

The Szilard–Chalmers effect in macrocyclic ligands to increase the specific activity of reactor-produced radiolanthanides: Experiments and explanations

By K. P. Zhernosekov¹, D. V. Filosofov² and F. Rösch^{1,*}

¹ Institute of Nuclear Chemistry, Johannes Gutenberg-University, 55128 Mainz, Germany

² Joint Institute of Nuclear Research, Laboratory of Nuclear Problems, 141980 Dubna, Russian Federation

(Received December 13, 2011; accepted in final form April 11, 2012)

(Published online August 13, 2012)

*Medical radionuclides / Szilard–Chalmers effect /
Reactor-produced radionuclides / Ho-166 /
Macrocyclic ligands / DOTA / Specific activity*

Summary. Successful utilization of medical isotopes in the radiolabeling reactions to a significant degree depends on the technically achievable specific activity. In this respect, the Szilard–Chalmers effect is considered in detail as a radiochemical tool to increase the specific activity of radionuclides produced by direct nuclear reactions. In the present study, a physico-chemical model is described utilizing the specific aspects of thermodynamically and kinetically stabilised metal-ligand complexes. The approach is applied as a proof-of-principle study to increase the specific activity of ¹⁶⁶Ho, produced *via* the (*n*, γ) nuclear reaction. As a target material, ¹⁶⁵Ho-DOTA is used. In this case, ¹⁶⁶Ho, the product nucleus of the neutron capture reaction, is obtained chemically as non-complexed cationic ¹⁶⁶Ho^{III} species *in situ*. Consequently, it can effectively and quantitatively be separated from the inactive ¹⁶⁵Ho-DOTA target material by means of fast and simple chromatographic, column-based methods.

We were able to verify the physico-chemical model by the experimentally obtained data. For the first time we quantitatively describe the interaction of the ligand-framework of the target material (*e.g.* the Ho-DOTA complex) with the radiation field of the nuclear reactor. The analysis of the experimental data allows to assume that radionuclides with half-lives of $T_{1/2} < 64$ h can be produced at a TRIGA II nuclear reactor *via* the Szilard–Chalmers effect with specific activities higher than in the case of direct irradiation of common target materials such as oxides.

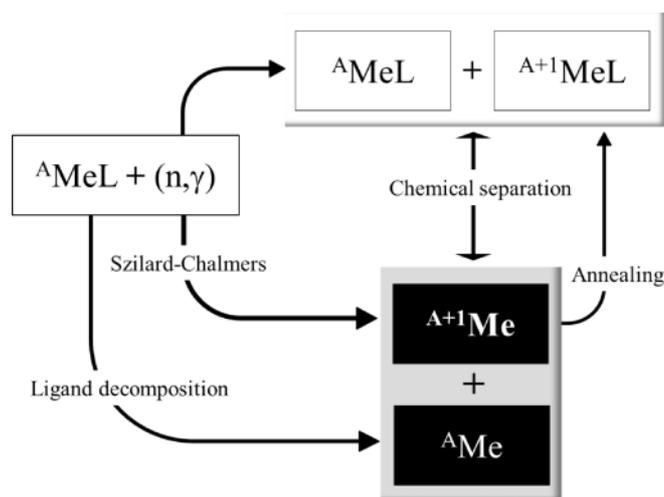
1. Introduction

The preparation of diagnostic or therapeutic radiopharmaceuticals strongly depends on the technically achievable specific activity of the radionuclides. There is a large number of radionuclides with decay characteristics useful for medical applications which, however, cannot be applied for the radiolabeling due to low achievable specific activity.

The Szilard–Chalmers effect is defined as the rupture of the chemical bond between an atom and the molecule of which the atom is part, as a result of a nuclear reaction of that atom (IUPAC 1994). Its discovery belongs to L. Szilard and T. A. Chalmers, who presented an isolation possibility of an iodine radioisotope from the irradiated target material, produced by neutron irradiation of ethyl iodide [1]. Due to the stabilisation of the produced radionuclide in a chemical species different from the initial and non-reacted one, its chemical isolation from the bulk of the target material species can be performed (this effect is in particular relevant, as “conventional” chemical separation techniques based on differences between chemical properties of the two isotopes of the element would fail to achieve sufficient separation). However, decomposition of the target materials due to primary irradiation effects (*i.e.* nuclear reactions with various atoms of the target material) and secondary effects like ionisation and retention may limit the efficacy of the yield of these “nuclear” processes. Thus, essential physico-chemical aspects and mathematical models were considered to predict the usefulness of the Szilard–Chalmers effect to increase the specific activity of radionuclides, produced in nuclear reactors [cf. *e.g.* 2]. The specific activity was shown to be a complicated dynamical function, owing mostly to the radiolytical decomposition of composite target materials (such as organohalides or metallo-complexes). Further, the theory was extended in an attempt to develop a relation between the retention of the produced radionuclide in the target material (and therefore not separable) and the radiation dose rate [3, 4].

