Production of $^{230}$Pa as a Source for Medical Radionuclides $^{230}$U and $^{226}$Th Including Isolation by Liquid–liquid Extraction

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ABSTRACT
Liquid–liquid extraction of protactinium with different extractants (1-octanol, MIBK, aliquat 336) was studied depending on concentration of nitric and hydrochloric acids, presence of bulk amount of thorium, fluoride ions, and addition of boric acid or Al$^{3+}$ions as a masking agent. The extraction with 1-octanol followed by back-extraction with 7 M HCl + 0.1 M HF solution proved to be appropriate for selective $^{230}$Pa isolation from thorium irradiated with medium-energy protons. The proposed procedure provided simultaneous production of medical $^{223}$Ac and $^{230}$Pa/$^{230}$U from the same Th-target. The experimental cross-sections of $^{230}$Pa formation in the reaction $^{232}$Th(p,3n)$^{230}$Pa were determined for the protons energy range of 140–35 MeV and compared with literature data. The yield of $^{230}$U and impurities of $^{232}$U and $^{233}$U depending on the energy of protons entering a thick thorium target were estimated.

KEYWORDS
$^{230}$Pa; $^{230}$U; proton irradiation; thorium target; protactinium isolation; Liquid–liquid extraction

Introduction
α-Particles exhibit high values of linear energy transfer in a very limited range of action (∼10 cell diameters), and this property promotes the development of targeted alpha therapy (TAT) – a fast-paced branch of nuclear medicine. The choice of a radionuclide for TAT is determined by its nuclear and chemical properties as well as the availability of up-scaling production.$^{[1]}$

$^{230}$U is one of potential medical α-emitters. The decay of $^{230}$U generates a chain of short-lived products and it is accompanied by the emission of five α-particles with a total energy of 33.5 MeV (Figure S1), resulting in effective cell damage.$^{[2]}$ $^{230}$U can be used as an independent therapeutic radionuclide or as a source for a $^{230}$U/$^{226}$Th generator. Effective bifunctional chelators that can firmly bind uranium in vivo is a challenge for upcoming investigations. The decay of the short-lived $^{226}$Th ($t_{1/2} = 30.6$ min) generates a rapid cascade of
four $\alpha$-particles with a total energy of 27.7 MeV; for comparison, the decay of $^{213}\text{Bi}$ ($t_{1/2} = 45.6$ min) produces only one $\alpha$-particle with an energy of 8.4 MeV. $^{226}\text{Th}$ due to a relatively short half-life is suggested to be delivered by rapidly diffusing peptide vectors as carrier molecules. Such therapy is promising for the treatment of easily accessible tumors.

The most productive way of direct formation of $^{230}\text{U}$ consists in irradiation of $^{231}\text{Pa}$ ($t_{1/2} = 3.3 \times 10^4$ y) with accelerated protons and deuterons by reactions: $^{231}\text{Pa}(p,2n)^{230}\text{U}$ and $^{231}\text{Pa}(d,3n)^{230}\text{U}$. The initial $^{231}\text{Pa}$ is a member of the $^{235}\text{U}$ decay chain, it must be isolated from aged uranium samples, which is a disadvantage of the method, taking into account the limited availability of the raw materials.

Another approach uses the reactions of the thorium nuclei with accelerated protons and deuterons resulting in the production of a precursor of $^{230}\text{Pa}$, decaying in $^{230}\text{U}$ with a branching ratio of 7.8%: $^{232}\text{Th}(p,3n)^{230}\text{Pa} \rightarrow ^{230}\text{U}$ and $^{232}\text{Th}(d,4n)^{230}\text{Pa} \rightarrow ^{230}\text{U}$. The maximum amount of $^{230}\text{U}$ accumulates in 27 days after the end of short-run irradiation. Many leading scientific organizations around the world such as TriLab cooperation, ARRONAX (France), TRIUMF (Canada) are actively working on the development of this method. The authors from ARRONAX have compared the yield of $^{230}\text{U}$ from thick targets of $^{231}\text{Pa}$ and $^{232}\text{Th}$. Both routes result in the yields around 0.24 MBq/(µA-h), which is higher than the corresponding yields for the reactions with deuterons. The maximum of the $^{232}\text{Th}(p,3n)^{230}\text{Pa}$ reaction excitation function corresponds to the proton energy of 19.9 ± 0.3 MeV; therefore, industrial production of $^{230}\text{U}$ can be organized on productive commercial cyclotrons operating at currents up to 1200 µA of protons with energies of 30 MeV, such as Cyclone 30 manufactured by IBA (Belgium).

