Radiochemical effects of thermal neutron capture in Cr(tmhd)₃: method development

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Abstract

The radiochemical effects of thermal neutron capture in tris(2,2,6,6-tetramethyl-3,5-heptandionato)chromium(III) (Cr(tmhd)$_3$) were investigated. A method was devised to quantify the amount of the induced ^{51}Cr activity recoverable in the original chemical form and to confirm that it is indeed Cr(tmhd)$_3$. The method is based on a combination of chemical separation (column chromatography and recrystallization) and analytical (radio-TLC, HPLC, and gamma spectrometry) techniques. Cr(tmhd)$_3$ samples were irradiated and purified in two steps after irradiation. We found that two of the (three) purification pathways yielded good agreement among final ^{51}Cr activity concentrations. The corresponding samples appeared to be of exceptional radiochemical purity.

Keywords Cr-51 · Szilard-Chalmers effect · Thermal neutron irradiation · Nuclear recoil · Thermal neutron capture

Introduction

When an atomic nucleus absorbs a thermal neutron, it transforms into an isotopic nucleus in an excited nuclear state. The de-excitation usually involves the emission of several high-energy gamma photons, which impart a relatively large recoil to the emitting nucleus. The respective nuclear recoil energies are often in the order of several hundred eV and allow the generated nuclide to (partially) rupture its chemical bonds [1]. The chemical form in which recoil species are later obtained is a priori unknown, but a significant fraction of these species can usually be separated chemically from the target material. For radioactive (daughter) nuclides, this is known as the Szilard-Chalmers effect [2] and has proven valuable for the production of high specific activities, e.g. for radiopharmaceuticals. The chemical effects of nuclear transformations, including thermal neutron capture, have been widely studied [3]. Potentially influencing factors [4–6] are numerous.

In the case of ^{50}Cr(n,γ)^{51}Cr in tris(2,2,6,6-tetramethyl-3,5-heptandionato)chromium(III) (Cr(tmhd)$_3$), the binding energy of the captured neutron is 9.26 MeV [7] and is released in the form of at least two gamma photons [8]. The associated recoil energies are sufficient to rupture the Cr–O bonds in Cr(tmhd)$_3$, which have a mean bond dissociation energy of 2.2 eV [9] each. Nevertheless, some of the induced ^{51}Cr activity is found in its original chemical (i.e. parent) form, commonly referred to as "retention", although the term is not used consistently in this sense.[1]

The following points should apply to the *true* "retention fraction":

(1) The fraction is chemically and radiochemically pure (i.e. it contains only the inactive and radioactive parent compound).
(2) The radioactive species cannot be chemically separated from the inactive parent compound; therefore, activity concentrations should remain constant from then on.

Concrete evidence for this is often missing in the literature. Exceptions do exist: Sutin and Dodson [11], for example, could not separate the activity in the supposed "retention" fraction from the inactive parent ferrocene in a series of chemical reactions, and Rosenberg and Sugihara [12] reported that the specific activity of the analyzed metalloporphines did not change during further purification steps.

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1 Even in one of the earliest definitions by Libby, it is defined as "the fraction of the radioactivity resisting aqueous extraction" [10].

Harbottle and Zahn [13] observed fairly constant specific activities for one of the ruthenium isotopes in ruthenocene in repeated cycles of purification, but not the other.

The present study addresses the following research hypothesis: When Cr(tmhd)$_3$ is irradiated with thermal neutrons, some of the ^{51}Cr activity can be recovered in the original chemical form. To investigate this, irradiated Cr(tmhd)$_3$ samples were subjected to different chemical purification procedures (including combinations of recrystallization and column chromatography). The "retention" fractions thus obtained should satisfy the above requirements, and the activity concentrations of the resulting fractions should be independent of the purification pathway. A method has been developed to quantify the "retention" and to authoritatively demonstrate it is in the claimed chemical form. This should provide the methodological basis for the precise quantification of radiochemical effects of nuclear transformations in Cr(tmhd)$_3$ and other compounds in future studies.

Materials and methods

Materials

Acetic acid ethyl ester, ROTIPURAN® ≥ 99.5%, p.a., ACS from Carl Roth (referred to as "ethyl acetate") was used for the preparation of the mobile phase for column chromatography pre- and post-irradiation and thin-layer chromatography. Acetic acid ethyl ester, ROTISOLV® HPLC from Carl Roth (≥ 99.9%) was used for preparing sample solutions post-irradiation before taking aliquots for further analyses. *n*-Hexane ROTISOLV® HPLC from Carl Roth (≥ 98%) (referred to as "hexane") was used for mobile phase preparation in chromatographic analyses. 2-propanol ROTISOLV® HPLC from Carl Roth (≥ 99.9%) was used for preparing HPLC sample solutions and for the mobile phases in the HPLC analysis and thin-layer chromatography. Ethanol absolute for analysis, EMSURE® ACS from Merck (≥ 99.9%) was used for the synthesis and recrystallization pre- and post-irradiation. Once-distilled water was used whenever "water" is referred to. All solvents were used without further purification.

Chromium(III) nitrate nonahydrate from Riedel-de Häen AG (now Honeywell Riedel-de-Haën™) and 2,2,6,6-tetramethyl-3,5-heptanedione (98%) (referred to as "H-tmhd") from Sigma-Aldrich were used for synthesis. Potassium hydroxide pellets (≥ 85%, p.a. from Carl Roth) were used as a drying agent whenever samples were dried in a desiccator for mass determination.

Silica gel (high-purity grade, 60 Å pore size, 70–230 mesh, 63–200 μm) from Fluka Analytical was used for column chromatography. For thin-layer chromatography (TLC), aluminum plates coated with (normal-phase) silica gel 60 F$_{254}$ from Merck and (reversed-phase) silica gel 60 RP-18 F$_{254}$s from Merck were used. A 10 μL Hamilton® 701 N syringe was used for applying sample solutions.

Synthesis

The preparation of tris(2,2,6,6-tetramethyl-3,5-heptandion-ato)chromium(III) or Cr(tmhd)$_3$ generally followed Stille et al. [14], taking into account suggestions made by Ahmed et al. [15] (mainly using 1:3 stoichiometry and avoiding sublimation for purification). Instead of chromium(III) chloride hexahydrate, chromium(III) nitrate nonahydrate was used as a starting material. The crude material was purified by column chromatography with silica gel as the stationary phase and a 95:5 (*v/v*) mixture of hexane:ethyl acetate as the mobile phase, followed by dissolution in boiling ethanol, filtration, and subsequent recrystallization from ethanol[2] upon cooling to room temperature. Purity was confirmed by high-performance liquid chromatography (HPLC). The relative area of the Cr(tmhd)$_3$ peak was 99.2%. The elemental analysis of the material of a different batch produced in the same way gave results of C: 65.62 and H: 9.49 (expected C: 65.88 and H: 9.55) wt%, and a slightly higher relative area of 99.3% in the HPLC analysis.

Irradiation

Solid samples in polyethylene vials were packed in larger irradiation capsules and irradiated for 14 h[3] at a thermal neutron flux density of 1.7×10^{12} s^{-1} cm^{-2} in the central of the five dry irradiation channel positions of the TRIGA Mark II reactor at the TRIGA Center Atominstitut in Vienna. The irradiation took place at a temperature of about 30 °C. Irradiated substance amounts varied between about 70 mg for two samples to be treated post-irradiation and about 20 mg for reference samples. Samples rested at room temperature for 5 days before subsequent separation and analysis.

