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Production of medical radionuclide ^{44}Sc from ^{44}Ti by extraction with organophosphorus compounds

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1. Materials and Methods

1.1. General materials

All chemicals were of p.a. (pro analysis) quality or higher, obtained from Merck (Germany), and were taken without additional purifications. De-ionized "Milli-Q" water (18 MΩ·cm) was used for preparation of aqueous solutions.

Extraction experiments were carried out with the organophosphorus compounds di(2-ethylhexyl)phosphoric acid (DEHPA, from Sigma-Aldrich, USA), tri-n-octylphosphine oxide (TOPO, from Sigma-Aldrich, USA), and tributyl phosphate (TBP, from Acros Organics, Belgium). Toluene was used for preparation of organic solutions.

An extraction chromatographic resin TEVA (quaternary ammonium salt Aliquate 336 as an extracting agent) with 50–150 μm particle size was produced by Triskem, France. A strongly acidic cation exchange resin Dowex 50×8, particle size 100-200 mesh, was obtained from Dow, USA.

Ammonium acetate NH_4OAc buffer solutions were prepared by adding small portions of 13 M NH_4OH solution to acetic acid solutions up to a required pH value. Measurements of operational pH values were performed with an Econix-Expert Expert-001 pH meter using an InLab Flex-Micro Mettler Toledo combination pH electrode.

The experiments were carried out at ambient temperature 21 ± 2 °C.

1.2. γ-Ray spectroscopic measurements

The stock solution of ^{44}Ti in 4M HCl was purchased from JSC Cyclotron (Russia). The activities of ^{44}Ti and its daughter product ^{44}Sc were determined by γ-ray spectroscopy with high-resolution HP Ge detector GR3818 and HP Ge detector GC3020 (both by Canberra Industries, USA). Spectra analysis was performed by means of SpectraLine software (LSRM, Russia).

The characteristic γ-lines at 67.9 keV (abundance 93.0 %) and 78.3 keV (abundance 96.8 %) were used for quantification of ^{44}Ti, and the γ-line at 1157.0 keV (abundance 99.9 %) – for ^{44}Sc[S1]. Measurement uncertainties did not exceed 10 %.

For higher accuracy in the determination of distribution ratios of Sc^{III} (see Section 1.3.3), a laboratory ^{44}Ti/^{44}Sc generator was prepared by loading ^{44}Ti (70 kBq) onto a column filled with TEVA resin[S2]. ^{44}Sc was eluted and purified from oxalic acid using a column with Dowex 50×8 according to the procedure previously reported[S3]. In order to take into account the decay of ^{44}Sc during γ-ray measurement, the correlation (S1) between the activity and the number of peak counts

$$A_{\mathrm{Sc}}(t) = A^{m}_{\mathrm{Sc}} e^{-\lambda_{\mathrm{Sc}} t} = \left(\frac{dN}{dt}\right)\frac{1}{\varepsilon\eta}\frac{t_R}{t_L} \qquad \text{(S1)}$$

was used in the integrated form:

$$A^{m}_{\mathrm{Sc}} = \frac{N}{\varepsilon\eta}\frac{t_R}{t_L}\frac{\lambda_{\mathrm{Sc}}}{\left(1-e^{-\lambda_{\mathrm{Sc}} t_R}\right)} = \frac{N}{\varepsilon\eta}\frac{t_R}{t_L T_{\mathrm{Sc}}} \qquad \text{(S2)}$$

where A_{Sc}, A^{m}_{Sc} and λ_{Sc} are the activities at any moment and at the start of measurement, respectively, and the decay constant of ^{44}Sc; η is the abundance of characteristic γ-line at 1157.0 keV; N and ε are the number of peak counts and the detector efficiency for the given γ-ray energy; t_R and t_L are the real time

and live time of measurement. $T_{\mathrm{Sc}} = \frac{\left(1-e^{-\lambda_{\mathrm{Sc}} t_R}\right)}{\lambda_{\mathrm{Sc}}}$ is the time parameter depending on ^{44}Sc decay during the measurement. Then, the ^{44}Sc activity was recalculated to the moment of phase separation (A^s_{Sc}) after an extraction experiment.

