous two methods because of its high value compared with the organic separated activity. The difference between retentions obtained by sublimation, and by column chromatography could be explained by the formation of different organic species as a result of hot reactions. It looks that these different organic species could not be sublimated with the parent target $(C_5H_5)_3$Ho using sublimation, but they were eluted as organic species using column chromatography.

Table 2. Parent yield and extraction yield of the studied compounds using different methods of separation

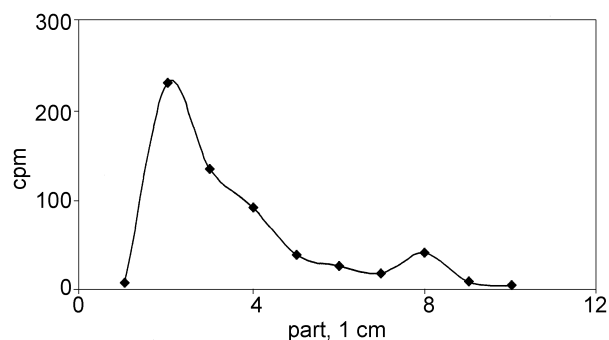| Target compound	Radioisotope	Method of separation	Retention (%)	Extraction yield (%)
$(C_5H_5)_3$Ho(III)	^{166}Ho	Sublimation	0.2 ± 0.1	99.80
		Column chromatography	0.4 ± 0.1	99.60
		Paper chromatography Whatman Chr. 1	0.11 ± 0.05	99.89
		Paper chromatography Whatman Chr. 4	0.4 ± 0.1	99.60
		Thin-layer chromatography THF	0	–
		Thin-layer chromatography Toluene	0	–
$(C_5H_5)_3$Sm(III)	^{153}Sm	Paper chromatography Whatman Chr. 1	0.06 ± 0.01	99.94
		Paper chromatography Whatman Chr. 4	0.5 ± 0.1	99.50
		Thin-layer chromatography THF	0	–
		Thin-layer chromatography Toluene	0	–

Fig. 1. ^{166}Ho activity distribution along 10 cm Whatman Chr. 4 chromatographic paper.

Paper chromatography, using Whatman Chr. 1 and Whatman Chr. 4, gave different values of retention $0.11 \pm 0.05\%$, and $0.4 \pm 0.1\%$, respectively. It is possible that, as a result of hot reactions, different kind of recoiled species affected by the type of chromatographic paper were formed. Recoiled species developing by Whatman Chr. 4 were more distinct than those developing by Whatman Chr. 1. It was also noticed that, the developing process using Whatman Chr. 4 was faster than using Whatman Chr. 1. This could be explained as a result of thickness difference between Whatman Chr. 1 and Whatman Chr. 4, and as a result of the difference of the interaction forces between the recoil products of these two compounds and the used chromatographic paper. It was also found that the retention value which was obtained using column chromatography, was equal to that one obtained using Whatman Chr. 4. This could lead to consider that using Whatman Chr. 4 was better than using Whatman Chr. 1 for $(C_5H_5)_3$Ho. The distribution of the activity of ^{166}Ho measuring Cherenkov-photons along the Whatman Chr. 4 chromatographic paper was shown in Fig. 1.

The obtained retention value of zero in both different cases, when toluene and THF where used as developers using TLC/SG, could be explained by suggesting that some of organic species of the studied compounds were able to be absorbed on the SG plate making the activity of the rest fraction of the organic species beyond of the detection limit of the detector (the relative efficiency 60%). Recoil products were not affected by the different polarity of toluene and THF, nevertheless the developing process was very slow comparing with the paper chromatography.

The difference in retention values resulted from the different methods of separation might be due to the polymeric different types of organometallic species which may be formed by the hot reactions during the irradiation process.

The obtained low retention values could be explained depending on the type of the chemical bonds in the studied compounds. The distinguishing feature of π-bonded compounds, like the compounds under investigation, was that the fragmented ligands could no longer gave rise to the same type of compounds or at least to another stable compounds at all. While it is possible that, for example, the atoms of C and O rapidly re-form a CO molecule which is then able to react further, the fragments of cyclopentadiene cannot be expected to arrange themselves so as to reform the original or any other π-bonding ligand. The molecule is

thus destroyed unless it can be reformed by an exchange reaction, or replaced by another molecule in which one or more ligands is σ-bonded [11].