Of special interest regarding the Szilard–Chalmers effect seems to be the possibility to increase the specific activity of reactor produced metallic radionuclides. Various investigations were performed at nuclear reactors utilizing metallo-complexes as targets, mainly phthalocyanines [5–7] or others [8]. The “free” radiometal species are produced *in situ*, and can subsequently be separated from the inactive bulk of the metallo-complex. In those works, however, the basic physico-chemical model [2] was as a rule neglected. However, research directed towards increasing the specific activity of reactor-produced medically relevant radiometals is ongoing. Recently, oxinate complexes of molybde-

*Author for correspondence (E-mail: frank.roesch@uni-mainz.de)
The corresponding author of this article is a member of the Editorial Advisory Board of this journal. Editor



Scheme 1. Principal processes involved in Szilard–Chalmers like nuclear reactions.

num and yttrium were used to generate ^{99}Mo and ^{90}Y of increased specific activities following neutron capture reactions [9].

Theoretically, metallo-complexes allow to expect a high isotope enrichment of reactor produced radiometals. Due to low cross sections of (n, γ) reactions on atoms involved in typical organic framework of the common complex ligands (basically C, H, O, N, S), a high radiolytic stability of the composite target can be provided. Nevertheless, the radiolytic decomposition needs to be quantitatively evaluated to consider the intense background radiation field (mainly photon radiation) of a nuclear reactor.

Retention of the produced radionuclide in the same chemical speciation as in the target material is a critical factor for efficient radionuclide separation and corresponding production yields. The existing models consider retention processes as induced by radiation annealing [2, 3]. Chemical properties of metallo-complexes, however, can be more relevant. Low kinetic inertness and thermodynamic stability may lead to high retention and decreased specific activity due to isotope exchange processes (defined as 2nd retention). Scheme 1 describes schematically the main processes involved.

Alternatively, ligands should be considered which combine high thermodynamic with high kinetic stability of the target metallo-complexes. In particular, those ligands are attractive which form stable complexes only after sophisticated reaction conditions, *e.g.* long reaction times and elevated temperatures. In this work we develop a new chemical strategy and discuss its physico-chemical model, meeting the essential factors mentioned above. As a proof-of-concept, the method is applied to (n, γ) produced ^{166}Ho , irradiating a ^{165}Ho -DOTA complex (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; $[\text{HoC}_{16}\text{H}_{24}\text{N}_4\text{O}_8]^-$) at the TRIGA II Mainz nuclear research reactor.

2. Chemistry

The nuclear reaction $^{165}\text{Ho}(n, \gamma)^{166}\text{Ho}$ was selected as a proof-of-principle system. ^{166}Ho itself represents a ra-

dionuclide used in nuclear medicine practice ($T_{1/2} = 26.80$ h, $\sigma = 61$ barn). Neutron capture cross section is relatively low and thus the specific activities are also relatively low – despite the 100% abundance of the target isotope ^{165}Ho . Consequently, an alternative route is applied utilizing double neutron capture on ^{164}Dy producing ^{166}Dy , which decays with a half-life of 81.5 h and leads to the carrier-free ^{166}Ho .

To apply a ^{165}Ho -complex as target material, in the present work a macrocyclic chelator, namely 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA, $\text{C}_{16}\text{H}_{28}\text{N}_4\text{O}_8$) was selected. A favourable property of DOTA is its exceptional kinetic inertness as well as high thermodynamic stability. Among the developed chelate ligands for trivalent lanthanides, DOTA seems to be still the best choice if stability and inertness of complexes are major requirements [10, 11]. DOTA and its metallo-complexes are water soluble. At neutral pH, DOTA forms negatively charged complexes with trivalent cations of type $[\text{Me-DOTA}]^-$. This property can be useful for subsequent chemical isolation of the metal released after the nuclear reaction. Thus, cationic Ln^{III} species can be quantitatively adsorbed on a cation-exchanger from aqueous solutions, while adsorption of a negatively charged complex such as $[\text{Me-DOTA}]^-$ onto the resin should be negligible.