Before the experiments described in Sections 1.3.1, 1.3.2 and 1.4, the solution of ^{44}Ti was stored at least two days to attain the transient equilibrium with ^{44}Sc. The distribution of Sc^{III} and Ti^{IV} ions between the organic and aqueous phases disturbed the equilibrium, and consequently, the values of A_{Sc} and A^m_{Sc} were determined by the equations (S3) and (S4):

$$A_{\mathrm{Sc}}(t) = \frac{\lambda_{Sc}}{\lambda_{Sc}-\lambda_{Ti}} A^m_{\mathrm{Ti}}\left(e^{-\lambda_{\mathrm{Ti}} t} - e^{-\lambda_{\mathrm{Sc}} t}\right) + A^m_{\mathrm{Sc}} e^{-\lambda_{\mathrm{Sc}} t} = \left(\frac{dN}{dt}\right)\frac{1}{\varepsilon\eta}\frac{t_R}{t_L} \qquad \text{(S3)}$$

$$A^m_{\mathrm{Sc}} = \frac{N}{\varepsilon\eta}\frac{t_R}{t_L T_{\mathrm{Sc}}} - \frac{\lambda_{Sc}}{\lambda_{Sc}-\lambda_{Ti}} A^m_{\mathrm{Ti}}\left(\frac{T_{\mathrm{Ti}}}{T_{\mathrm{Sc}}} - 1\right) \qquad \text{(S4)}$$

where A^m_{Ti} and λ_{Ti} are the activity at the start of measurement and the decay constant of ^{44}Ti. Since $t_R \ll \frac{1}{\lambda_{Ti}}$, i.e. the decay of ^{44}Ti is negligible, the parameter $T_{\mathrm{Ti}} = \frac{\left(1-e^{-\lambda_{Ti} t_R}\right)}{\lambda_{Ti}}$ is almost equal to t_R. Finally, the value A^s_{Sc} of ^{44}Sc activity at the moment of phase separation was obtained from:

$$A^m_{\mathrm{Sc}} = \frac{\lambda_{Sc}}{\lambda_{Sc}-\lambda_{Ti}} A^s_{\mathrm{Ti}}\left(e^{-\lambda_{\mathrm{Ti}}\Delta t} - e^{-\lambda_{\mathrm{Sc}}\Delta t}\right) + A^s_{\mathrm{Sc}} e^{-\lambda_{\mathrm{Sc}}\Delta t} \qquad \text{(S5)}$$

where A^s_{Ti} is the ^{44}Ti activity at the moment of phase separation ($A^s_{\mathrm{Ti}} \approx A^m_{\mathrm{Ti}}$); Δt is the time elapsed from the phase separation to the start of γ-ray measurement.

1.3. Liquid-liquid extraction experiments

The organic phases were prepared by dissolving the organophosphorus compounds DEHPA, TOPO and TBP in toluene to obtain the desired solution concentrations. Before extraction, an organic solution was pre-equilibrated with a corresponding solution of nitric or hydrochloric acid. For each extraction experiment performed in triplicate, 500 µL of the organic phase was added in a 1.5-mL conical Eppendorf tube to the same volume of spiked aqueous phase (1:1 of phase ratio). The tubes were vortexed at 3000 rpm for at least 5 minutes (Biosan V-32, Latvia). According to the preliminary studies, this time was sufficient for reaching the extraction equilibrium. On completion of stirring, the organic and aqueous phases were separated by centrifugation during 10 seconds. Afterward, 400-µL aliquots were taken from both phases for the determination of radionuclide activity by γ-ray spectroscopy.

The values of fraction extracted E and distribution ratio D were calculated by the following equations:

$$E = \frac{A^O}{A^O + A^A} \qquad \text{(S6)}$$

$$D = \frac{A^O}{A^A} \qquad \text{(S7)}$$

where A^O and A^A are the radionuclide activities in the organic and aqueous phases, respectively.

1.3.1. Distribution ratios depending on aqueous phase acidity

The distribution ratios of Sc^{III} and Ti^{IV} extracted from HCl and HNO_3 solutions in the acid concentration range from 0.1 to 9 M were determined. A sample of aqueous phase contained 0.2 kBq of ^{44}Ti in equilibrium with ^{44}Sc. Solutions of 1.5 M DEHPA, 1.8 M TBP and 0.1 M TOPO in toluene were used as organic phases.

1.3.2. Distribution ratios depending on concentration of extracting agent

Extraction of Sc^{III} and Ti^{IV} ions was studied by varying the concentration of two extracting agents TBP and TOPO in the ranges of 0.18 – 3.67 M and 0.01 – 0.18 M, respectively. As previously, 0.2 kBq of ^{44}Ti in equilibrium with ^{44}Sc was spiked in each aqueous phase. For extraction experiments with TBP, the aqueous phase was 9 M HCl solution. In the case of TOPO, 6.3 M HCl and 9 M HNO_3 solutions were investigated.