With an increase in proton energy, it becomes possible to obtain not only $^{230}\text{U}$ but also other promising alpha emitters $^{225}\text{Ac}$ and $^{223}\text{Ra}$. Radiopharmaceuticals containing $^{225}\text{Ac}$ and its daughter $^{213}\text{Bi}$ are successfully passing clinical trials for the treatment of leukemia, NHL, carcinoma, neuroendocrine tumor, glioma melanoma, and other malignant diseases. Radiopharmaceutical Xofigo on the base of $^{223}\text{Ra}$ is already approved for a common application in many countries for bone metastasis therapy. The maximum yield of $^{225}\text{Ac}$ is achieved at higher proton energy (more than 80 MeV). This proton energy range is not optimal for the production of $^{230}\text{Pa}$, and $^{230}\text{Pa}/^{230}\text{U}$ can be considered as an important by-product. The approach is considered promising in scientific centers where accelerators with a high flux of medium-energy protons are available (BNL, LANL, TRIUMF, INR RAS, etc.).
The chemical properties of protactinium are more complex and exhibit greater unpredictability than the properties of most elements. Protactinium is easily hydrolyzed in the absence of complexing agents, forming colloid and polymeric particles.\textsuperscript{18} They are adsorbed on almost any available surface, which often causes the loss of Pa during chemical manipulations.

Various chemical methods are implemented for Pa separation: co-precipitation, liquid–liquid extraction (LLE), ion exchange, and extraction chromatography. The works published in literature on the isolation of \( {^{230}}\text{Pa} \) from relatively thin thorium targets use largely chromatographic methods. The authors suggest using anion-exchange sorbents AG MP-1,\textsuperscript{19} AG 1 × 8,\textsuperscript{6} commercially available extraction-chromatographic sorbents TRU resin,\textsuperscript{6} UTEVA resin,\textsuperscript{6} TK 400,\textsuperscript{20} Cl resin,\textsuperscript{21} and DGA resin and its analogs.\textsuperscript{8}

Irradiation of massive targets in a wide energy range of protons results in processing large volumes of highly radioactive initial solutions. In this case, extraction methods seem more relevant than chromatographic ones. Despite a great amount of literature data on the LLE of Pa by various agents, for example, aliphatic alcohols, ketones, quaternary ammonium compounds, organophosphorus compounds,\textsuperscript{22–24} the selective extraction of protactinium remains under-researched. A more detailed study on the extractive separation of protactinium from the impurity of Nb, Zr, Ru, Sb radioisotopes in the presence of thorium and fluoride ions is necessary.

A new method for obtaining \( {^{230}}\text{Pa}/^{230}\text{U} \) along with \( {^{225}}\text{Ac} \) providing the production of therapeutic activity of these radionuclides in one irradiation run is considered in the present paper. The objectives of the work are to develop a fast and technological procedure for \( {^{230}}\text{Pa} \) isolation from ten grams of thorium irradiated with medium-energy protons; to test a simultaneous \( {^{230}}\text{Pa}/^{230}\text{U} \) and \( {^{225}}\text{Ac} \) production; and to determine the possible yield of \( {^{230}}\text{Pa}/^{230}\text{U} \) in the medium-energy proton range.

**Experimental**

All chemicals were of p.a. quality or higher, obtained from Merck (Darmstadt, Germany), and used without additional purifications. All experiments were carried out using de-ionized “Milli-Q” water (18 MΩ·cm\(^{-1}\)).

\( \gamma \)-Ray spectroscopy with high-pure Ge-detector ORTEC GEM15P4–70 was used for radionuclide determination. Spectra analysis was performed by means of Gamma Vision 32 software and IAEA Nuclear Data Services database\textsuperscript{25} (Table S1). Measured activities were corrected for decay. Uncertainties of activity measurements have not exceeded 10%. The details of calculations were reported in our previous paper.\textsuperscript{26}
**Irradiation and processing of thorium for radiochemical experiments**

Several targets made of Th plates with a mass of 8–14 g and a thickness of 1.5–2.0 mm each were irradiated with protons with initial energy of 120–130 MeV. The beam current was 3–5 μA; the total beam charge was 12–18 μA·h. The irradiated plates were dissolved in 100–150 mL of 7 M hydrochloric acid with the addition of HF up to $10^{-4}$–$10^{-3}$ M. The $^{230,233}$Pa fraction containing impurities of $^{95}$Nb and $^{103}$Ru was isolated by extraction chromatography with TEVA resin (Triskem Int., France) according to the procedure reported.-[27] About 100 kBq of $^{230}$Pa, 10–20 kBq of $^{103}$Ru and 10–20 kBq of $^{95}$Nb were obtained. The resulting solution was separated into two parts; each part was evaporated to dryness several times with HNO₃ for removal of HF. The residues were dissolved in 7 M nitric and hydrochloric acid and used as a spike in extraction experiments.

**Extraction experiments**

The solvent extraction experiments were conducted following the well-known procedure.[28] The organic solution containing a mixture of an extractant (1-octanol, methyl isobutyl ketone (MIBK), aliquat 336), and a solvent (dodecane for 1-octanol and toluene for aliquat 336, 1:1 by volume) was pre-equilibrated with the acidic stock solutions. For each extraction experiment, 2.0 mL of an aqueous solution containing $^{230,233}$Pa, $^{95}$Nb, $^{126}$Sb, and $^{103}$Ru tracers was mixed with an equal volume of the organic solution. The tubes were shaken for 20 min at $21 \pm 2 \, ^\circ$C. According to the preliminary kinetic studies, this time is enough to reach the extraction equilibrium. Afterward, 1.0 mL aliquots were taken from both phases for the determination of the radionuclides by γ-ray spectroscopy.