3. Experimental

3.1 Target material

Only analytical-reagent grade chemicals and Milli-Q water (18.2 M Ω cm) were used in the experiments performed. 60 mg of ^{165}Ho , in nitrate form, were irradiated at the TRIGA II Mainz reactor to obtain about 14 MBq of ^{166}Ho activity. For preparation of $\text{K}[\text{Ho-DOTA}]$ complexes, 10 ml of the aqueous solution of $^{166/165}\text{Ho}(\text{NO}_3)_3$ (60 mg Ho) was mixed with 122 mg of DOTA, providing a molar ratio of $\sim 6 : 5$, respectively. About 1 mmol of KOH was added to achieve a pH of ~ 6 . The mixture was kept at 98 °C for 30 min. The yield of complex formation was analysed by TLC (aluminium sheets silica gel 60; 0.1 M sodium citrate eluent). Radio-TLC analysis was possible due to the presence of radioactive $^{166}\text{Ho}^{\text{III}}$ in the system. Within about 1 h a stable reaction yield of $\sim 80\%$ was achieved.

Separation of $[\text{Ho-DOTA}]^-$ from un-complexed Ho^{III} was done on a chromatographic column of 8×140 mm dimension, filled with cation-exchanger Bio-Rad AG 50W-X8, 200–400 mesh, in K^+ -form. The reaction mixture was passed through the column. Free $^{166/165}\text{Ho}^{\text{III}}$ was quantitatively absorbed on the resin while the $^{165}\text{Ho-DOTA}$ complex (1 : 1 stoichiometry) could be obtained in the eluate. $^{166/165}\text{Ho}^{\text{III}}$ was subsequently washed from the resin by 4 M HCl solution. The activity of ^{166}Ho in the obtained fractions was analysed by γ -ray spectrometry using a Ge-detector.

Final chemical control of the obtained $^{166/165}\text{Ho-DOTA}$ solution by TLC confirmed the absence of free holmium in the system. Therefore, the $\text{K}[\text{Ho-DOTA}]$ complex was prepared without an excess of the ligand or the metal in the system.

3.2 Irradiation and target processing

For irradiations, the aqueous solution of K[¹⁶⁵Ho-DOTA] (1 mg Ho) was evaporated in a polyethylene capsule at < 100 °C. The irradiations were performed at the TRIGA II Mainz nuclear reactor at a thermal neutron flux of $4 \times 10^{12} \text{ cm}^{-2} \text{ s}^{-1}$, external temperature $\sim 21 \text{ °C}$, for different irradiation periods of 0.5–6 h, resulting in 10–120 MBq batch activities of ¹⁶⁶Ho.

Irradiated samples were dissolved in 3 ml of water and loaded on a chromatography column of $4 \times 50 \text{ mm}$ dimension, filled with cation-exchanger Bio-Rad AG 50W-X8, minus 400 mesh, in NH_4^+ -form. The [^{165/166}Ho-DOTA]⁻ was removed by washing the column with water. The cationic ^{166/165}Ho^{III} species was eluted with 0.20 M α -HIBA (α -hydroxy-isobutyric acid, adjusted with ammonium hydroxide to pH 4.75). Quantitative distribution of the radioactivity was determined by γ -ray spectrometry using a Ge-detector.

In order to determine the amount of stable ¹⁶⁵Ho, remaining in the ionic ^{166/165}Ho fraction obtained after Szilard–Chalmers effect, aliquots of the ^{166/165}Ho- α -HIBA fraction were evaporated. At least after 10 half-lives of the radionuclide they were irradiated under the same conditions as the initial target material.

4. Physico-chemical model of the process

In the following, some parameters are defined with individual symbols and units. Those are summarized in Table 1.

If the target burn-up is neglected, the accumulation of a radionuclide production rate during a nuclear reaction can

be described by the differential equation:

$$\frac{dN^*}{dt} = \Phi_0 \sigma N - \lambda N^* \quad (1)$$

where N^* represents the number of the formed radioactive nuclei, N the number of target nuclei at the start of irradiation, Φ_0 the neutron flux [$\text{cm}^{-2} \text{ s}^{-1}$], σ the cross section of the nuclear reaction [cm^2], and λ [s^{-1}] the decay constant. The solution for the differential Eq. (1) is

$$N^*(t) = \frac{\Phi_0 \sigma N}{\lambda} (1 - \exp(-\lambda t)), \quad (2)$$

and the ratio S of the produced “hot” atoms to stable target atoms after a given irradiation time t can be found as:

$$S(t) = \frac{N^*(t)}{N} = \frac{\Phi_0 \sigma}{\lambda} (1 - \exp(-\lambda t)). \quad (3)$$

The limiting S_∞ -value, which can be achieved at saturation ($t \rightarrow \infty$) may be found by:

$$S_\infty = \frac{\Phi_0 \sigma}{\lambda}. \quad (4)$$

After a Szilard–Chalmers effect, following an irradiation of a composite target, an accumulation of the radionuclide as a chemical species separable from the target material N_{SC}^* is given, considering the retention of the isotope formed as an inseparable chemical species (same as the target isotope) (1st retention) and/or after that, due to isotope exchange processes (2nd retention):

$$\frac{dN_{\text{SC}}^*}{dt} = \Phi_0 \sigma N(1 - R) - \lambda N^*, \quad (5)$$

Table 1. Parameters used in the experimental and theoretical explanations.