1.3.3. Distribution ratios of Sc^{III} depending on concentration of extracting agent

Experiments on extraction of a generator-produced ^{44}Sc (see Section 1.2) with TBP and TOPO solutions of the same concentration ranges were performed as well. A purified ^{44}Sc was obtained from the Dowex 50×8 column by passing the 6.3 M HCl solution, which then served directly as aqueous phase for TBP extraction. For experiments with TOPO, ^{44}Sc was eluted from the Dowex 50×8 column with 0.5 M

NH_4OAc buffer solution (pH 4) followed by evaporating to dryness and converting into 0.1 M HNO_3 or 3 M HCl solution. Each sample of aqueous phase contained about 1 kBq of ^{44}Sc at the start of extraction.

1.4. Multistep separation of ^{44}Ti and ^{44}Sc

The extraction systems 1.8 M TBP – 7 M HCl, 0.18 M TOPO – 3 M HCl, and 0.18 M TOPO – 0.1 M HNO_3 were tested for iterative separation of ^{44}Sc from ^{44}Ti. In the chosen systems, Sc^{III} ions were mainly extracted while Ti^{IV} ions remained in the aqueous phase. Equal volumes of 2 ml of aqueous and organic phases were taken for each extraction step. An initial aqueous solution spiked with 1 kBq of ^{44}Ti in equilibrium with ^{44}Sc was added to a corresponding organic solution in a polypropylene vial. The mixture was vortexed and separated as it is described in Section 1.3. The radionuclide activities A_{11}^O and A_{11}^A in the organic and aqueous phases were measured by γ-ray spectroscopy, and the value of fraction extracted E_{11} was calculated by eq. (S6). Then, the organic and aqueous phases were put in contact with a fresh portion of aqueous and organic solutions, respectively (Figure S1a), and, in the same way, two sets of values A_{12}^O, A_{12}^A, E_{12} and A_{21}^O, A_{21}^A, E_{21} were obtained.

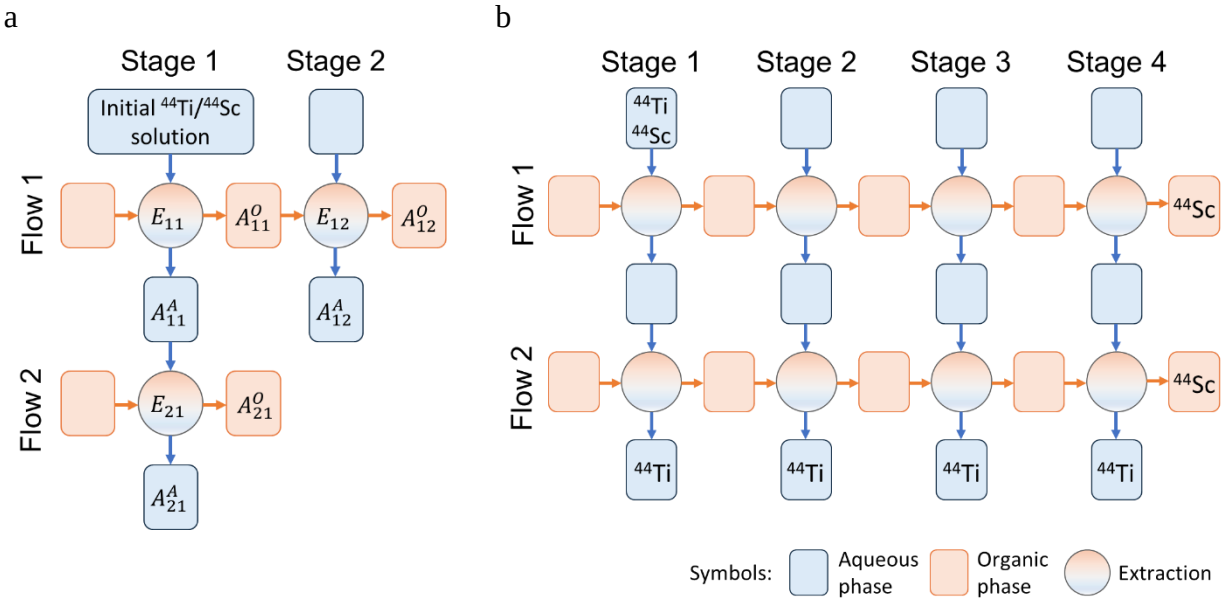

Figure S1. A scheme of multistep separation of ^{44}Sc from ^{44}Ti: *a* – three initial extraction steps; *b* – the "2 flows/4 stages" separation procedure implemented in this work.