Similar behavior of $(C_5H_5)_3$Sm(III) and $(C_5H_5)_3$Ho(III), and approximately equal retention values were found with respect to paper chromatography as well as to TLC. It seemed that neither the difference of electron configuration between Ho(III) $(4f^{10}5d^06S^2)$ and Sm(III)$(4f^65d^06S^2)$, nor the difference of ionic radii between them, which were 1.02 A^0, and 1.08 A^0, respectively, did affect the produced recoil products of corresponding compounds under investigation [4]. The calculated recoil energies from γ-emissions for ^{153}Sm (237.21 eV) and ^{166}Ho (213.72 eV) from the conservation of energy and momentum, supposing that the exciting energy were given off in a single γ-ray [11], seemed to have a neglected effect as well.

The obtained retention values of ^{166}Ho and ^{153}Sm in this work were obviously low comparing with the retention values of ^{59}Fe (38.24%), ^{97}Ru (12.10%), ^{60}Co (25%), and ^{65}Ni (65%) in their bis(cyclopentadienyl) compounds taking into consideration that the calculated recoil energies of these radionuclides were as follows: ^{59}Fe (696.31 eV), ^{97}Ru (409.09 eV), ^{60}Co (683.45 eV), and ^{65}Ni (629.37 eV) [12]. This could be explained by the influence of different factors, for example, the additional C_5H_5 ring of the compounds under investigation, or it could be explained by the influence of the internal conversion and Auger ionization as a competitive de-excitation mode, especially that ^{153}Sm and ^{166}Ho have higher atomic numbers, in which the atomic and nuclear wave functions have a greater overlap [11]. Moreover, the molecules containing atoms that undergo internal conversion or electron capture are a subject to extensive decomposition. This decomposition results from the large number of electrons that an atom loses as it adjusts to a vacancy in one of its inner shells. Electrons are pulled from the rest of the molecule to the region of high positive charge, and the whole molecule literally exploded by Coulombic repulsion [10], so the retention will be lower.

The obtained gain of the extraction yields in this work was high (about 50%) compared with the only reported case of holmium organometallic compounds to date by Zeisler *et al.* [14]. The big difference of the extraction yields between the compounds under investigation in this work and the mentioned holmium organometallic compounds of which the highest recorded result was 48.0% could be explained as a result of many factors. Firstly, the recoil energy of compounds, which studied by Zeisler *et al.*, had a good chance of being dissipated throughout the molecule before the recoil atom could leave its immediate neighborhood assuming that at least the ligands remain intact, which is slightly probable in the case of compounds under investigation. Secondly, the possible effect of the donor atoms (oxygen or nitrogen), which existed in the compounds studied by Zeisler *et al.*, did not exist in the investigated compounds in this work. Thirdly, the effect of different chemical bonding type. Finally, the big difference of the spatial arrangement of the ligands around the metal.

Besides, the obtained extraction yields in this work were high compared with the other lanthanide ^{142m}Pr recorded by Zeisler *et al.* [13]. The difference of the

Table 3. The obtained enrichment factor for ^{166}Ho in $(C_5H_5)_3$Ho(III) compound using sublimation as a method of separation

Sample no.	After separation			Without separation			E_f
	A (µCi)	W (µg/ml)	S_A (Ci/g)	A (µCi)	W (µg/ml)	S_A (Ci/g)	
1	117.94	1.00E-05	11 794 000	118.27	184	0.64	1.8E+07
2	92.52	1.00E-05	9 252 266	92.59	138	0.67	1.4E+07

extraction yields between the compounds under investigation and the other praseodynium organometallic compounds could be because of the previously mentioned reasons of holmium organometalic compounds in addition to the effect of different recoil energies of ^{166}Ho and ^{142m}Pr. Table 3 represents the obtained enrichment factor which is defined as follows: $E_f = (S_A$ (after separation)$/S_A$ (before separation)) where: S_A – (after separation) the specific activity using the separation and S_A – (before separation) the specific activity without considering the effect of nuclear recoil for the same sample; A – the activity of ^{166}Ho; w – the concentration of ^{165}Ho in the sample.