The following extraction experiment series were conducted:

1. **Kinetic study.** The pilot set of samples was prepared with varying times of shaking of the tubes. The aqueous phase contented 7 M HNO₃ and the shaking time varied from 0.5 to 60 min.

2. **Influence of mineral acids concentration on LLE of Pa.** The second set of samples was prepared with various nitric and hydrochloric acids concentrations (1–9 M) taking into account the content of the acid in the spike solution.

3. **Influence of macro amounts of thorium in the aqueous phase on LLE of Pa.** The third set of experiments repeated the previous one in the presence of 0.4 M thorium(IV) nitrate or chloride in the aqueous phase as a macro component.
(4) **Dependence of LLE of Pa on the concentration of extractant.** In the fourth set, the content of the aqueous phase was fixed (7 M HNO₃) while the concentration of 1-octanol in the organic phase varied from 3 to 100%.

(5) **Influence of fluoride ions concentration in the aqueous phase on LLE of Pa.** The fifth set was prepared at the constant nitric or hydrochloric acids concentration of 7 M varying the HF concentration in the aqueous phase in the range 10⁻⁵–1 M.

(6) **Dependence of LLE of Pa on masking agent concentration in the aqueous phase at fixed content of fluoride ions.** In the last set, the aqueous phase included the fixed concentration of HNO₃ (7 M) and HF (0.01 or 0.001 M) and varying addition of boric acid or aluminum nitrate as a masking agent.

Back-extraction of Pa from octanol–dodecane solution (1:1) and MIBK was studied as well. Pa was preliminary extracted with the organic phase from 7 M HNO₃ (about 50 mL of each phase). The phases were separated completely. 2.0 mL aliquot of the organic solution was mixed with an equal volume of the aqueous solution. The tubes were shaken for 20 min at 21 ± 2°C. Aliquots of 1.0 mL were taken from both phases for the determination of the radionuclides by γ-ray spectroscopy. The experiments with solutions of hydrofluoric acid, nitric acid, and their mixture, hydrochloric, oxalic acid of different concentrations were carried out.

**Modeling separation of Pa and Ac fractions from irradiated thorium**

The irradiated Th plate was dissolved in 8 M nitric acid with the addition of HF up to 10⁻³–10⁻⁴ M. 85 mL of the solution with Th concentration 0.4 M and nitric acid about 7 M were taken for the model experiment. Aluminum nitrate was added to make the Al concentration up to 0.25 M. The organic solution containing a mixture of 1-octanol dodecane (1:1 by volume) was pre-equilibrated with the aqueous stock solutions. The solution of irradiated Th was mixed with an equal volume of the organic solution. The tube was shaken for 20 min at 21 ± 2°C. Phases were separated, and 1.0 mL aliquots were taken from both phases for the determination of the radionuclides by γ-ray spectroscopy and returned back afterwards.

Organic phase was mixed with 20 mL of aqueous solution containing 7 M HCl and 0.1 M HF. The Teflon tube was shaken for 20 min at 21 ± 2°C. Phases were separated, and 1.0 mL aliquots were taken from both phases for the determination of the radionuclides by γ-ray spectroscopy and returned back afterward.
The aqueous phase after extraction of Pa with 1-octanol was used for further Ac separation.\textsuperscript{[12]} The bulk quantity of thorium was separated by two sequential extractions with a solution of di(2-ethylhexyl)orthophosphoric acid (HDEHP) in toluene (1:1 by volume) that was preliminarily equilibrated with 7 M HNO\textsubscript{3}. The volume of the organic phase was equal to the volume of the aqueous one. The equilibration time was about 30 min. The aqueous phase was rinsed with 20 mL toluene twice to ensure complete separation.

The aqueous phase containing actinium, and most fission products was then loaded onto a column \((V = 3 \text{ mL}, \Theta = 6 \text{ mm})\) filled with extraction chromatographic sorbent DGA Resin (Triskem Int.) with 100–150 µm particle size having \(N\,,N\,,N'\,,N''\)-tetra-octyldiglycolamide as an extracting phase. The retention and elution of actinium and other elements was studied by collecting eluate solution after the column. After washing the column with 50 mL of 5 M HNO\textsubscript{3} solution, the actinium–lanthanide fraction was stripped off with a small amount (\(\sim 3 \text{ mL}\)) of 0.01 M HNO\textsubscript{3} solution (Figure S2) and further processed accordingly to the procedure reported.\textsuperscript{[12]}

\textbf{Cross-Section measurement}

The metal foils with a thickness of \(0.045 \pm 0.003 \text{ to } 0.065 \pm 0.004 \text{ mm}\) made of high chemical purity thorium (99.9\%) were manufactured in the RIAR (Dimitrovgrad, Russia). Each thorium foil of \(17 \times 50 \text{ mm}^2\) was placed between aluminum and copper foils of the same size. Al and Cu were used to monitor the proton beam passing through the targets. The thickness of Al and Cu was \(0.100 \pm 0.004 \text{ and } 0.038 \pm 0.002 \text{ mm}\), respectively.