The vertical and horizontal lines in the scheme shown in Figure S1 are marked as stages and flows. A separation procedure involving two flows and four stages (Figure S1b) was studied for the chosen extraction systems. Each extraction cell results in the partitioning of Ti^{IV} and Sc^{III} between the aqueous and organic phases according to their distribution coefficients (D). Because the D value for Ti^{IV} is below 0.5 in the selected systems, each stage of the Flow 1 served to purge the organic phase of ^{44}Ti. The Flow 2 was used to recover the ^{44}Sc that was partially back-extracted into the aqueous phases from the Flow 1 (Figure S2a).

1.5. Back-extraction of ^{44}Sc with buffer solutions

^{44}Sc produced accordingly to the multistep separation procedure (Figure S1b) was back-extracted with the equal volume of deionized water or NH_4OAc buffer solutions having the acetate ion concentration of 0.5 M. The pH values of buffer solutions varied from 2.7 to 10. The extraction conditions were as described in Section 1.3. The separated phases were analyzed by γ-ray spectroscopy, and the pH values of the aqueous phases after back-extraction were monitored.

1.6. Radiolabeling of DOTA with ^{44}Sc

The obtained ^{44}Sc solution in dilute HCl was washed three times with toluene to remove any potential organic impurities. For the radiolabeling, 500 µL of the ^{44}Sc solution was mixed with 500 µL of 0.5 M NH_4OAc to create a buffered environment. The pH of the solution was adjusted to 4 by adding 3 M NaOH. The DOTA chelator was then added to a final concentration of 10^{-4} M. The samples were heated at 90 °C for 15 minutes.

The radiochemical purity of ^{44}Sc-DOTA was assessed using instant thin-layer chromatography (iTLC-SG, Agilent Technologies). The iTLC strips were eluted with a mobile phase consisting of 0.04 M NH_4OAc (pH = 5) and methanol in a 1:1 (v/v) ratio[S4]. The developed chromatograms were exposed and the activity distribution on the chromatographic strips was analyzed using digital autoradiography with a PerkinElmer Cyclone Plus system. For quantitative analysis, the iTLC strips were cut in half; the free ^{44}Sc ($R_f = 0$) remained at the origin, while the ^{44}Sc-DOTA complex ($R_f = 0.9$) migrated with the solvent front. The activity in each segment was measured using gamma-spectrometry, monitoring the 1157 keV gamma line.

2. Effect of acid concentration on extraction of ^{44}Ti and ^{44}Sc

Table S1. Distribution ratios D of Ti^{IV} and Sc^{III} ions extracted with 1.5 M DEHPA, 1.8 M TBP and 0.1 M TOPO solutions in toluene as a function of HCl and HNO_3 concentration (the data below or above a certain value were estimated from the detection limit of characteristic γ-peak).

Extractant	Acidity	HCl				HNO_3			
	C, M	Ti^{IV}		Sc^{III}		Ti^{IV}		Sc^{III}	
		D	$\pm D$	D	$\pm D$	D	$\pm D$	D	$\pm D$
1.5 M DEHPA	0.1					310	70	90	30
	0.5	1600	500	>250		>300		240	120
	1	160	35			160	30	250	170
	3	43	8			190	40	>150	
	5	75	13			190	40		
	7	540	200			540	140		
	9					650	140		
1.8 M TBP	0.1	<0.005		<0.005		<0.008		0.02	0.01
	0.5							0.11	0.05
	1							0.04	0.02
	3							0.08	0.02
	5			0.20	0.05			0.10	0.02
	7	0.05	0.01	12	5	0.014	0.004	0.21	0.05
	9	1.3	0.2	58	39	0.08	0.02	0.6	0.1
0.1 M TOPO	0.1	<0.005		<0.005		0.07	0.02	2.3	0.5
	0.5			0.016	0.009	0.08	0.02	2.5	0.6
	1			0.04	0.01	0.04	0.01	1.1	0.4
	3	0.03	0.01	3.3	0.9	0.014	0.006	0.27	0.06
	5	0.31	0.06	17	6	0.023	0.005	0.18	0.04
	7	14	2	92	39	0.08	0.02	0.20	0.04
	9	340	170	8	2	0.32	0.05	0.23	0.05