Parameter	Physical meaning	Unit
N	Number of stable nuclei of the irradiated isotope	
N^*	Number of the radioactive nuclei formed after the neutron capture	
Φ_0	Neutron flux	$\text{cm}^{-2} \text{ s}^{-1}$
σ	Cross section for the neutron capture reaction	cm^2
λ	Decay constant	s^{-1}
t	Time of irradiation	s
S	Ratio of the formed radioactive nuclei to stable nuclei of the target N^*/N	
S_∞	Ratio of the formed radioactive nuclei to stable nuclei of the target N^*/N at saturation	
S_{SC}^*	Ratio of the radioactive nuclei after Szilard-Chalmers effect to the stable nuclei of the target in separable form	
N_{SC}^*	Number of the radioactive nuclei formed after the neutron capture and which are released from the original complex	
N_s^*	Number of radioactive nuclei formed after the neutron capture, not separable from the target material	
R	Fraction of the radioactive nuclei formed after the neutron capture and which remain in the original complex	
$1 - R$	Loss of the formed radionuclide in the form chemically inseparable from the target material	
k	Constant of the radiolytic decomposition rate of the complex	cm^2
ζ	Fraction of the target material, remaining intact after chemical processing	
$1/\zeta$	Decontamination factor of the nuclide fraction from the original target material by the chemical separation	
ψ	Radioisotope enrichment factor	

where R represents the fraction of N^* remaining as the inseparable chemical species.

Radiolytical decomposition of the target material (e.g. metallo-complex) due to the decomposition of the ligands chemical structure and transition of the stable isotope into a cationic form (the same as the radionuclide produced), i.e. $\text{MeL} \rightarrow \text{M}^{x+} + \text{L}^{y-}$, can be given by:

$$\frac{dN_s}{dt} = \Phi_0 k N, \quad (6)$$

where N_s is the number of the stable nuclei as the separable chemical species and k the constant of the radiolytic decomposition rate [cm^2]. Here, k reflects an intensity of the interaction of the ligand framework with the radiation field. The solutions of the differential Eqs. (5) and (6) lead to:

$$N_{\text{SC}}^*(t) = \frac{\Phi_0 \sigma N(1-R)}{\lambda} (1 - \exp(-\lambda t)), \quad (7)$$

$$N_s(t) = N(1 - \exp(-\Phi_0 k t)), \quad (8)$$

and the S_{SC}^* after the Szilard–Chalmers effect at any time of the irradiation can be found as:

$$S_{\text{SC}}^*(t) = \frac{N_{\text{SC}}^*(t)}{N_s(t)} = \frac{\Phi_0 \sigma}{\lambda} (1-R) \frac{1 - \exp(-\lambda t)}{1 - \exp(-\Phi_0 k t)}. \quad (9)$$

The efficiency of the Szilard–Chalmers effect to increase the specific activity can be assessed by the ratio of the rate of radiolytic decomposition of the target material to the decay of the formed radionuclide, i.e.

$$(1-R) \frac{\Phi_0 k}{\lambda}. \quad (10)$$

R considers the fraction of the radionuclide in a form chemically inseparable from the target material. If the rate of the radiolytic decomposition of the target is lower than the decay rate of the formed radionuclide $\Phi_0 k / \lambda < 1$ and $R \rightarrow 0$, accordingly to Eq. (9), a ratio S higher than the limiting value, $S_{\text{SC}}^* > S_{\infty}$, can be achieved.