Irradiations of two foil stacks were performed at the linear accelerator of INR RAS\textsuperscript{[29]} by protons with an initial energy of 158.5 and 100.1 MeV. The beam current was about 1 µA. Graphite degraders with a thickness of 2–4 mm were used to obtain the desirable proton energies. The calculation of energy and a current of protons bombarding the studied targets and monitors was performed using a modified STRAGL code,\textsuperscript{[30]} considering the straggling and scattering of protons. The cross-section values of the monitor reactions \(^{27}\text{Al}(p, x)^{22}\text{Na}\) and \(^{64}\text{Cu}(p,x)^{62}\text{Zn}\) recommended by the IAEA for the corresponding proton energy ranges\textsuperscript{[31]} were used in the calculation: Al, 35–145 MeV; Cu, 15–100 MeV.

\(\gamma\)-Ray spectrometric measurements of Th foils were initiated approximately a day after the irradiation and were then carried out repeatedly. Theoretical calculations of cross-sections were carried out with the ALICE-IPPE nuclear code.\textsuperscript{[32]}
Results and discussion

Liquid–liquid extraction of Pa

Protactinium easily forms anionic complexes in acidic solutions. Therefore, it can be extracted by oxygen-containing solvents capable of attaching protons when contacting with mineral acid solutions. Compounds consisting of an anionic complex of protactinium and an oxonium-type cation formed by the extractant are transferred into the organic phase. Since protactinium tends to form strong chloride complexes, hydrochloric acid solutions of Pa are more resistant to hydrolysis, and the extraction efficiency from hydrochloric acid solutions is usually higher than from nitric acid solutions.\[33\]

According to the literature data,\[23\] aliphatic alcohols are attractive for selective Pa extraction. There was found to be no significant difference in extraction of Pa from the alcohol chain length or position of the – OH group so long as the extractant is water-immiscible.\[23\] We have investigated extraction with 1-octanol which has already been tested in literature for Pa separation by LLE and extraction chromatography (sorbent TK400, Triskem Int.). There are no data in the literature on the extraction of protactinium with 1-octanol in the presence of macro amounts of thorium, as well as data on the behavior of other products of Th irradiation with medium-energy protons

![Figure 1](image_url). Extraction of Pa, Nb, and Ru with 1-octanol (1:1 in dodecane) depending on the acid concentration in the aqueous phase: (a) for nitric acid solutions; (b) for hydrochloric acid solutions. Gray curves indicate the results of Pa extraction in the presence of 0.4 M Th\(^{4+}\) in the aqueous phase.
under these conditions. The efficiency of Pa extraction with 1-octanol (1:1 in dodecane) depending on the concentration of the nitric and hydrochloric acid in the aqueous phase is shown in Figure 1.

It can be seen that the extraction efficiency of protactinium exceeds 90% for both mineral acids at their concentration in the aqueous phase of more than 5 M. These results are in good agreement with the literature data for 1-octanol,[23] 1-ethylhexanol,[23] 2,4-dimethyl-3-heptanol,[34] and 2,6-dimethyl-4-heptanol.[23,24] The presence of macro amounts of thorium (0.4 M) does not reduce the efficiency of Pa extraction in the strongly acidic region (Figure 1). Extraction is noticeably higher in the presence of thorium in the area of low acid concentration. Thorium nitrate/chloride salts dissociate to form 4 anions; therefore, the concentration of nitrate and chloride ions in the presence of 0.4 M thorium is up to 1.6 M. A higher concentration of the counterion increases the extraction efficiency, and the lower the acid concentration, the more noticeable the effect. It was found that the extraction dependence of Pa for 2,6-dimethyl-4-heptanol on the counter-ion concentration in log $D$–log[An–] coordinates has a slope of 5.5–5.7 for 1–4 M HCl and 1.9–2.1 for 1–4 M HNO$_3$.[23]

The dependence of the extraction of two main impurities, radioisotopes of Nb and Ru, on the acid concentration is also given in Figure 1. Their behavior needs to be considered, since the isolation of Pa from these contaminants is difficult.[8] It can be seen that the efficiency of Nb and Ru extraction from nitric acid solutions is noticeably inferior compared to hydrochloric acid solutions; less than 15% Nb and 5% Ru pass from 7 M HNO$_3$ into the organic phase. The other problematic irradiation product Sb remains completely in the

![Figure 2](image-url)

Figure 2. (a) Extraction of Pa, Nb, and Ru with 1-octanol (in dodecane) from 7 M HNO$_3$ depending on the 1-octanol concentration in the organic phase. (b) Plot of distribution ratios of Pa versus 1-octanol concentration in the organic phase.
aqueous phase under these conditions. We can conclude that nitric acid solutions make it possible to obtain a purer fraction of $^{230}\text{Pa}$. This correlated with the fact that the $^{225}\text{Ac}$ isolation procedure involves dissolving the target in nitric acid$^{[35]}$, therefore, nitric acid solutions were mainly investigated as an aqueous phase for LLE of Pa.