3. Effect of extracting agent concentration on extraction of ^{44}Ti and ^{44}Sc

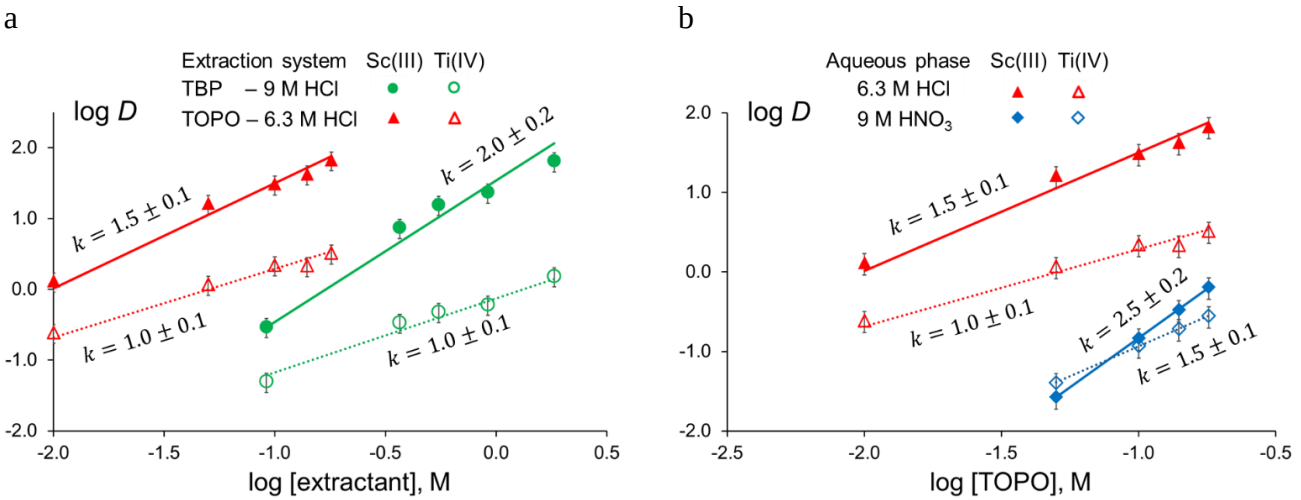

Figure S2. Log-log plots of D versus the concentration of extracting agent: *a* – distribution of Ti^{IV} and Sc^{III} in the extraction systems TBP – 9 M HCl and TOPO – 6.3 M HCl; *b* – distribution of Ti^{IV} and Sc^{III} in the extraction systems TOPO – 6.3 M HCl and TOPO – 9 M HNO_3.

For the TOPO and TBP extraction from hydrochloric solutions (Figure S2a) we observed the linear relationships with different slopes for Ti^{IV} and Sc^{III}. The values of line slope for Ti^{IV} ions are close to 1 indicating that under these conditions the Ti extraction into the organic phase occurs *via* a 1:1 interaction with the extractant, and the formation of complexes $TiOCl_2 \cdot Ex$ (where *Ex* = TOPO or TBP) can be suggested. According to the reported data[S5], the slope values for Ti^{IV} in the TBP – HCl system varied from 1 to 3 depending on the concentration of titanium, TBP and acidity, which is in line with the results of this work. The Sc^{III} slope values are 1.5 and 2 for the TOPO and TBP extraction, respectively, assuming the formation of complexes $ScCl_3 \cdot$(1-2)TOPO and $ScCl_3 \cdot 2$TBP.

Considering the linear relationships obtained for TOPO extraction from 9 M HNO_3 solutions (Figure S2b), the Ti^{IV} ions were suggested to form complexes $TiO(NO_3)_2 \cdot$(1-2)TOPO, while the TOPO complexes with Sc^{III} ions can be described as $Sc(NO_3)_3 \cdot$(2-3)TOPO. The complex $Sc(NO_3)_3 \cdot 3$TOPO was also reported for the extraction of Sc with TOPO from 2 M HNO_3 solution[S6].