Experimental design

An overview of the experiment is depicted in Fig. 1. After irradiation, to remove all species (inactive and radioactive) in any other form than Cr(tmhd)$_3$, the two irradiated samples 1 and 2 were purified twice by either column chromatography or recrystallization. Of the three reference samples irradiated, treatment of two (R1 and R2) mimicked that of the purified samples, but rather than being subjected to the actual separation, they were only exposed to the

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[2] A higher degree of purity was actually achieved with recrystallization from acetonitrile in later experiments.

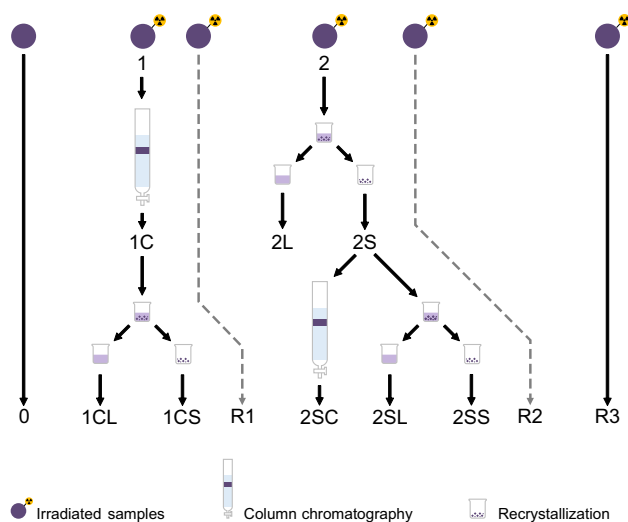[3] 2 × 7 h with a 17 h break in between two consecutive reactor operation days.

Fig. 1 Overview of the experiment. Irradiated samples were either chromatographed over a silica gel column or recrystallized from ethanol. Reference samples R1 and R2 followed the purification pathway of samples 1 and 2, respectively, in that they were exposed to the same solvents. The inactive sample 0 and the reference sample R3 were left untreated prior to the final analysis

corresponding solvents for the same amount of time as the samples treated chemically. The third reference sample (R3) was left to stand for the whole duration of the experiment and will be therefore referred to as the "untreated" reference sample. Together with a sample of the inactive material before irradiation (sample 0), sample R3 was only analyzed in the very last step.

Post-irradiation separation

Sample 1 (72.6 mg) was taken up in 2 mL of 95:5 (*v/v*) hexane:ethyl acetate, while reference sample R1 (21.1 mg) was taken up in 1 mL. Sample 1 was chromatographed according to the procedure described below. Subsequently, both samples were dried in air for 1 day and under reduced pressure (500 mbar) for 1 day in a desiccator with potassium hydroxide as a drying agent. The mass of the chromatographed ("C") sample 1C was 57.6 mg. Samples 1C and R1 were taken up in 5.8 and 2 mL of ethyl acetate, respectively, and subjected to analysis (see below). After analysis, samples were dried in air for 4 days.

Samples 1C and R1 were then taken up in 12 and 5 mL room temperature ethanol and sample 1C was recrystallized according to the procedure described below. The recovered fractions were dried in air for 1 day and under reduced pressure in the desiccator for 2 days. The masses of the solid ("S") and the liquid fraction ("L") were 33.4 and 20.8 mg, respectively. Samples 1CS, 1CL and R1 were again subjected to analysis after being taken up in 3.2, 2, and 2 mL of ethyl acetate, respectively.

In parallel to the processing of sample 1, samples 2 (72.7 mg) and reference sample R2 (21.4 mg) were taken up in 15 mL and 2 mL of ethanol, respectively. Sample 2 was recrystallized according to the procedure described below. Subsequently, all samples were dried in air for 1 day and under reduced pressure in the desiccator for another day. The mass of the recovered fractions was 32.6 mg for the solid (sample 2S) and 35.4 mg for the liquid (sample 2L) fraction. The samples were taken up in 3.2 mL (sample 2S), 3.5 mL (sample 2L), and 2 mL (sample R2) of ethyl acetate and subjected to analysis. After analysis, sample 2S was divided into two samples of approximately equal mass. All samples were dried in air for 1 day and under reduced pressure in the desiccator for 1 day.

One part of sample 2S was taken up in 1 mL of the 95:5 (*v/v*) hexane:ethyl acetate mobile phase and chromatographed according to the procedure described below. The recovered sample 2SC was dried in air for 1 day and under reduced pressure the desiccator for 2 days. The mass of this chromatographed sample 2SC amounted to 14.9 mg. It was taken up in 1.5 mL of ethyl acetate and subjected to analysis.

The other part of sample 2S was taken up in 3.6 mL of ethanol and recrystallized according to the procedure described below. The reference sample R2 was again taken up in 2 mL of ethanol. After the recrystallization and separation, all samples were dried for in air 1 day and under reduced pressure in the desiccator for another day. The recovered masses were 12.5 mg (sample 2SS) and 2.9 mg (sample 2SL) for the solid and liquid fractions, respectively. Samples were taken up in 1.2 mL (sample 2SS), 0.5 mL (sample 2SL) and 1 mL (sample R2) of ethyl acetate. In addition, the inactive sample 0 (9.76 mg) was taken up in 1 mL, and samples R1 and R3 (21.2 mg) in 2 mL of ethyl acetate and subjected to analysis together with the other samples.

All sample solutions were stored in (20 mL) borosilicate glass vials at all times during the experiment to avoid reactions of organic solvents with plastic sample containers.

Column chromatography

A glass column (Ø 1.5 cm) was packed with silica gel (~ 10 g) using the slurry method [16]. The 95:5 (*v/v*) hexane:ethyl acetate mobile phase was used for packing the column. The column height amounted to about 10 cm, plus a top and bottom layer of sea sand (each about 1 cm high). The column was loaded with 1 to 2 mL of the sample solution (depending on total sample mass), and eluted with 95:5 (*v/v*) hexane:ethyl acetate at room temperature. The eluate was collected in three fractions, the second of which contained the parent Cr(tmhd)$_3$. The head and tail of the purple Cr(tmhd)$_3$ band were discarded into the first and last fraction, respectively. The Cr(tmhd)$_3$ fraction was filtered

through a folded black band paper filter to remove any silica gel residue from the sample.

Recrystallization

For recrystallization, irradiated samples were taken up in room temperature ethanol. Sample solutions with concentrations of approximately 4.8 mg mL^{-1} were filtered through a folded black band paper filter to remove residual undissolved material and collected in a glass vial. The glass vial was placed in a (90 mL) polypropylene vial containing 30 mL of water. This plastic vial was sealed and recrystallization occurred by slow diffusion over 6 days. Afterward, the liquid phase was carefully removed with a syringe and collected in a separate glass vial. The crystals were washed with 2×1.5 mL of ice-cold ethanol. The ethanol used for washing was added to the liquid fraction. The crystals (i.e. the solid fraction) were taken up in room temperature ethanol and transferred to another glass vial.

Analysis

Analyses of samples, including radio-thin-layer chromatography (radio-TLC), high-performance liquid chromatography (HPLC), and gamma spectrometry, were performed after each separation step. Reference samples that followed the path of the other samples were analyzed concomitantly. Aliquots of the inactive material (sample 0) and the "untreated" reference sample (R3) were analyzed in the last step only.