The specific activity after separation (S_A (after separation)) was calculated by dividing the activity of separated inorganic species (A), upon the concentration of ^{165}Ho in this separated inorganic species after the decay of ^{166}Ho (W). This content of Ho carrier was analyzed by ICP-MS. It was found that, the content of Ho carrier was beyond the detection limit of the used ICP-MS spectrometry (10 ppt, which means that the maximum concentration of ^{165}Ho was 1.00E-05 µg/ml). The specific activity without separation or before separation (S_A – (before separation)) (i.e. without considering of the effect of the nuclear recoil for the same sample) was calculated by dividing the activity of the whole sample upon the concentration of ^{165}Ho in the whole sample (W). The activity of separated inorganic species and the activity of the whole sample were measured by gamma spectrometry (HPGe 60%) after the necessary calibration.

Comparing with the highest enrichment factor that was obtained by Zeisler [14], which was equal to 66, a considerable gain was achieved in this work. It is also worth to notice that the averaged enrichment factor was greater than 1.6×10^7 and was obtained for only 2 h of irradiation, and this value might be increased many orders when irradiation for a longer period of time is carried out.

Conclusion

The results showed that the specific activities of ^{166}Ho and ^{153}Sm could be extremely increased by using hot atom reactions in tris(cyclopentadienyl) compounds of holmium and samarium irradiated in a low flux reactor like the Syrian MNSR. It was found that $(C_5H_5)_3$Ho(III), and $(C_5H_5)_3$Sm(III) had very small retention values and low dissociation showing a great importance with respect to radioisotope productions, where almost all resulting ^{166}Ho formed in inorganic form that could be quantitatively separated. Considerable gains in the extraction yield, as well as in the enrichment factor were achieved. Sublimation and column chromatography were methods of choice for $(C_5H_5)_3$Ho(III) separation. Paper chromatography was a method of choice for analysis, but TLC was out of choice neither for analysis, nor for separation for both compounds under investigation.

References

1. Burgess J, Cotton SA, Criddle AJ *et al.* (1995) Dictionary of organometallic compounds. Chemical database, 2nd ed. Chapman & Hall, London
2. Chakraborty S, Unni PR, Venkatesh M, Pillai MRA (2002) Feasibility study for production of ^{175}Yb a promising therapeutic radionuclide. Appl Radiat Isot 57:295–301
3. Collins KE, Catral JC, Toh WT, Detera SD, Kapauan PA (1972) A novel preparation of high specific activity radionuclides. Radiochem Radioanal Lett 11;5:303–305
4. Crabtree RH (2005) The organometallic chemistry of the transition metals, 4th ed. John Wiley & Sons, INC Publication, New Jersey
5. Iqbal M, Ejas M (1978) Enrichment of ^{51}Cr through Szilard-Chalmers effect. J Radioanal Chem 45:185–188
6. Mani RS, Chowdhary SY (1966) Preparation of chromium-51 of high specific activity for medical use. Curr Sci 9:230–232
7. Mausner LF, Mirzadeh S, Srivastava SC (1992) Improved specific activity of reactor produced ^{117m}Sn with the Szilard-Chalmers process. Appl Radiat Isot 43;9:1117–1122
8. Mednis IV (1991) Cross section for nuclear reactions for neutron activation analysis. Izdatelstvo 'Zinatne', Riga
9. Sekine T, Kimura K, Yoshihara K (1986) Application of nuclear recoil to radioisotope enrichment of copper-64. J Nucl Sci Technol 23;12:1064–1068
10. Walton GN (1979) Source papers in hot atom chemistry. Prog Nucl Energy 4:183–214
11. Wiles DR (1973) The radiochemistry of organometallic compounds. Adv Organomet Chem 11:207–252
12. Yassine T (1987) The hot atom chemistry of some metal complexes and its application to radioisotope production. PhD thesis, Salford University
13. Zeisler SK, Backer DW, Weber K (1999) Szilard-Chalmers effect in praseodymium complexes. J Radioanal Nucl Chem 240:637–641
14. Zeisler SK, Weber K (1998) Szilard-Chalmers effect in holmium complexes. J Radioanal Nucl Chem 227:105–109