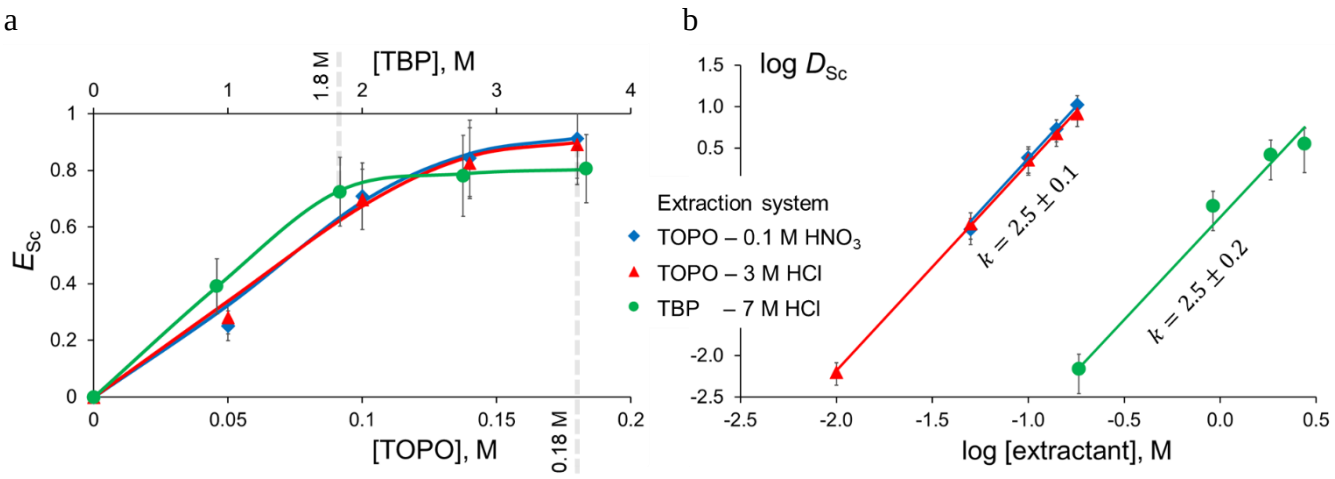

Figure S3. Dependence of ^{44}Sc fraction extracted (*a*) and distribution ratio (*b*, log scale) on TOPO and TBP concentration.

4. Modeling of a multistep extraction ^{44}Ti/^{44}Sc generator

The rate of purification from ^{44}Ti (Figure S2b) remains constant for the extraction systems TBP – 7 M HCl and TOPO – 3 M HCl, however, for the system TOPO – 0.1 M HNO_3 the purification becomes less

effective from one stage to another. In other words, for two first systems the D values of Ti^{IV} do not depend on the number of stages, while they grows exponentially for the last system, as can be seen in Figure S4. The fact that an increasing fraction of titanium remains in the organic phase from stage to stage can be explained by the slow back-extraction kinetics of $TiO(NO_3)_2 \cdot nTOPO$ complexes into the dilute (0.1 M HNO_3) aqueous phase.

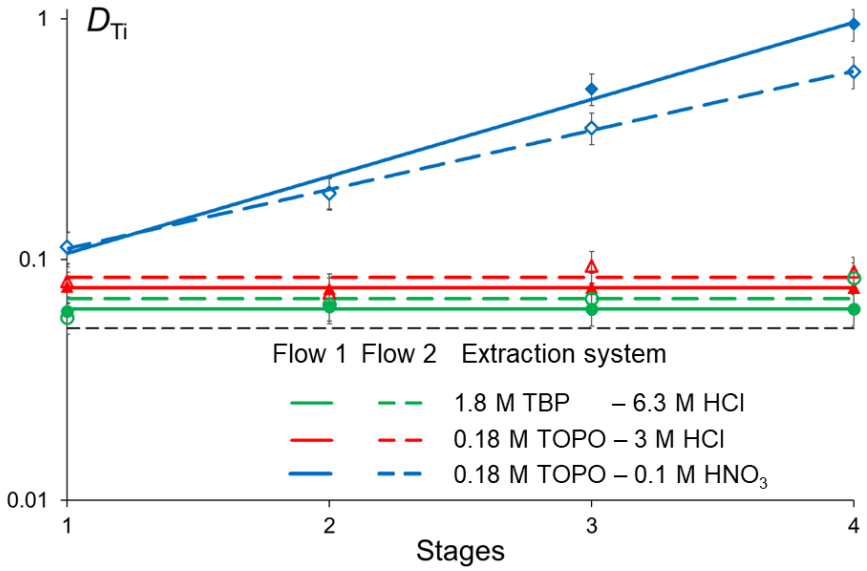

Figure S4. Distribution ratio D of Ti^{IV} versus the number of stages.

Assuming that the value of distribution ratio D (and fraction extracted E) remains constant regardless of the number of extractions, the fraction of extracted substance can be evaluated for any number of stages and flows using the binomial distribution. Since at each step the substance is distributed in the proportion of E and $(1 - E)$, the stages and flows form the sides of Pascal's pyramid with binomial coefficients as shown in Figure S5.