Fig. 1 represents the dependences of S_{SC}^* on the time of irradiation for ^{166}Ho ($T_{1/2} = 26.80$ h, $\lambda_{^{166}\text{Ho}} = 0.259$ h $^{-1}$) produced using Szilard–Chalmers effect after (n, γ) nuclear reaction. The different values of ratio (Eq. 10) at $R = 0$ (lines 2–4) are compared to S (Eq. 3; line 1). There is a positive effect (namely $S_{\text{SC}}^* > S$), for any values of the ratio (Eq. 10). If the rate of the radiolytic decomposition is higher than the rate of the radioactive decay (line 2 – $\Phi_0 k = 2\lambda_{^{166}\text{Ho}}$) the S increases and approaches the limiting value. In the case of $\Phi_0 k = \lambda$ the S does not depend on the time of irradiation (line 4) and is equal to S_{∞} . For $\Phi_0 k < \lambda$ (line 3 – $\Phi_0 k = 0.33\lambda_{^{166}\text{Ho}}$) S_{SC}^* decreases, having a maximum value of $S_{\text{SC}}^* = S_{\infty} \lambda_{^{166}\text{Ho}} / \Phi_0 k$ at the beginning of irradiation, and approaches the limiting value S_{∞} .

In Fig. 2, lines (2', 3') represent the same conditions as those given in Fig. 1 for (2, 3), reflecting additionally 50% retention of the formed radionuclide as chemically inseparable species ($R = 0.5$). The S_{SC}^* approaches the value $S_{\infty}(1-R)$ and due to losses of the activity, at some point, becomes even lower than S .

The chemical isolation of the produced radionuclide after the irradiation provides a purification factor which should be

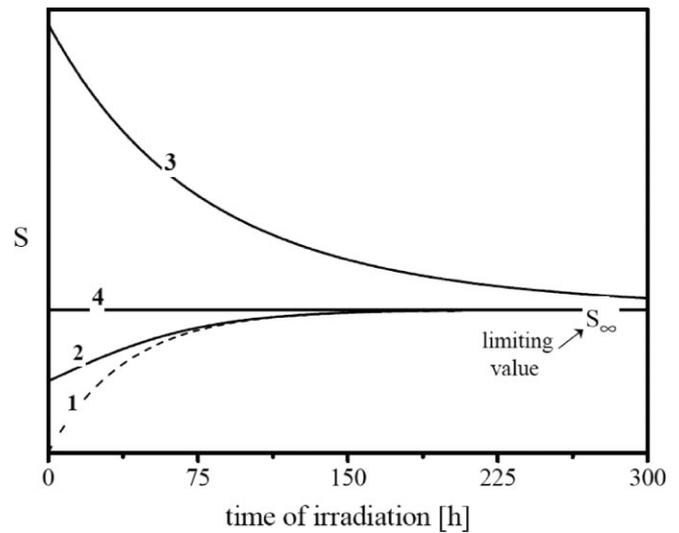


Fig. 1. S values (ratio of the formed radioactive nuclei to stable nuclei of the target N^*/N) as calculated by Eq. (3) (no effect) (line 1); S_{SC}^* by Eq. (9) (after Szilard–Chalmers effect) for different value of ratio (Eq. 10) and $R = 0$; $k\Phi_0 = 2\lambda$ (line 2); $k\Phi_0 = \lambda$ (line 4); $k\Phi_0 = 0.33\lambda$ (line 3). Y axis is linear.

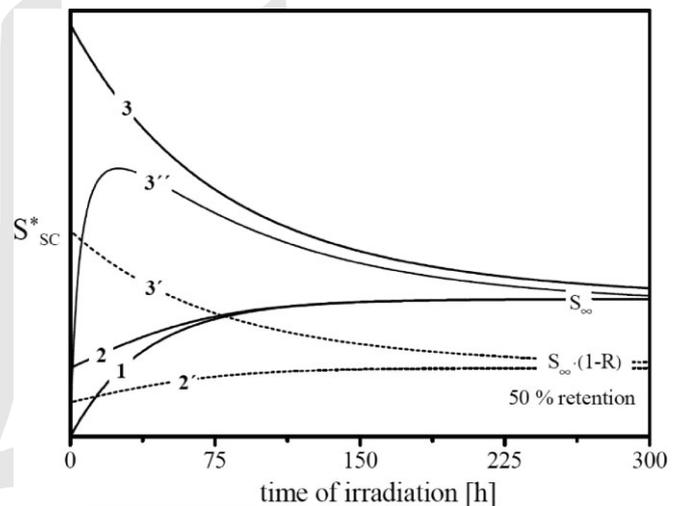


Fig. 2. S_{SC}^* values (ratio of the radioactive nuclei after Szilard–Chalmers effect to the stable nuclei of the target as separable chemical species) as calculated by Eq. (9) for different values of ratio (Eq. 10). Lines (1–3) identical to those in Fig. 1; lines (2' and 3') are given with consideration of 50% retention, $R = 0.5$; line (3'') with consideration of subsequent chemical separation factor of 20 (Eq. (11), see text). Y axis is linear.

taken into account by an additional member in Eq. (9):

$$S_{\text{SC}}^*(t) = \frac{N^*}{N_{\text{st}}} = \frac{\Phi_0 \sigma}{\lambda} (1-R) \frac{1 - \exp(-\lambda t)}{\zeta + (1 - \exp(-\Phi_0 k t))}, \quad (11)$$

where ζ is the fraction of the original target material, which was not removed after the chemical separation.