Radio-thin-layer chromatography (radio-TLC)

For TLC analysis after each separation step, after samples had been dried and weighed, they were brought to matching concentrations of approximately 10 µg mL^{-1} by adding varying amounts of (HPLC grade) ethyl acetate (see supplementary material, Table S1, for sample masses and concentrations). Of sample solutions thus prepared, 2 µl were applied to normal-phase (NP) and 0.5 µL to reversed-phase (RP) plates with a 10 µl Hamilton® syringe, corresponding to about 20 and 5 µg of spotted mass, respectively. NP plates were developed using a 95:5 (*v/v*) mixture of hexane:ethyl acetate as the mobile phase. A 95:5 (*v/v*) mixture of 2-propanol:water was used for RP plates. Development took place in glass TLC chambers lined with filter paper at room temperature. Development times were about 5 min for NP-TLC and 20 min for RP-TLC.

The TLC plates were packaged in polyethylene bags and used to expose a phosphor imaging plate (NDT HCR from DÜRR NDT) to obtain radiographs showing the distribution of ^{51}Cr along the TLC plates. Exposure times were between 4 and 6 days. (Longer exposure times were chosen during later stages of the experiment due to the decrease in sample activity by that time.) The imaging plate was read out using a computed radiography scanner HD-CR 35 NDT from DÜRR NDT. The peak evaluation of the radiographs was done with OptiQuant Software version 5.0 (RRID:SCR_016769) by Perkin Elmer. Lane regions were drawn over the TLC lanes and peaks were included in regions of interest. One region preceding and one following the actual TLC lane was used to determine the background for the lane. "Background Baseline" was used as the background subtraction method. Areas of peaks of interest were determined as a net percentage of the total lane. For qualitative assessment of the radiographs, radio-chromatograms ("profile plots") were generated with Fiji (RRID:SCR_002285, [17]). TLC plates were also inspected under UV light (at 254 nm) to qualitatively assess the chemical purity of samples. The retardation factors were obtained as the migration distances substances traveled on the TLC plates relative to the migration distance of the solvent front.

High-performance liquid chromatography (HPLC)

From the approximately 10 µg µL^{-1} (ethyl acetate) solutions prepared for TLC analysis, 10 µL were withdrawn (with a 10 µL pipette) into HPLC vials and diluted 1:100 with HPLC grade 2-propanol.

Aliquots were withdrawn at various points during the experiment and analyzed together at the end of the experiment. A blank sample (containing only the 2-propanol solvent) was also included. HPLC analyses were performed on a Thermo Scientific™ UltiMate™ 3000 (with an LPG-3400SD pump, a WPS-3000 autosampler, a TCC-3200 column oven, and a 3400 VWD UV–Vis detector) system. A C8 analytical column (ZORBAX Eclipse XDB-C8, 80 Å, 4.6×150 mm, 5 µm from Agilent Technologies) was used at 40 °C. Runs lasted for 15 min, plus a 4 min equilibration time in between runs. 2-propanol:water (0.1% *v/v* trifluoroacetic acid) was used as the mobile phase, with a linear gradient from 30:70 until 3 min to 95:5 (*v/v*) at 12 min. Equilibration took place at 30:70 (*v/v*). The flow rate remained constant at 1 mL min^{-1}. The injection volume was 5 µL. The detection wavelength was set to 254 nm.

HPLC chromatograms (i.e. UV detector signal as a function of the measuring time[4]) were evaluated using the integrated Chromeleon 7.2.9 (Chromeleon™ Chromatography Data System (CDS) Software, RRID:SCR_016874). For the determination of relative Cr(tmhd)$_3$ peak areas, only sample peaks that did not also appear in the chromatogram for the blank sample were included. Relative peak areas serve as an approximate indication of chemical purity.

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[4] Referred to as "retention time", not to be confused with the "retention" meaning "activity in parent form".

Gamma spectrometry

Ethyl acetate sample solutions as prepared for TLC analysis were brought to equal volumes (15 mL) for gamma measurement.

The ^{51}Cr activity of samples was measured in a reproducible geometry on a High Purity Germanium (HPGe) detector (1.8 keV resolution at the 1332 keV ^{60}Co peak, 50.1% relative efficiency) connected to a Loss Free Counting System. The duration of the measurements varied between samples due to different total count rates and was chosen so that the counting uncertainty reached values below 0.3% for all samples. (Measurement times ranged from 10 min for high-activity samples to over 16 h for lower-activity samples and late stages of the experiment.)

The Genie 2000 Basic Spectroscopy Software version 3.4 from Canberra (RRID:SCR_021933) was used for the evaluation of the ^{51}Cr peaks at 320 keV. Count rates were decay-corrected for comparison. Activity concentrations [18] (activity per sample mass, expressed in Bq kg^{-1}) were calculated for all samples and every measurement. Ratios of activity concentrations of samples and the "untreated" reference sample R3 were calculated.

Determination of activity in Cr(tmhd)$_3$ form

The relative ^{51}Cr activity recovered in the original chemical form was determined in two complementary ways, based on either gamma measurements or the evaluation of radio-TLC plates.

Gamma-spectrometric method

If the ^{51}Cr activity concentrations (activity as determined by gamma spectrometry per sample mass) of purified samples that ideally contain only radio- and inactive species in the form of Cr(tmhd)$_3$ are compared with that of the "untreated" reference sample R3, the ratio of activity concentrations gives the percentage of activity in parent form (R) [12, 13, 19]:

$$R = \frac{A_P}{m_P} \cdot \frac{m_R}{A_R} \tag{1}$$

A_P and A_R denote the activity concentrations and m_P and m_R the sample masses of the parent (Cr(tmhd)$_3$) fraction (as obtained after column chromatography and/or recrystallization) and reference sample, respectively. By scaling the activity concentration to the total mass of the reference sample, one implicitly assumes a 100% mass contribution from the parent Cr(tmhd)$_3$ and does not account for impurities

present before or introduced through irradiation. Depending on the relative amount of impurity, this could lead to an overestimation of "retention" values.

This "gamma-spectrometric method" is only applicable to *purified* (i.e. treated) samples that (ideally) only contain the parent compound.

Radio-TLC method

In this method, the relative area of the peak from radioactive species that run with Cr(tmhd)$_3$ (as determined with OptiQuant) on the normal-phase silica gel TLC plate is used as a measure for the relative amount of the activity that is recovered in its original chemical form. The activity in parent form is then given as:

$$R = \frac{X_P}{X_T} \tag{2}$$

X_P is the net area of the parent peak and X_T is the net area of the whole TLC lane. Net areas are expressed in digital light units or DLU in OptiQuant. Note that it is not necessarily accurate to assume that radioactive species running with the parent compound are in that same chemical form. Compounds could run so close together that they appear as one peak in the radio-TLC.

The "radio-TLC" method is applied to the evaluation of the radio-TLC plate of the *"untreated"* reference sample.

Results and discussion

Purity of parent fractions

"Parent fractions" refers to fractions obtained after each purification step that were supposed to contain the parent compound Cr(tmhd)$_3$ only. If that is the case, the parent fractions are both radiochemically and chemically pure.