A study of the kinetics of Pa extraction with 1-octanol solution in dodecane (1:1) demonstrated that the extraction process is fast and the equilibrium in the system is established in less than 1 min.

The dependence of the extraction efficiency of Pa, Nb, and Ru on the concentration of the extractant in the organic phase is shown in Figure 2. The slope analysis in log $D$–log[1-octanol] coordinates allows us to determine the apparent stoichiometry of the process. We observe the linear relationship with the slope is 1.51 ± 0.06, which is in good agreement with the literature data. Namely, Knight reported that for extracting Pa from 6 M HCl (other conditions are similar) the slope is 1.58 ± 0.08.$^{[23]}$ Kumari observed a slope of around 1.6 for the extraction of Pa with diisobutyl carbinol (DIBC) and concluded formation of monobasic complex of general formula $\text{HPa(OH)}_m(\text{NO}_3)_n\cdot1\text{–2DIBC}$, with $m + n = 6$, and $n \geq 1$.$^{[24]}$ It should be noted that self-association of 1-octanol takes place in hydrocarbon solutions as soon as the total concentration becomes greater than about 0.01 M.$^{[36,37]}$ 1-Octanol exists mainly in the form of monomer and tetramers, while tetramers are the predominant species. More comprehensive investigations at higher concentration of Pa are required for profound study of its stoichiometry and coordination.

It is well known that Pa forms strong complexes with fluoride and oxalate ions. This property is often used in separation chemistry for protactinium leaching and back-extraction. In particular, the non-extractable Pa$^7\text{F}_2^{2–}$ complex is formed with fluoride ions.$^{[38]}$ At the same time, there are no data in the literature on the extraction of Pa with 1-octanol from solutions containing fluorides. Dissolving the irradiated thorium in hydrochloric or nitric acids requires the addition of HF, which is necessary to destroy the thorium oxide film formed on the metal surface. The developed technology of $^{225}\text{Ac}$ production includes the addition of HF for Th dissolution.$^{[35]}$ Preliminary experiments have shown that this concentration may reduce the efficiency of the subsequent isolation of Pa by LLE.

The effect of the addition of HF on extraction with a solution of 1-octanol in dodecane from 7 M HCl and HNO$_3$ was investigated (Figure 3). It can be seen that hydrofluoric acid up to a concentration of $10^{-4}$ M or $10^{-3}$ M may be added to 7 M nitric or hydrochloric acid solutions of protactinium, respectively, without significant decrease of extraction efficiency. At higher concentrations of fluoride ions, the extraction falls rapidly to zero. Chloride complexes of Pa are stronger than nitrate ones, and therefore the influence of fluoride ions on nitric acid solutions is more pronounced.
Figure 3. Extraction of Pa with 1-octanol (1:1 in dodecane) from 7 M nitric and 7 M hydrochloric acids depending on the HF concentration in the aqueous phase (the solid lines). Back-extraction of Pa with from 1-octanol (1:1 in dodecane) depending on the HF concentration in 7 M HNO₃ is shown by the dashed line.

Figure 4. Extraction of Pa with 1-octanol (1:1 in dodecane) from 7 M nitric acid depending on the concentration of masking agents in the aqueous phase at fixed content of HF.
Masking agents can be added to restore the extractability of Pa into the organic phase in the presence of HF. Aluminum salts and boric acid are most often used in these cases. They form fluoride complexes competing for F⁻ ions, destroying fluoride complexes of Pa.⁴⁸,⁴⁹ Figure 4 shows the extraction of Pa with a solution of 1-octanol in dodecane from 7 M HNO₃ with the addition of HF, depending on the concentration of the masking agents in the aqueous phase. The experimentally determined solubility of boric acid in 7 M HNO₃ does not exceed 0.3 M. It can be seen that the aluminum salt is more effective for binding fluoride ions than boric acid at the same concentration. Thus, at least 0.25 M Al³⁺ is needed to restore the extractability of Pa in the presence of 0.01 M HF, while boric acid is less effective.

Solutions containing fluoride ions are appropriate for Pa back-extraction. The dependence of Pa back-extraction from a solution of 1-octanol in dodecane on the content of F⁻ in 7 M HNO₃ is represented by the dashed line in Figure 3. It can be seen that the extraction and back-extraction curves are almost identical, implying that the extraction and back-extraction of Pa may be regarded as equilibrium and reversible process. The addition of 0.05–0.1 M HF is sufficient for quantitative back-extraction of Pa into the aqueous phase. The back-extraction with oxalic acid solutions is also effective and allows Pa to be quantitatively transferred to the aqueous phase. However, further removal of oxalic acid may be problematic. Dilute solutions of hydrochloric or nitric acids do not allow extraction of more than 80% of Pa (V organización = V agua). Pa in such solutions is extremely unstable, and it tends to hydrolyze and adsorb on the labware surface.⁵⁸