Fig. 2 represents an example of a profile of the S_{SC}^* -value on the time of irradiation for $\Phi_0 k < \lambda$, ($R = 0$) (line 3), line 3'' with consideration of the subsequent chemical purification with a reduction of the target material by a factor of 20 ($\zeta = 0.05$). ζ decreases the S_{SC}^* value and has the highest impact at the beginning of the irradiation, i.e. short irradiation periods.

An enrichment factor Ψ can be defined as a ratio of the S_{SC}^* -value after the Szilard–Chalmers effect to the S -value defined by the Eq. (3):

$$\Psi = \frac{S_{SC}^*}{S} = (1 - R) \frac{1}{\zeta + (1 - \exp(-\Phi_0 kt))}. \quad (12)$$

It can be concluded from Eqs. (9)–(12) and the discussion above, that the Szilard–Chalmers process is most effective if the rate of the radiolytic decomposition of the target material is lower than the rate of the radioactive decay of the radionuclide produced, *i.e.* ($\Phi_0 k < \lambda$). The method seems to be especially promising for production of short-lived radionuclides and for limited conditions of irradiation—low neutron flux and/or limited period of irradiation.

5. Results and discussion

An elution profile of processing the irradiated target on the cation-exchange column is shown in Fig. 3. $^{166/165}\text{Ho}^{\text{III}}$ as stabilised in a “free” cationic form was quantitatively absorbed on the resin. In contrast, both the non-radioactive target material ^{165}Ho -DOTA and ^{166}Ho retained in the form of ^{166}Ho -DOTA complex passed the column (*cf.* Fig. 3). As described above this fraction of ^{166}Ho inseparable from the target material is referred as R -value (Eqs. 5–12).

After the $^{165/166}\text{Ho}$ -DOTA fraction had passed, the column was additionally washed well with water until the activity level in the eluted fractions was reduced to a level $< 10^{-3}$ of the total ^{166}Ho activity. This avoids a contamination of the enriched ionic $^{166/165}\text{Ho}^{\text{III}}$ with the target material. Finally, ionic $^{166/165}\text{Ho}^{\text{III}}$ could be effectively eluted with 2 ml of 0.2 M α -HIBA. In order to determine the specific activity of ^{166}Ho achieved after the Szilard–Chalmers effect, the obtained fractions of ^{166}Ho were stored for ≥ 10 half-lives of the radionuclide. ^{166}Ho decays to stable ^{166}Er , with the amount of stable ^{165}Ho unchanged. The samples were finally irradiated at the same neutron flux within a standard neutron activation process. This time the absolute ^{166}Ho activity determined after the irradiation reflected the amount of stable ^{165}Ho retained in the enriched ^{166}Ho fraction. The ratio of

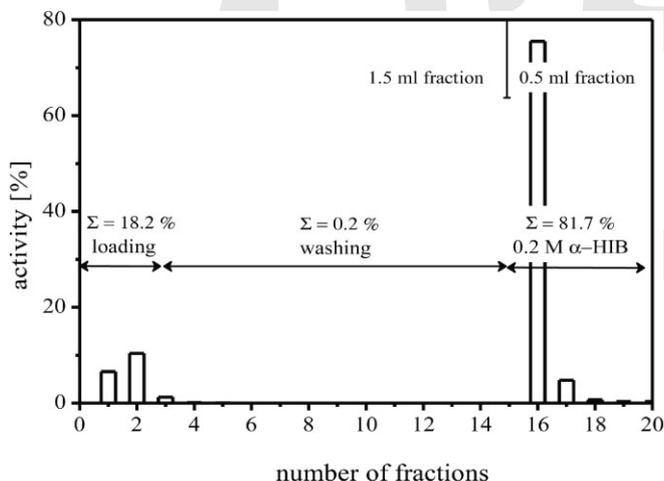


Fig. 3. Elution profile while processing the irradiated target material on the chromatography column 4×50 mm Bio-Rad AG 50W-X8, minus 400 mesh, NH_4^+ -form.