Radiochemical purity

Figure 2 depicts the distribution of the ^{51}Cr activity along the NP-TLC silica gel plate ("radio-chromatogram") after the first purification step for samples 1C and 2S. Only one peak is observed for the chromatographed sample 1C (see Fig. 2a), and it falls into the gray-shaded region where also the inactive Cr(tmhd)$_3$ is located on the plate. Therefore, sample 1C already appears radiochemically quite pure after only one purification step. The same was not true for the solid fraction 2S after the recrystallization of sample 2, where a rather significant baseline peak (i.e. right where the sample was applied, indicated by the left black vertical line in Fig. 2) is visible in addition to the Cr(tmhd)$_3$ peak (see
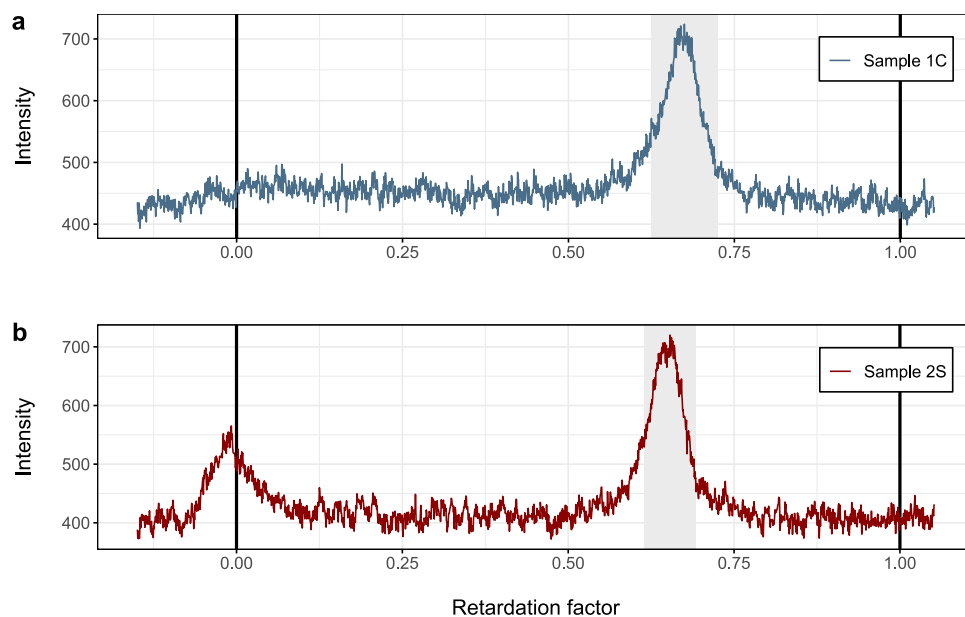
Fig. 2 Radio-TLC chromatograms for once-purified samples, displayed as the intensity (as a gray value) against the retardation factor (migration distance normalized to the migration distance of the solvent front). The black vertical lines mark the baseline (left) and solvent front (right). The gray-shaded area denotes the approximate location of the inactive Cr(tmhd)$_3$ spot. Samples were developed on normal-phase silica gel TLC plates in 95:5 (*v/v*) hexane:ethyl acetate. **a** Sample 1C, **b** Sample 2S

Fig. 3 Radio-TLC chromatograms for twice purified samples, displayed as the intensity (as a gray value) against the retardation factor (migration distance normalized to the migration distance of the solvent front). The black vertical lines mark the baseline (left) and solvent front (right). The gray-shaded area denotes the approximate location of the inactive Cr(tmhd)$_3$ spot. Samples were developed on normal-phase silica gel TLC plates in 95:5 (*v/v*) hexane:ethyl acetate. **a** Samples 1CS and 2SC, **b** Sample 2SS
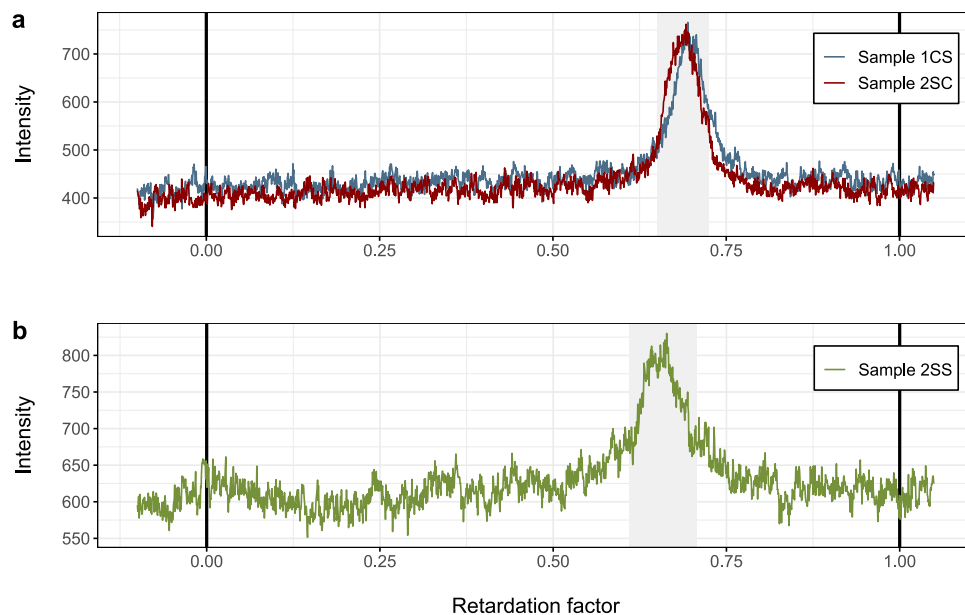

Fig. 2b). However, radioactive impurity species re-appeared in the liquid fraction 1CL after recrystallization of sample 1C (see supplementary material, Fig. S1), which could indicate that not all radioactive species appearing to run with Cr(tmhd)$_3$ in the TLC of sample 1C were actually in that form. Another possibility is reactions of Cr(tmhd)$_3$ itself in or with the ethanol during recrystallization leading to the formation of species that would then remain in the liquid fraction. If radioactive and inactive Cr(tmhd)$_3$ participate equally in such reactions, this should not affect the activity concentration of the (assumedly pure) solid fraction. A

similar phenomenon was also observed in the radio-TLC of sample 2SL (see Fig. S2), in which a more intense baseline peak appears compared to sample 2S.

Figure 3 shows the radio-chromatograms for NP-TLC plates (i.e. distribution of ^{51}Cr along the plate) of twice purified samples 1CS and 2SC (Fig. 3a), and 2SS (Fig. 3b). For samples 1CS and 2SC, only one peak appears in the region where the spot for the inactive Cr(tmhd)$_3$ also occurs (again denoted by the gray-shaded rectangular region), whereas for sample 2SS an additional small peak is located at the baseline (and potentially other small "bumps" between the

Table 1 Relative areas of the Cr(tmhd)$_3$ peak at 13.51 min in HPLC chromatograms for all samples

Sample ID	Relative peak area (%)
Sample 1C	97.73(25)
Sample 1CS	99.0(3)
Sample 1CL	96.29(25)
Sample 2S	98.8(3)
Sample 2L	94.73(24)
Sample 2SC	99.0(3)
Sample 2SS	99.1(3)
Sample 2SL	98.1(3)
Reference R1	96.51(25)
Reference R2	96.55(25)
Reference R3	96.34(25)

"C" refers to the chromatographed sample, "S" to the solid, and "L" to the liquid phase after recrystallization

baseline and the Cr(tmhd)$_3$ region[5]). The radiochemical purity did increase from sample 2S to 2SS based on the relative areas of the ^{51}Cr(tmhd)$_3$ peak in the radio-TLC (namely 54 and 77%, respectively). The remaining radioactive impurities in samples 2S and 2SS were probably due to incomplete separation of the liquid from the solid fraction after recrystallization. On this basis, two successive recrystallization steps appeared to be inferior in terms of radiochemical purity compared to the other two purification pathways. The combination of two techniques (recrystallization and column chromatography), regardless of the order of application, led to better results.