Separation of Pa from irradiated thorium by LLE with 1-octanol

Based on the obtained results, it was possible to develop a procedure that allowed the simultaneous production of ²²⁵Ac and ²³⁰Pa/²³⁰U from the same irradiated thorium target. Our goal was to propose a technologically adaptable approach to selective ²³⁰Pa isolation complying with the method of ²²⁵Ac production established previously.⁵⁵ The widely used extraction chromatography method has limitations, namely, relatively low radiation resistance of organic sorbents.⁵⁷ Chromatography is good for processing natural samples or for isolating small laboratory activities of radionuclides. For a large volume of the initial solution, column separation becomes time-consuming and reveals reduced efficiency in the case of solutions containing a macro component. In this work, extraction chromatography on TEVA resin was used to isolate the Pa, Nb, and Ru fraction for studying their extraction behavior. The LLE was considered as primary method for Pa isolation from the solution of irradiated thorium. An important advantage of LLE is the ability to quickly isolate both large and ultra-small amounts of a substance.
The possibility for isolation of protactinium by LLE from a hydrochloric and nitric acids solution of irradiated thorium by various classes of organic extractants was analyzed. We examined tributyl phosphate (TBP), trioctylphosphine oxide (TOPO), di-2-ethylhexylphosphoric acid (HDEHP), methyl isobutyl ketone (MIBK), aliquat 336, and 1-octanol. These extractants and their analogs are most often used for the isolation and concentration of protactinium.\[38\]

TBP, TOPO, and HDEHP make it possible to efficiently transfer Pa to an organic phase at high concentrations of hydrochloric or nitric acid in the aqueous phase, but they do not provide selective thorium separation.\[41,42\] The macro amounts of thorium follow Pa under the same conditions of extraction, which makes further Pa isolation problematic.

Preliminary experiments were carried out with MIBK, aliquat 336, and 1-octanol on the isolation of protactinium at different concentrations of thorium in hydrochloric and nitric acid solutions. MIBK allows extracting Pa with high efficiency from hydrochloric acid solutions with a concentration of more than 5 M. 99% Pa, 15% Ru, 20% Nb, and more than 95% Sb passed into the organic phase from 5 M HCl (\(V_{\text{org}} = V_{\text{aq}}\)). The extractability of impurities grows with an increase in the acidity of the solution. The purification of Pa from these irradiation products causes certain difficulties because of the similarity of the behavior of Nb and Pa, as well as the complex and diverse chemistry of Ru and Sb.\[6\] The efficiency of Pa extraction from nitric acid solutions is low. The back extraction can be effectively provided by solutions of HF (\(\geq 0.1\) M) or oxalic acid (\(\geq 0.9\) M).

Solutions of aliquat 336 in toluene (1:1 vol.) extracted more than 99% protactinium at a concentration of hydrochloric or nitric acid higher than 3 M, while there was no noticeable difference in the efficiency of extraction in these acids. It was found that an increase in the concentration of thorium enhanced the extractability of protactinium from hydrochloric acid solutions like it was observed for 1-octanol. Meanwhile, bulk thorium amounts were extracted with aliquat from nitric acid solutions, which reduced the extractability of protactinium. It restricts the applicability of this extractant for \(^{230}\)Pa isolation from irradiated thorium.

The results of the extraction of protactinium with 1-octanol solutions show that this extractant is best suited for the isolation of Pa from an irradiated thorium target. The \(^{230}\)Pa separation procedure includes the following steps (Figure 5).

The irradiated thorium is dissolved in 7–8 M nitric acid with the addition of HF, and corresponding amounts of a masking agent should be added to bind free fluoride ions. Then Pa is extracted with a solution of 1-octanol in dodecane (1:1), pre-equilibrated with 7–8 M HNO\(_3\), while the aqueous phase is further processed according to the established route for \(^{227}\)Ac
Finally, Pa is back-extracted with a small volume of acid with the addition of 0.1 M HF. The extraction efficiency of protactinium and the main products of thorium irradiation is presented in Table 1.

The yield of Pa at this stage was 96%. The back-extract contains impurities of Nb, Ru, and Zr, while bulk amounts of Th as well as U and Ac remain in the initial nitric acid solution. The higher Nb impurity compared to the model experiments can be explained both by the salting-out effect of thorium nitrate in solution and the associated higher content of the nitrate counterion. $^{230}$Pa is an intermediate product for nuclear medicine, so the back-extracted protactinium stabilized as a fluoride complex is further stored for $^{230}$U accumulation. The $^{230}$U can be easily separated chromatographically, for example, on TEVA.
resin.\[^{27}\] If additional purification Pa or U is required, a masking agent (0.3 M Al\(^{3+}\)) is added to the resulting solution again and Pa can be purified using various ion exchange\[^{6,19}\] or extraction chromatography\[^{6,8,20,21}\] methods.

The proposed LLE procedure (Figure 5) makes it possible to isolate and concentrate \(^{230}\)Pa from the irradiated thorium target with a yield of at least 95%. The main impurities in the isolated \(^{230}\)Pa are \(^{95}\)Nb (SF 2–3), \(^{103}\)Ru (SF 20–25), and \(^{95}\)Zr (SF 20–25).