Table 2. Experimentally obtained enrichment factor ξ and retention value R of $^{166}\text{Ho}^{\text{III}}$ for different times of irradiation of the ^{165}Ho -DOTA complex (TRIGA II research reactor Mainz, thermal neutron flux = $4 \times 10^{12} \text{ cm}^{-2} \text{ s}^{-1}$).

Period of irradiation [h]	Fluence [neutron/cm ²]	Enrichment factor Ψ	R [%]
0.5	7.2×10^{15}	90.0	13.2
1	1.4×10^{16}	50.6	24.5
2	2.9×10^{16}	31.1	11.3
4	5.8×10^{16}	21.5	18.0
6	8.6×10^{16}	7.3	10.3

the initial activity of the fraction to the activity obtained after the subsequent irradiation, normalized to the time of the first and second irradiations, respectively, corresponds to the experimental $\Psi/(1 - R)$ value (Eq. 12). In all cases, the second irradiation of the isolated cationic fraction provided a lower radioactivity of ^{166}Ho in comparison to the initial irradiation of the ^{165}Ho -DOTA complex. It immediately indicated an increase of the technically achievable specific activity after the Szilard–Chalmers effect.

Experimentally obtained enrichment factors and retentions of ^{166}Ho obtained for different irradiation periods are summarised in Table 2.

5.1 Enrichment factor Ψ

The enrichment factor Ψ decreases with the increasing irradiation period and/or the neutron fluence, as it was predicted by the physico-chemical model of the process discussed above [2]. The experimentally obtained data represent resultant $\Psi/(1 - R)$ values and are presented for different periods of irradiation graphically in Fig. 4. The enrichment factor is high for short irradiations, *e.g.* about 100 for 0.5 h, and decreases rapidly with the prolongation of the irradiation time.

5.2 Radiolytic decomposition

According to Eq. (12) it is possible to derive the rate constant of the radiolytic decomposition k [cm²] of the target

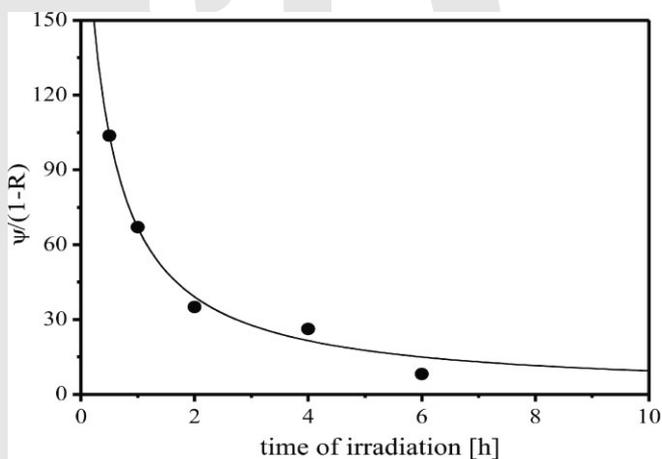


Fig. 4. Experimentally obtained resultant $\Psi/(1 - R)$ values for different irradiation periods (Table 2); solid line depicts the fit of experimental data with Eq. (12).

material. According to its unit of cm^{-2} it could be understood as a cross section analogue. The experimental values of $\Psi/(1-R)$ for different irradiation periods are given in Fig. 4. The data were fitted with Eq. (12) (solid line in Fig. 4). The best approximation ($R^2 = 0.987$) was achieved with two variables k and ζ , resulting in $k = 7.5(1.5) \times 10^{-19} [\text{cm}^2]$ and $\zeta = 4(1) \times 10^{-3}$ (for ζ see Sect. 5.3).

For the first time we quantitatively describe the interaction of a metallo-organic compound with the radiation field of a nuclear reactor. The experimentally obtained cross section of decomposition k value of $\sim 750\,000$ barns [$1 \text{ barn} = 10^{-24} \text{ cm}^2$] is much higher than the sum of the cross sections for all (n,x) reactions on the nuclei being part of the ligands framework, *i.e.* those of Ho-DOTA complex (for DOTA = $\text{C}_{16}\text{H}_{24}\text{N}_4\text{O}_8$, the $\Sigma\sigma$ is 15.6 barns). It reflects the intense interaction of the complex with the background component of the radiation field, accompanying thermal neutrons. In particular the photon irradiation in the reactor core can lead to the decomposition of the organic component of the metal-ligand target complex and therefore to the release of the stable $^{165}\text{Ho}^{\text{III}}$.

5.3 Retention

Retention of the produced ^{166}Ho as chemically inseparable species (*i.e.* in the form of a ^{166}Ho -DOTA complex) was in the range of 10.3–24.5%. There is no correlation of $^{166}\text{Ho}^{\text{III}}$ retention with the duration of irradiation. This may be explained by the absence of an influence of radiation annealing on the retention mechanism.