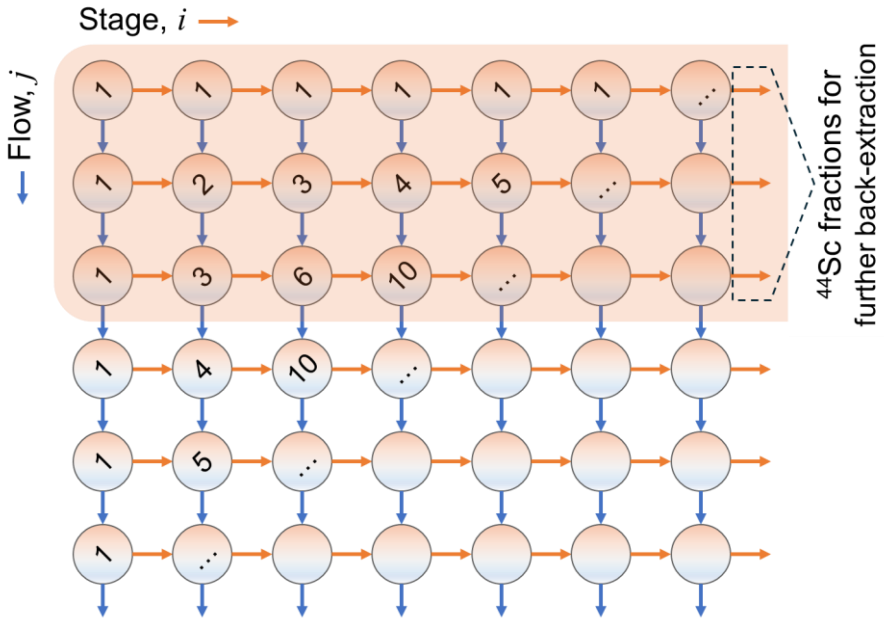

Figure S5. Description of the multistep separation scheme in terms of the binomial distribution. The circles represent extraction cells (see Figure S1). Orange and blue arrows denote organic and aqueous phases, respectively, resulted from extraction cells. The numbers inside the circles are the binomial coefficients.

The substance fraction a_{ij} in the i,j-extraction cell is given by the equation:

$$a_{ij} = C_{i+j-2}^{i-1} E^{i-1}(1-E)^{j-1} \quad \text{(S8)}$$

where i,j are the numbers of stages and flows, respectively; $C_{i+j-2}^{i-1} = \frac{(i+j-2)!}{(i-1)!(j-1)!} = C_{i+j-2}^{j-1}$ is the binomial coefficient. The fraction of substance in the organic phase after the i,j-extraction cell is equal to $a_{ij}E$. Summing by the index j, we collect the fraction of substance in the organic phases from j flows after the i-th stage (as it is shown in Figure S5):

$$E\sum_{k=1}^{j} a_{ik} = E^i \sum_{k=1}^{j} C_{i+k-2}^{i-1}(1-E)^{k-1} \quad \text{(S9)}$$

TOPO extractant showed high ^{44}Ti retention from 9 M HCl (Table S1, Figure S1a) and it can be used for ^{44}Ti concentration during regeneration according to Figure S5. For this purpose, 12 M HCl is added to the collected aqueous fractions to adjust 9 M HCl concentration and the flow of ^{44}Ti concentration is conducted in the opposite direction. The concentrated ^{44}Ti is re-extracted into 0.1 M HCl solution for subsequent reuse.