The effect of masking agent (0.25 M Al\(^{3+}\)) presence on the further isolation of \(^{225}\)Ac was tested. According to the previously developed procedure\[^{12,35}\] the isolation of Ac was performed from the nitric acid solution containing thorium and its irradiation products obtained after separation of Pa. The macro quantities of thorium were removed by double extraction with solution of HDEHP in toluene, and then the actinium–lanthanide fraction was isolated by extraction-chromatography on a column with a DGA resin (Triskem Int.). It was shown that the \(^{225}\)Ac yield does not decrease in the presence of 0.25 M Al\(^{3+}\), which was additionally confirmed by measuring the capacity factors \(k^\prime\) Ac (III) from a 5 M HNO\(_3\) solution in static conditions without \((k^\prime = 680 \pm 30)\) and with adding 0.25 M Al\(^{3+}\) \((k^\prime = 660 \pm 50)\). We can conclude that macro amounts of Al did not affect the sorption of Ac on the DGA resin.

![Figure 6](image-url).

**Figure 6.** Experimental and theoretical (calculated by ALICE-IPPE model) \(^{230}\)pa formation cross-sections.\[^{2,6,43–48}\]
The yield of $^{230}\text{Pa}/^{230}\text{U}$ in the reaction of natural thorium with medium-energy protons

In order to calculate the activity of $^{230}\text{Pa}$ that can be obtained using this method, the cross-section of its formation should be considered. The cross-sections of the $^{230}\text{Pa}$ formation obtained experimentally are shown in Figure 6 in comparison with the literature data $^{[2,6,43-48]}$ and the results of theoretical calculations and in Table S2. $^{230}\text{Pa}$ is the product of one nuclear reaction: $^{232}\text{Th} (p,3n)^{230}\text{Pa}$ (Figure S3). Irradiations with different initial energies were carried out to determine cross-sections with good accuracy in a wide energy range of 35–140 MeV. The results of the theoretical calculation are noticeably overestimated in the studied energy range.

Other protactinium isotopes were also determined in γ-ray spectra of irradiated thorium targets: $^{228}\text{Pa}$ ($t_{1/2} = 22.1$ h), $^{229}\text{Pa}$ ($t_{1/2} = 1.5$ d), $^{232}\text{Pa}$ ($t_{1/2} = 1.32$ d), and $^{233}\text{Pa}$ (27.0 d) (Figure S3). The first three radionuclides are formed by reactions with neutron emission, and $^{233}\text{Pa}$ is produced mainly as a result of a reaction of Th with secondary neutrons: $^{232}\text{Th}(n,\gamma)^{233}\text{Th}$ (22 min, $\beta^-$, 100%) $\rightarrow$ $^{233}\text{Pa}$. The number of secondary neutrons depends on the irradiation parameters (the initial energy of protons, the energy of protons entering and leaving the target), and the configuration of the irradiation chamber (the amount of cooling water and other materials exposed under irradiation).

![Figure 7](image-url). The yield of $^{230}\text{U}$, $^{232}\text{U}$, and $^{233}\text{U}$ depending on the energy of protons bombarding a thick thorium target at fixed output energy of 13.7 MeV (calculation for 10-day irradiation and 23-days accumulation of $^{230}\text{U}$).
The formation of uranium isotopes during irradiation is going on through the β-decay of protactinium parent isotopes. Three isotopes of uranium are forming:

\[ ^{232}\text{Th}(p, 3n) \rightarrow ^{230}\text{Pa}(\beta^-, 7.8\%) \rightarrow ^{230}\text{U}; \]

\[ ^{232}\text{Th}(p, n) \rightarrow ^{232}\text{Pa}(\beta^-, 100\%) \rightarrow ^{232}\text{U}(t_{1/2} = 68.9\gamma); \]

\[ ^{232}\text{Th}(n, \gamma)^{233}\text{Th}(\beta^-, 100\%) \rightarrow ^{233}\text{Pa}(\beta^-, 100\%) \rightarrow ^{233}\text{U}(t_{1/2} = 1.6 \cdot 10^5\gamma). \]

After 10 days of irradiation, the maximum amount of the goal $^{230}\text{U}$ accumulates in 23 days. For this mode of irradiation and cooling, the physical yield of $^{230}\text{U}$ and long-lived impurities $^{232}\text{U}$ and $^{233}\text{U}$ in a thick target were calculated and presented in Figure 7. The yield of $^{230}\text{U}$ was calculated using the experimental cross-sections of $^{230}\text{Pa}$ formation published in the work\[^2\] for proton energies below 35 MeV, and the results of the present work (Table S2) for proton energies above 35 MeV. The $^{232}\text{U}$ impurity was calculated using experimental cross-sections of $^{232}\text{Pa}$ formation from the paper\[^4\] and the $^{233}\text{U}$ impurity was calculated based on experimentally determined in the present work activities of $^{233}\text{Pa}$ for the initial proton energy of 159 MeV.