The fraction of the target material ζ (Eq. 11) which cannot be isolated chemically after the processing of the irradiated target was estimated to be about 0.004(1) (0.4%), corresponding to a decontamination factor of about 250.

5.4 Specific activity

Since $\Phi_0 k < \lambda_{^{166}\text{Ho}}$, a specific activity for ^{166}Ho higher than the maximum achievable value at saturation $\sim 0.9 \text{ GBq/mg}$ for the standard (n, γ) irradiation at the TRIGA II reactor Mainz, could be achieved. In practice, with a maximum available irradiation period of 6 h at that reactor, ^{166}Ho can be produced with a specific activity of 128 MBq/mg only, if a simple target such as the oxide is irradiated. In contrast, it was possible to achieve specific activities of up to $\sim 2 \text{ GBq/mg}$ by irradiation of ^{165}Ho -DOTA, following a relatively simple chemical processing of the irradiated target material.

6. Conclusion

The Szilard–Chalmers effect is considered in detail as a radiochemical tool to increase the specific activity of radionuclides produced at nuclear reactors. In the present study, this

approach was extended by utilizing macrocyclic chelators to coordinate lanthanides with high thermodynamic and high kinetic stability. The concept was successfully applied to produce ^{166}Ho *via* the (n, γ) nuclear reaction, with a specific activity much higher than any common value available for the Mainz TRIGA II nuclear reactor. The model was successfully applied considering the radiolysis of the metallo-complex caused by the interaction with the radiation field of nuclear reactor.

With an assumption that a value of $k = 750\,000$ barns would remain for different Me-DOTA complexes, radionuclides with half-lives of $T_{1/2} < 64 \text{ h}$ could be produced at the Mainz TRIGA II nuclear reactor with a specific activity higher than any common one available using standard irradiation protocols.

The approach may be more or less efficient for different nuclear reactor designs. The method thus seems to be very promising for production of relatively short-lived radionuclides with significantly increased specific activity, especially under irradiation conditions of limited neutron flux and/or irradiation periods.

References

1. Szilard, L., Chalmers, T. A.: Chemical separation of the radioactive element from its bombarded isotope in the Fermi effect. *Nature* **134**, 462 (1934).
2. Williams, R. R.: The Szilard–Chalmers reaction in the chain-reaction pile. *J. Phys. Chem.* **52**, 603–611 (1948).
3. Matsuura, T.: Various parameters affecting retention and specific activity in Szilard–Chalmers reaction of hexamine- and triethylendiamine-cobalt ions on an ion-exchanger. *J. Inorg. Nucl. Chem.* **28**, 313–321 (1966).
4. Matsuura, T.: Theoretical analysis of retention and specific activity in Szilard–Chalmers reaction. *J. Inorg. Nucl. Chem.* **28**, 2093–2109 (1966).
5. Herr, W., Götze, H.: Gewinnung eines praktisch trägerfreien Radio-Kupfer Präparates ^{64}Cu von hoher Aktivität aus Cu-Phthalocyanin. *Z. Naturforsch.* **5a**, 629–630 (1950).
6. Herr, W.: Trägerfreie Isolierung der durch Neutroneneinfangreaktion entstandenen Radioisotope der Seltenen Erden. *Angew. Chem.* **65**, 303–304 (1953).
7. Shapkin, G. N., Soroka, M. A., Moskalev, P. N.: Use of sulfurated diphtalocyanins of the lanthanides for the enrichment of radioisotopes. *Radiokhimiya* **19**, 857–859 (1977).
8. Zeisler, S. K., Weber, K.: Szilard–Chalmers effect in holmium complexes. *J. Radioanal. Nucl. Chem.* **227**, 105–109 (1997).
9. Tomar, B. S., Steinebach, O. M., Terpstra, B. E., Bode, P., Wolterbeek, H. Th.: Studies on production of high specific activity ^{99}Mo and ^{90}Y by Szilard Chalmers reaction. *Radiochim. Acta* **98**, 499–506 (2010).
10. Caravan, P., Ellison, J. J., McMurry, T. J., Lauffer, R. B.: Gadolinium chelators as MRI contrast agents: structure, dynamics, and applications. *Chem. Rev.* **99**, 2293–2352 (1999).
11. Liu, S., Edwards, D. S.: Bifunctional chelators for therapeutic lanthanide radiopharmaceuticals. *Biocon. Chem.* **12**, 7–34 (2001).