Because equal masses had been spotted in the radio-TLC analysis, the fact that the (presumed) ^{51}Cr(tmhd)$_3$ peaks for samples 1CS and 2SC overlap so well in Fig. 3a is a strong indication that the radioactive ^{51}Cr species are in the same chemical form as the bulk material since radioactivity and sample mass were almost completely decoupled as a consequence of the initial nuclear event. Sample 2SS was analyzed separately from the other samples at a later time, therefore the absolute peak heights are not directly comparable in this case. However, the ^{51}Cr(tmhd)$_3$ peaks for samples 2SS and 2SL also overlap nicely (see supplementary material, Fig. S2), so at least this portion of ^{51}Cr-containing species also seemed to follow the mass of the bulk material.

Chemical purity

Table 1 shows the relative areas of the Cr(tmhd)$_3$ peaks (appearing at 13.51 min) in HPLC chromatograms as an

indicator of the chemical purity of the samples. Uncertainties are based on relative standard measurement uncertainties [20] (corresponding to one standard deviation) from ten repeated HPLC measurements of a test sample since no uncertainties were obtained with HPLC results. The values provided for reference samples R1 and R2 correspond to measurements of aliquots taken after the second chemical separation step.

The relative peak area for the irradiated but "untreated" reference sample R3 is 96.34(25)%, which is less than the value of 99.2(3)% for the inactive material before irradiation. The irradiation introduces macroscopic but small amounts of inactive impurities into the system. These appear as several small peaks in addition to the main Cr(tmhd)$_3$ peak at 13.51 min in the HPLC chromatogram for the irradiated reference sample R3 compared to the inactive sample 0 (see Fig. 4). They are also visible on TLC plates under UV light (see supplementary material, Fig. S3). Outside of the displayed retention time between 9.5 and 15 min in Fig. 4, no other peaks occur that are not also present in the solvent blank.

The introduced impurities could be a limiting factor for achieving high specific activities of ^{51}Cr when using Cr(tmhd)$_3$ as a target, especially for longer irradiation times—a known problem for Szilard-Chalmers enrichment processes [21]. In addition to these impurities, a peak is visible at 14.42 min in Fig. 4 for an impurity also present in the material before irradiation (sample 0). Especially in early studies, varying amounts of impurities in investigated substances posed a problem and were responsible for a lack of reproducibility in some cases [22, 23]. The importance of using substances of high purity was later emphasized by Müller [24]. The presence of even small amounts of impurities (before or after irradiation) in the investigated system is not ideal, as a possible influence on results cannot be ruled out.

The small peak visible at 9.92 min in Fig. 4 corresponds to the ligand (H-tmhd) of Cr(tmhd)$_3$, which is present in the irradiated but not in the inactive sample, and is therefore likely the result of the decomposition of Cr(tmhd)$_3$ during irradiation. Macroscopic amounts of the ligand could facilitate reactions of recoil species in general as well as reactions leading to a re-formation of the parent molecule. For bis(benzene) chromium, Baumgärtner and Zahn [19] reportedly observed no increase in "retention" values when they dissolved the irradiated material in benzene, but this does not mean that this is generally the case.

The chemical purity increased down purification pathways, although it improved only marginally, if at all, from sample 2S (98.8(3)%) after the first recrystallization step to samples 2SS (99.1(3)%) and 2SC (99.0(3)%). The change was slightly larger between sample 1C (97.73(25)%) after the column chromatography step and the final purification

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[5] The "double recrystallization" pathway took the longest, so the signal-to-noise ratio is worse for sample 2SS compared to 1CS and 2SC due to the decrease in activity.

Fig. 4 HPLC chromatograms (UV absorbance against the retention time) for the inactive sample 0, the irradiated "untreated" reference sample (R3), and the blank. Only the part of the chromatogram marked in the top left inset is displayed in the plot. HPLC conditions: Agilent Zorbax Eclipse XDB-C8, 5 μm column (4.6×150 mm). Mobile phase: 2-propanol:water (0.1% *v/v* trifluoroacetic acid), 30:70 for 3 min, then to 95:5 over 10 min, 95:5 for 3 min, then 4 min equilibration at 30:70. Flow rate: 1 mL min⁻¹. UV detection at 254 nm
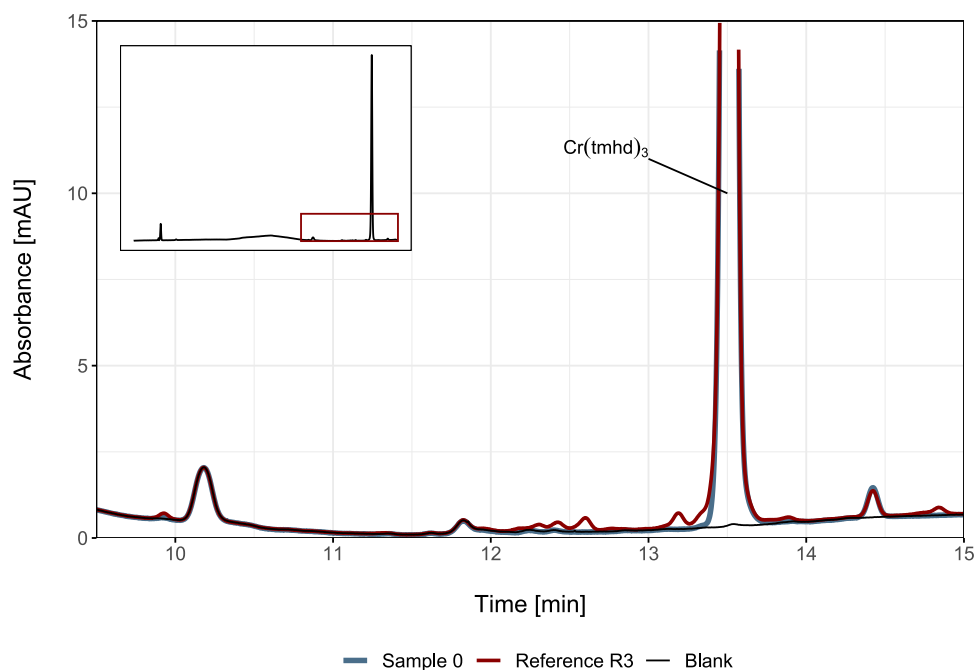
step (99.0(3)%). Even though sample 1C looked radiochemically pure in the radio-TLC analysis, it apparently still contained inactive impurities after column chromatography that were also visible in TLC and HPLC (see supplementary material, Fig. S4) analyses. Therefore, a radioactive impurity not clearly separable from $Cr(tmhd)_3$ by radio-TLC under the conditions applied cannot be excluded.

In view of the above, it is not surprising that the chemical purity also decreased in sample 1CL relative to 1C (from 97.73(25) to 96.29(25)%[6]), since any impurities in the latter would become enriched in the liquid fraction of recrystallization. A spot at the baseline was also visible for sample 1CL on the NP-TLC plate under UV light that had been much less intense for sample 1C (see supplementary material, Fig. S5). This could be an indication of the above-mentioned possible reactions of (inactive and radioactive) $Cr(tmhd)_3$ with or in ethanol during recrystallization or reactions of impurity species present in sample 1C.