The yield of $^{230}\text{U}$ reaches 0.48 MBq/(µA∙h) at the initial energy of protons of 140 MeV. Protons with energy below 40 MeV make the greatest contribution to the formation of $^{230}\text{Pa}/^{230}\text{U}$. The range of proton energy of 60–140 MeV is

![Figure 8. Accumulation of $^{230}\text{U}$ (A) and $^{232}\text{U}$ (B) for a thorium target irradiated for 10 days with a proton current of 100 µa and $E_p$ below 140 MeV. Dotted lines show the accumulation of $^{230}\text{U}$ and $^{232}\text{U}$ in the protactinium fraction separated from the uranium fraction 5 days after the EOB.](image-url)
optimal for the formation of $^{225}$Ac. \cite{17} The yield of $^{230}$U in this energy range decreases to 0.18 MBq/($\mu$A·h), which is comparable to the value of 0.24 MBq/($\mu$A·h) obtained by Morgenstern et. al.\cite{2} for proton energies of 15–35 MeV.

The impurity of $^{233}$U is small and falls within (2–7)$\times$10$^{-4}$. $^{233}$U decays into a long-lived $^{229}$Th, locking up a further chain of decay. The admixture of $^{233}$U is decreasing significantly with a decrease in the initial energy of protons. The impurity of $^{232}$U reaches 0.7%, which is an obstacle to the direct medical application of $^{230}$U; however, $^{230}$U with an admixture of $^{232,233}$U can be used as a source for $^{230}$U/$^{226}$Th generator.\cite{49} This case is similar to the pair of $^{225}$Ac/$^{213}$Bi with an impurity of $^{227}$Ac with the difference that the level of the impurity of $^{232}$U can be regulated by cooling time after irradiation and radiochemical separation of protactinium from uranium (Figure 8).

When the Pa and U isotopes are separated by the LLE with 1-octanol on the 5th day after the end of irradiation the impurity of $^{232}$U can be reduced by 50 times due to the shorter half-life of the parent $^{232}$Pa (1.3 days versus 17.4 days of $^{230}$Pa). The yield of $^{230}$U decreases by about 1.5 times, and the maximum accumulation is reached in $5 + 27 = 32$ days after the end of bombardment, while the admixture of $^{233}$U increases slightly.

The cooling of the target for 4–5 days and the subsequent accumulation of $^{230}$U in isolated Pa fraction for 27 days is in perfect consistency with the scheme and timing for producing the other medical radionuclide $^{225}$Ac.\cite{12,35} Up to 3 GBq $^{230}$U with an admixture of 0.02% $^{232}$U and 0.001% $^{233}$U can be obtained along with the isolation of about 100 GBq $^{225}$Ac from the same thorium target irradiated with protons with energy of 120–60 MeV and current of 100 $\mu$A. The target maximal mass is about 80 g, the duration of its irradiation is 10 days followed by 5 days cooling. The activity of $^{230}$U is quite sufficient for the development of therapeutic drugs labeled with $^{230}$U or $^{226}$Th and implementation of preclinical and clinical trials. The production of $^{230}$U for wide medical use can be organized via conventional compact cyclotrons that accelerate protons to lower energies.

**Conclusion**

Solutions of 1-octanol in hydrocarbons efficiently extract protactinium from nitric and hydrochloric acid solutions containing macro quantities of thorium and the products of its irradiation with protons. Nb, Ru, and Zr are the main impurities in the resulting Pa solution. The influence of fluoride ions on the extraction and back-extraction of Pa was investigated, and aluminum nitrate and boric acid were tested as fluoride ion masking agents.

The cross-sections of the $^{230}$Pa formation in the energy range of 140–35 MeV were determined using the stacked-foil technique. The yields of the goal irradiation product $^{230}$U, as well as the main isotopic impurities $^{232}$U and $^{233}$U in a thick target irradiated by medium energy protons, have been
estimated based on the obtained values and literature data. The yield of $^{230}\text{U}$ is 0.18 MBq/(µA∙h) at the energy of protons in the range of 140–60 MeV which is comparable to the yield for $^{230}\text{U}$ producing on 30 MeV cyclotrons. The method of liquid–liquid extraction with 1-octanol provides quick and selective separation of Pa from the solution of the irradiated thorium. It is optimal to carry out the isolation of Pa in 5-day cooling after the end of bombardment, and then store the fraction of $^{230}\text{Pa}$ to accumulate $^{230}\text{U}$ for 27 days. The developed procedure makes it possible to produce several of GBq of $^{230}\text{U}$ per irradiation session as a by-product of $^{225}\text{Ac}$. The $^{230}\text{Pa}$ separation technique can be as well applied for thorium irradiated with lower energy protons using wide-spread 30 MeV cyclotrons, when $^{230}\text{U}$ is the main product of irradiation.

Future work is supposed to be focused on upscaling the developed procedure to obtain high activity of $^{230}\text{U}$ and loading the $^{230}\text{U}/^{226}\text{Th}$ generator.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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