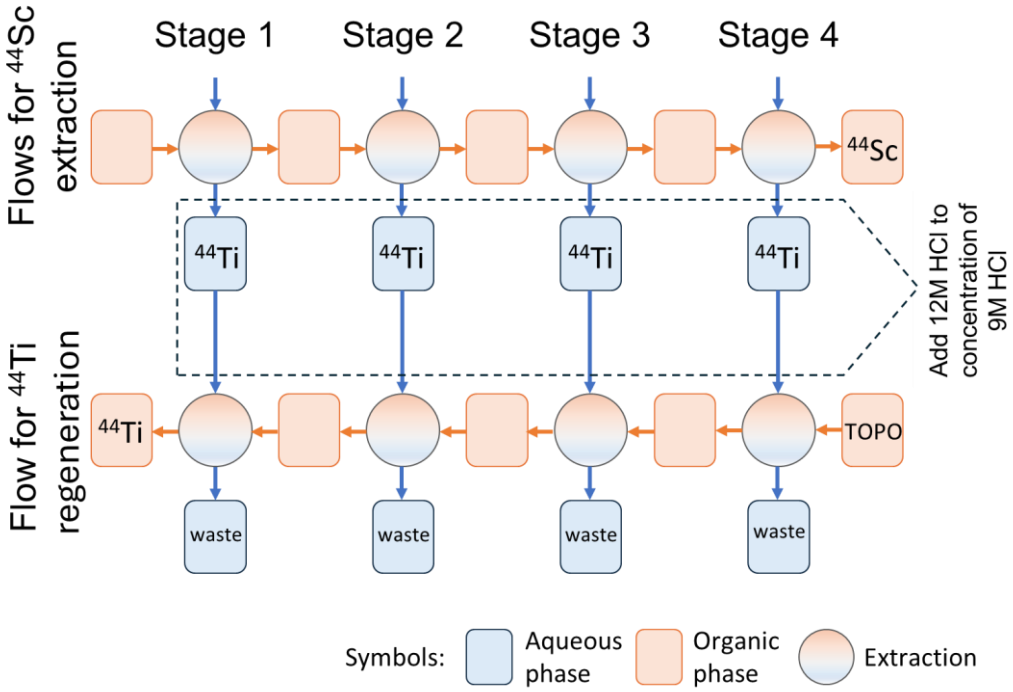

Figure S6. A scheme of ^{44}Ti concentration for the recurrent use.

5. Production of ^{44}Sc solution for synthesis of labeled compounds

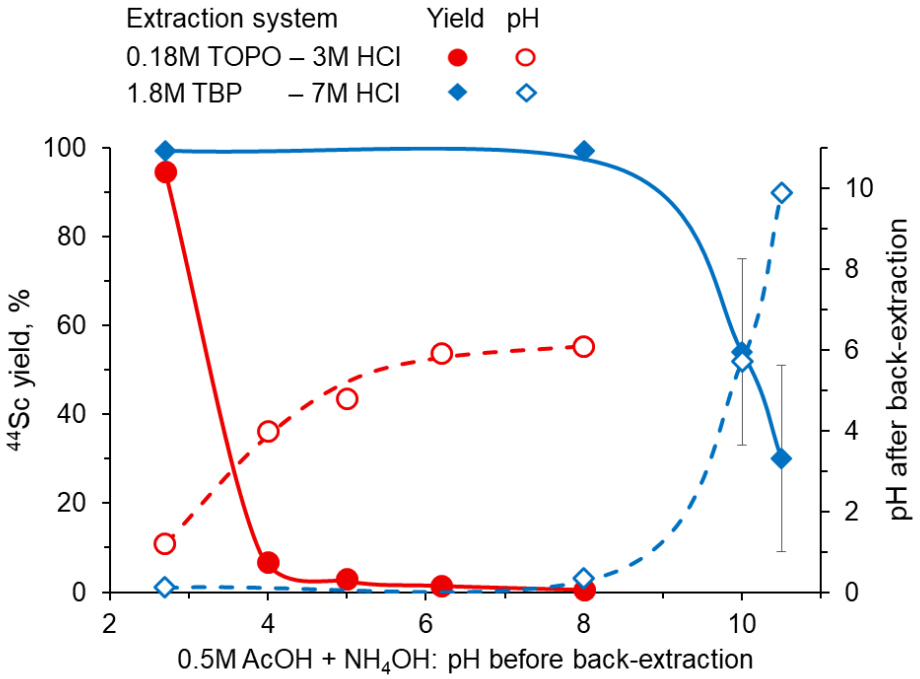

Figure S7. Yield of ^{44}Sc back-extraction and pH of aqueous phase after back-extraction depending on the pH of acetate buffer solution before back-extraction.

Since the labeling of various compounds with ^{44}Sc is typically carried out in 0.25 M – 0.5 M acetate buffer media with pH at 4 – 5[S7], 0.5 M acetic acid buffer solutions were used for back-extraction. A certain amount of ammonia was also added to the buffer solutions with the idea to neutralize the back-coextracted acid and create a favorable pH-environment for subsequent ^{44}Sc labeling. The results of ^{44}Sc back-extraction into the acetate buffer solutions are shown in Figure S7.

The ^{44}Sc yield up to 100% was observed for the back-extraction both into 0.5 M acetic acid and water supposed that the pH-value of aqueous phase after back-extraction was below 2. The excessive addition of NH_4OH to the buffer solution before back-extraction resulted in sharp decrease of ^{44}Sc yield. Based on these data, it can be assumed that the main driving force of ^{44}Sc back-extraction is the redistribution of HCl between the organic and aqueous phases. The neutralization of the HCl with NH_4OH leads to dropping rate of acid transfer to the aqueous phase and hydrolysis of Sc^{III} which can prevent its back-extraction.

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