For twice purified samples 1CS, 2SC, and 2SS, relative $Cr(tmhd)_3$ peak areas of 99.0(3), 99.0(3), and 99.1(3)%, respectively, were obtained. This suggests that samples still contained small amounts of impurities after two purification steps. Nevertheless, most impurities introduced through irradiation were effectively removed, as can be seen in the HPLC chromatogram in Fig. 5 for sample 2SS. Chromatograms for samples 1CS and 2SC are almost identical and can be found in the supplementary material (Fig. S6 and Fig. S7). Apart from $Cr(tmhd)_3$ at 13.51 min, a small but reduced amount of the impurity present before irradiation (retention time of 14.42 min) remains, as well as an impurity (at 14.84 min) introduced through irradiation. The latter seems to be quite resistant to purification attempts since the peak appears consistently in almost all samples independent of the purification method.[7] (Mass concentrations of sample solutions were matched and equal volumes withdrawn and injected for HPLC analysis, so absolute peak heights are comparable between Figs. 4 and 5). In the TLC analysis, sample 1CS appeared slightly purer than samples 2SC and 2SS. For the latter two, a faint spot was visible at the baseline under UV light that was missing in sample 1CS (see supplementary material, Fig. S8). Note that this is not reflected in the HPLC results, which could mean that these compounds may be adsorbed on the HPLC (guard) column. If that is in fact the case, the values in Table 1 could slightly overestimate chemical purity.

Together with the observations from the previous subsection on radiochemical purity (in particular Fig. 3a and its discussion) the chemical purity of the twice purified samples 1CS and 2SC now indicates that the ⁵¹Cr activity in those samples was indeed in the form of ⁵¹$Cr(tmhd)_3$, since it was already established that the activity behaves like the bulk material in the radio-TLC.

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[6] Sample 2CL contains the impurities corresponding to the "combined masses" of samples 2CL and 2CS.

[7] Except for the liquid fractions of recrystallization, interestingly, where it is almost non-existent.

Fig. 5 HPLC chromatograms (UV absorbance against the retention time) for the twice recrystallized sample 2SS and the blank. Only the part of the chromatogram marked in the top left inset is displayed in the plot. HPLC conditions: Agilent Zorbax Eclipse XDB-C8, 5 μm column (4.6×150 mm). Mobile phase: 2-propanol:water (0.1% *v/v* trifluoroacetic acid), 30:70 for 3 min, then to 95:5 over 10 min, 95:5 for 3 min, then 4 min equilibration at 30:70. Flow rate: 1 mL min^{-1}. UV detection at 254 nm
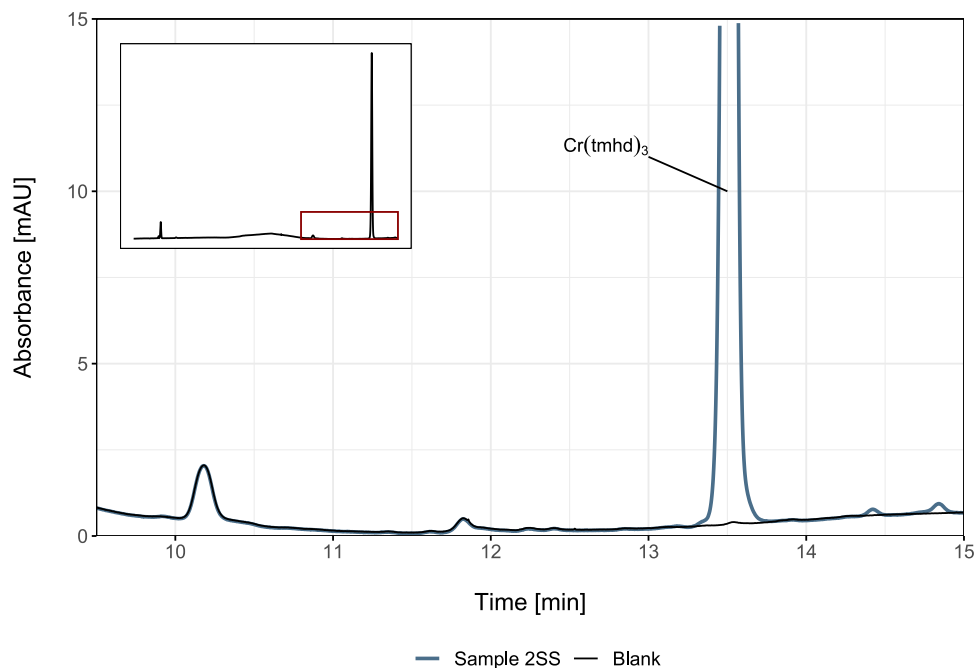
Relative activity concentrations

Table 2 shows the ^{51}Cr activity concentrations of samples relative to that of the "untreated" reference sample R3. For the determination of the measurement uncertainty, an uncertainty of 1.96 standard deviations was used for each gamma measurement (resulting in relative uncertainties between 2.1 and 2.2% for all samples), and for the mass, an uncertainty of ± 0.2 mg was assumed. The total uncertainty was then calculated by differential propagation of uncertainty.

After the first purification step of either column chromatography or recrystallization, the activity concentration decreased to 10.3(3)% and 13.3(4)% of that of R3 in samples 1C and 2S, respectively. The column chromatography step removed a larger fraction of the originally induced activity compared to recrystallization. When the once-chromatographed material was recrystallized, the relative activity concentration decreased to 8.2(3)% in the solid fraction 1CS. For the once-recrystallized sample that was chromatographed (2SC), it decreased to 8.5(3)%. Those values agree well within the error of measurement. However, for the sample that was recrystallized twice (2SS), the relative activity concentration of 10.7(4)% is still considerably higher. As seen in the subsection on radiochemical purity, this can likely be explained by the fact that sample 2SS still contained radioactive impurity species. Multiplying the value of 10.7% for sample 2SS by the percentage of the spotted ^{51}Cr activity that runs with Cr(tmhd)$_3$ in NP-TLC determined with OptiQuant (77%) yields 8.2%. It agrees well with the values for samples 1CS and 2SC. This supports

Table 2 Activity concentrations after chemical separation steps for samples 1 and 2 relative to that of reference sample R3

Sample ID	Relative activity concentration (%)
Sample 1C	10.3(3)
Sample 1CS	8.2(3)*
Sample 1CL	13.1(4)
Sample 2S	13.3(4)
Sample 2L	185(6)
Sample 2SC	8.5(3)*
Sample 2SS	10.7(4)*
Sample 2SL	19.8(15)

"C" refers to the chromatographed sample, "S" to the solid, and "L" to the liquid phase after recrystallization

*Values corresponding to the relative ^{51}Cr activities in Cr(tmhd)$_3$ form as determined by the "gamma-spectrometric method"

the assumption that the discrepancy is due to radiochemical impurities in sample 2SS.

Generally, activity concentrations decreased down purification pathways,[8] implying that the "final" activity concentration was not reached after one purification step for

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[8] The only exceptions, of course, are the liquid fractions of recrystallization where activity is enriched, especially in the first recrystallization step.

either column chromatography or recrystallization. This was evident for sample 2S obtained after the first recrystallization step since radioactive impurity species were clearly visible in the radio-TLC (see Fig. 2b), but not for sample 1C. Even for sample 1C, however, it is possible that it still contained radioactive impurities after column chromatography, as discussed in the previous subsections. Since the activity concentration decreased from sample 1C to 1CS, reactions of the (^{51}Cr-labelled) Cr(tmhd)$_3$ alone cannot be the sole reason for the re-appearance of radioactive impurity species in sample 1CL in the radio-TLC. The presence and reaction of ^{51}Cr impurity species in sample 1C could explain both of the above observations.

An additional (third) purification step may have been beneficial to assure that the activity concentrations remain constant for samples 1CS and 2SC, similar to [12] and [13]. Nonetheless, the agreement in the values obtained for samples 1CS and 2SC is persuasive, especially considering that the radio-TLC chromatograms in Fig. 3 are almost identical, and the radioactive species were not separable from inactive Cr(tmhd)$_3$.

Activity in Cr(tmhd)$_3$ form

The results for the fraction of the total ^{51}Cr activity in the form of Cr(tmhd)$_3$ ("retention") are as follows: For the gamma-spectrometric method, the values can be obtained from the relative activity concentrations in Table 2, as they correspond exactly to Eq. (1). This gives "retention" values of 8.2(3), 8.5(3), and 10.7(4)% for samples 1CS, 2SC, and 2SS, respectively. As discussed, the value is higher for sample 2SS because it still contained radioactive species other than ^{51}Cr(tmhd)$_3$.

By the radio-TLC method and Eq. (2), 7% of the total activity ran with the inactive Cr(tmhd)$_3$ for the "untreated" reference sample R3. Figure 6 displays the radiograph and corresponding radio-chromatogram for reference sample R3 that were used in the OptiQuant evaluation. As can be seen, the large majority of the applied ^{51}Cr activity remains right at the baseline. The shaded gray area marks the region in which the inactive Cr(tmhd)$_3$ spot is located on the TLC plate. One ^{51}Cr peak also falls into that region, an indication that the corresponding radioactive species behave like the inactive Cr(tmhd)$_3$ in the TLC analysis. Retardation factors for the inactive and the radioactive Cr(tmhd)$_3$ (measured for the center of the spot and the maximum of the radiographic peak, respectively) are 0.73 in both cases.

The values determined by the gamma-spectrometric method can be easily overestimated if the reference sample contains macroscopic amounts of impurities. However, even the presence of 5 wt% of impurities (leading to a relative overestimation of the "retention" values of ~5% by the gamma-spectrometric method) is not sufficient to explain potential discrepancies between the two complementary methods. Another aspect has been briefly mentioned in the methods section: Post-irradiation treatment (e.g. exposure to solvents) varied between the twice purified samples used in the gamma-spectrometric method and the "untreated" reference sample used in the radio-TLC method, hence results might be inherently difficult to compare. This is discussed in more detail in the next subsection.

The value for the activity in parent form determined by the radio-TLC method is not higher than that for the gamma-spectrometric method, although the reference sample R3 was analyzed at the very end of the experiment, almost 4 weeks after irradiation. This suggests that back reactions

Fig. 6 Radio-TLC chromatogram for the reference sample R3, displayed as the intensity (as a gray value) against the retardation factor (migration distance normalized to the migration distance of the solvent front). The vertical black lines mark the baseline (left) and the solvent front (right). The gray-shaded region denotes the approximate location of the inactive Cr(tmhd)$_3$ spot. The image of the corresponding radiography is annotated at the top. The normal-phase silica gel TLC plate was developed in 95:5 (*v/v*) hexane:ethyl acetate
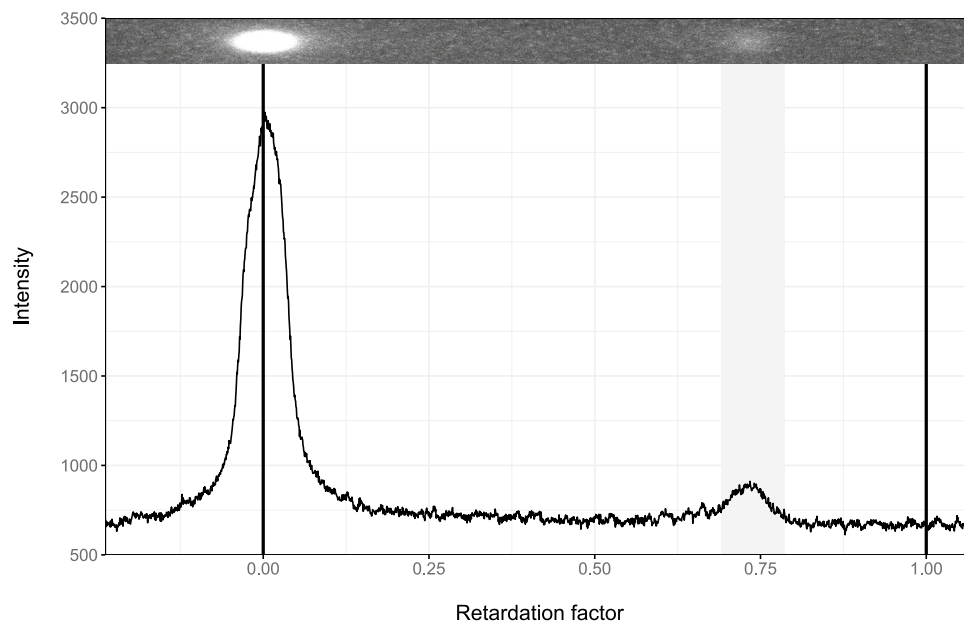
Fig. 7 Radio-TLC chromatograms for irradiated reference samples, displayed as the intensity (as a gray value) against the retardation factor (migration distance normalized to the migration distance of the solvent front). The vertical black lines mark the baseline (left) and the solvent front (right), the gray-shaded region denotes the approximate location of the inactive Cr(tmhd)$_3$ spot. **a** normal-phase silica gel TLC plates, developed in 95:5 (v/v) hexane:ethyl acetate, **b** reversed-phase silica gel TLC plates, developed in 95:5 (v/v) 2-propanol:water
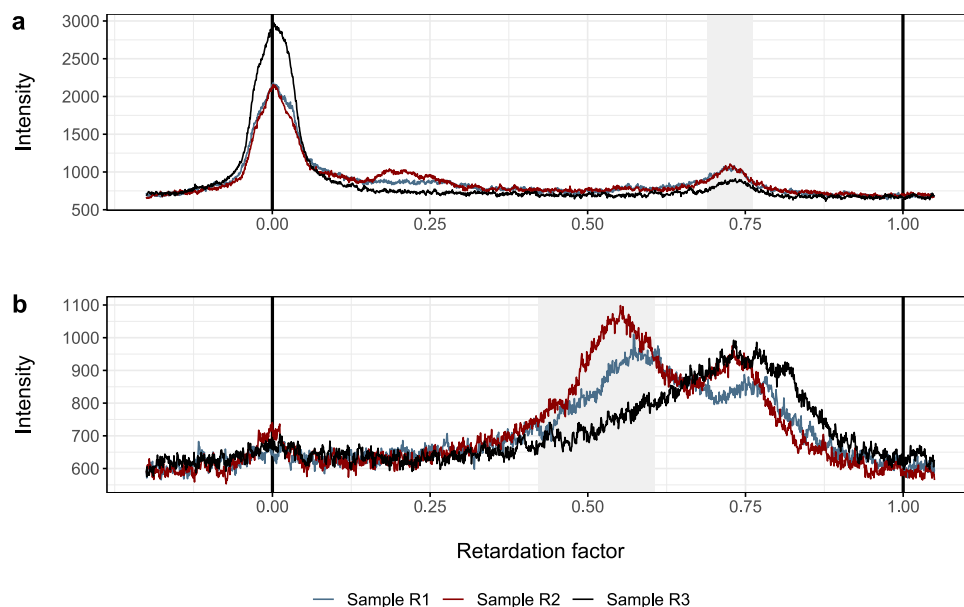
of ^{51}Cr-containing species to ^{51}Cr(tmhd)$_3$ in sample R3 did not occur to a significant extent after the start of workup of samples 1 and 2 five days post-irradiation. However, they may well have occurred in the first days following irradiation. Such an increase in "retention" has been observed by Sutin and Dodson [11] for ferrocene when a sample stood at room temperature for 6 days after irradiation before being processed. In addition, long irradiation times have also been observed to increase "retention" [25–27]. Either factor may have also increased the amount of ^{51}Cr found in the form of Cr(tmhd)$_3$ in this present study. For the related compound tris(acetylacetonato)chromium(III) (Cr(acac)$_3$), Matsuura et al. found "retention" values between 4 and 6% [28], although for different irradiation conditions (especially shorter irradiation times between 2 and 4 min). "Retention" values were, however, reported as the percentage of the activity remaining in the organic phase in the liquid–liquid extraction step following irradiation and might therefore not be strictly comparable. Nevertheless, it seems promising that the values lie in a very similar range.

According to both the gamma-spectrometric and the radio-TLC method, more than 90% of the total induced ^{51}Cr activity is present in a chemical form other than Cr(tmhd)$_3$. Moreover, as seen in Fig. 6, this majority of the activity separates well from inactive Cr(tmhd)$_3$ chromatographically. It might be possible to use Cr(tmhd)$_3$ as a target for the production of ^{51}Cr of a potentially high specific activity if most of the separated activity can be recovered and is not heavily diluted by inactive decomposition products. Other popular pathways to produce enriched ^{51}Cr via neutron activation usually focus on chromates [29–32], especially potassium chromate. Tsai and Yeh [31] also included Cr(acac)$_3$ as a target, but the results were not very promising when they

tried to extract the ^{51}Cr activity into the aqueous phase after irradiation. Other methods of chemical separation may prove more profitable.

Exposure to different solvents

A comparison between reference samples R1 (that followed sample 1), R2 (that followed sample 2), and R3 ("untreated") reveals a significant re-distribution of radioactive species due to exposure to different solvents during the experiment. Figure 7 shows the radio-chromatograms for NP- and RP-TLC plates. In both cases, an increase in peak heights in the Cr(tmhd)$_3$ regions (denoted by shaded gray areas) is visible for samples R1 and R2 compared to R3.[9] If (prolonged) solvent exposure encourages reactions of radioactive species back to Cr(tmhd)$_3$, this may be a possible explanation for the slightly different results of the gamma-spectrometric method compared to the radio-TLC method in terms of the amount of the ^{51}Cr activity in the original chemical form. Also, exposure to different solvents has already been raised as an influencing factor in "hot-atom chemistry" [33].

On a bulk level, induced changes were comparatively small. The HPLC chromatograms of samples R1 and R2 looked practically identical. Slight differences can be observed when comparing them to the chromatogram for the "untreated" reference sample R3 (see supplementary material, Fig. S9). Relative net peak areas were similar

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[9] For some reason, the integrated intensity of the reversed-phase radio-TLC chromatogram was higher for sample R2 compared to the other two samples, so the absolute peak heights are not comparable in Fig. 7b. If the chromatograms are scaled by this integrated intensity, the peaks appear about as high as those for sample R1.

for all reference samples, namely 96.51(25), 96.55(25), and 96.34(25)% (see Table 1) for samples R1, R2, and R3, respectively. This strongly suggests that radioactive species are more reactive than inactive species, including $Cr(tmhd)_3$ as well as decomposition products.

However, apart from the general effect of solvent exposure, the influence on the ^{51}Cr activity in the form of $Cr(tmhd)_3$ appeared to be nonspecific in terms of type and/or order of solvent(s) used, since the activity concentrations agreed very well for different purification pathways (except for sample 2SS, but the discrepancy could be readily accounted for by radioactive impurities). This is consistent with Fig. 7, in which differences between samples R1 and R2 in the $Cr(tmhd)_3$ region were small (taking into account footnote 9). It is also in accordance with a hypothesis formulated by Harbottle [5], that [radioactive] recoil fragments might be so unstable that they do not distinguish between different solvents upon dissolution. Stucky and Kieser [33], on the other hand, did observe differences in the "retention" values for some of the compounds they investigated depending on the type of solvent used, so the above statement may not be generally true. A difference in the respective distribution of ^{51}Cr activity along the NP-TLC plates is also evident for samples R1 and R2 in Fig. 7a, albeit outside the $Cr(tmhd)_3$ ("retention") region. Overall, it is clear that exposure to solvents did have an effect on the activity distribution, and for at least some of the ^{51}Cr recoil species, the particular history of solvent exposure seemed to matter as well. The extent of the effect of solvent exposure on the ^{51}Cr activity in parent form, however, is difficult to estimate because additional radioactive species were present in samples R1 and R2 that did not separate well from $Cr(tmhd)_3$ on the NP-TLC plate (see Fig. S10). It is also possible that such an effect is more pronounced in samples R1 and R2 compared to samples 1 and 2, since most of the radioactive impurity species were removed from the latter in the first purification step, while they were still available for further reactions in samples R1 and R2.

Conclusions

After irradiating $Cr(tmhd)_3$ with thermal neutrons, two complementary methods (one based on radio-TLC, the other on gamma-spectrometric measurements of purified samples) were applied to determine the amount of the induced ^{51}Cr activity recovered in the form of $Cr(tmhd)_3$ following neutron capture. About 7–8% of the total activity was found to be in this form, depending on the method applied. Despite the small discrepancy between the results, one method can be used to validate the results of the other method within a certain margin of error. Since more than 90% of the ^{51}Cr

activity was in a chemical form other than the parent form, $Cr(tmhd)_3$ might be a worthwhile target to investigate for producing high specific activities of ^{51}Cr.

It has to be noted that, at this point, we cannot discriminate between $^{51}Cr(tmhd)_3$ surviving neutron capture and ^{51}Cr recoil species re-forming the parent molecule at a later time (i.e. between primary and secondary "retention" [34]). Therefore, the "retention" values stated above can only be considered as a combination of the two, with possibly little information remaining about the immediate consequences of the initial nuclear event. In addition, the time delay between irradiation and sample processing may have allowed reactions of recoil species back to $^{51}Cr(tmhd)_3$. Although this is of no real concern in this present study, since the comparison between the two methods was of primary interest, it certainly is important to keep this in mind when interpreting the absolute values.

In order to effectively remove radioactive and inactive impurities from the irradiated $Cr(tmhd)_3$, at least two purification steps (either column-chromatography followed by recrystallization or vice versa) had to be performed after irradiation. The material thus purified was found to be radiochemically very pure, even though a small amount ($\leq 1\%$) of chemical impurities remained. The thorough investigations of radiochemical as well as chemical purity after the post-irradiation chemical separation steps to confirm the identity of the ^{51}Cr species in the "retention" fraction are a useful addition to the study of radiochemical consequences of nuclear transformations. On this basis, more in-depth studies will be carried out in the future. With slight modifications, the method presented should also be applicable to metal–organic compounds other than $Cr(tmhd)_3$.

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