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Thermal behaviour of hafnium diethylenetriaminepentaacetate studied using the Perturbed Angular Correlation Technique

Abstract: Polyaminecarboxilic ligands like diethylenetriaminepentaacetic acid form stable complexes with many heavy metal ions, excelling as cation chelants especially in the field of radiopharmacy. The aim of this work is to characterize, by using the Time Differential Perturbed Angular Correlations (TDPAC) technique, the hyperfine interactions at hafnium sites in hafnium diethylenetriaminepentaacetate and to investigate their evolution as temperature increases.

TDPAC results for $KHfDTPA \cdot 3H_2O$ obtained by chemical synthesis yield a well defined and highly asymmetric interaction of quadrupole frequency $\omega_Q = 141$ Mrad/s, which is consistent with the existence of a unique site for the metal in the crystal lattice.

The thermal behaviour of the chelate is investigated by means of differential scanning calorimetry and thermogravimetrical analyses revealing that an endothermic dehydration of $KHfDTPA \cdot 3H_2O$ takes place in one step between $80\,°C$ and $180\,°C$. The anhydrous KHfDTPA thus arising is characterized by a fully asymmetric and well defined interaction of quadrupole frequency $\omega_Q = 168$ Mrad/s.

Keywords: Hafnium diethylenetriaminepentaacetate, Time Differential Perturbed Angular Correlations, Thermogravimetric analysis, Differential scanning calorimetry, Dehydration.

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1 Introduction

During the last 50 years, metal complexes have been used as diagnostic agents for gamma scintigraphy, positron emission tomography (PET) and more recently for enhancing contrast of magnetic resonance imaging (MRI) [1]. Nowadays, medical research focuses in the development of better diagnostic radiopharmaceuticals and contrast agents [2], together with novel investigations in the field of therapeutic radiopharmaceuticals [3].

Designing metal complex based imaging agents requires correlating aspects of coordination chemistry with *in vivo* behaviour. For the complexes intended for medical use, it is of great interest the strong complexation of the metal ion in order to avoid toxicity. Other factors to consider include redox properties, stability, stereochemistry, charge and lipophilicity of the metal complex. Thus, a good understanding of the conformation and dynamical behaviour of the chelates is of great interest.

Among many organic molecules used for the metal complexation, the utilization of the classic polyaminecarboxilic ligands ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA) are still good choices for the diagnostic agents formulations. Several metal polyaminecarboxilate chelates were obtained and characterized in the crystalline state [4] whereas no truly crystallization could be reached in other cases.

Time Differential Perturbed Angular Correlations (TDPAC) spectroscopy is a highly efficient tool to investigate the electric field gradients (EFG) at atomic sites in solids allowing the determination of the atomic configuration around them. The method requires a radioactive probe with special nuclear properties located at the site where the EFG is to be measured.

A lot of efforts have been made in order to extend the field of application of this technique to chemistry and biology. In particular, the possibility of preparing low molecular weight complexes to be studied using this technique has attracted the attention of the interdisciplinary TDPAC community for many years [5–9]. Among the TDPAC reports that deal with the study of the solids that result from

the complexation of metal ions with EDTA or DTPA in solution, the search in the literature indicate few investigations that involve ^{181}Hf as probe atom. In the first one [6], the authors communicate TDPAC spectra of the solid that was obtained, by radiochemical synthesis, from EDTA and HfOCl$_2$. In this work the quality of the experimental results is poor due to the low temporal resolution of the used NaI(Tl) detectors and the statistics of the measurements. The same system was object of study in the work of Amaral *et al.* [7], where the solid was obtained from EDTA and HfF$_4$. In this case the adequate temporal resolution of the BaF$_2$ detectors and the statistics of the measurements provide confident TDPAC results. However, the verification of the identity of the obtained solid with a complementary technique is not reported. Meanwhile, Das *et al.* [8] investigated the solid that result from the mixing of adequate amounts of HfOCl$_2$ and DTPA in solution. Although the temporal resolution of the BaF$_2$ detectors and the statistics are adequate, an additional characterization of the obtained solid is again missing. In this way, the interpretation of the TDPAC results on the basis of the assumption that ^{181}Hf is complexed by the polyaminecarboxylic acid could result, in all these cases, incorrect.

In this work the electric field gradients at hafnium sites in crystalline KHfDTPA·3H$_2$O and their thermal evolution from room temperature to 277 °C have been investigated by means of the Time Differential Perturbed Angular Correlations technique. The sample was obtained by chemical synthesis from HfOCl$_2$·8H$_2$O and characterized by X ray diffraction analysis. Also, calorimetric experiments were carried out in order to get a broader base for explaining the TDPAC spectra.

2 Materials and methods

The diethylenetriaminepentaacetate complex of Hf was synthesized according Davidovich [10] with the addition of small amounts of ^{181}Hf-HfOCl$_2$·8H$_2$O. The radioactive hafnium oxychloride resulted from the activation of the ^{180}Hf present in natural HfOCl$_2$·8H$_2$O (98+%, Alfa Aesar GmbH & Co KG) by thermal neutron capture at the CNEA (Comisión Nacional de Energía Atómica-Argentina) RA3 reactor. Briefly, equimolar amounts of HfOCl$_2$·8H$_2$O and diethylenetriaminepentaacetic acid (0.03 mole each) together with 60 μCi of ^{181}Hf-HfOCl$_2$·8H$_2$O were dissolved in 10 ml of distilled water with heating and stirring. Once a transparent solution was obtained, 67 mg of potassium carbonate were added in small portions with stirring. At this point, the pH increased from 1 to 2 and the solution became turbid. The precipitate was removed by filtration,

and then, the solution was slowly evaporated during 24 h until a colourless salt crystallized.

An equivalent preparation done without the addition of ^{181}Hf-HfOCl$_2$·8H$_2$O was subjected to X ray diffraction (XRD) analysis and calorimetric experiments.

XRD experiments were performed using a Phillips X'pert PW 1710 diffractometer with Cu K_α radiation in the range $6° \leq 2\theta \leq 35°$ with steps of $0.05°$ every two seconds. Temperatures where changes could be expected were estimated *via* differential scanning calorimetry and thermogravimetric analysis (DSC-TGA), performed in Shimadzu instruments (DSC-50 and TG-50 respectively) between room temperature and 300 °C under a dynamic nitrogen atmosphere using a heating rate of 5 °C/min.

The TDPAC method is based on the hyperfine interactions of nuclear moments with extra nuclear fields. A detailed description of this method can be found in the literature [11]. The γ–γ cascade at (133–482) keV, populated by the β^- decay of ^{181}Hf, was used to measure the quadrupole interaction of the 482 keV (+5/2) state of ^{181}Ta. The γ–γ PAC measurements were done using a standard setup with four conical BaF$_2$ scintillation detectors with a time resolution of 0.6 ns (FWHM).

In this way, coincidence spectra $N(\theta, t)$ are obtained, where the angle between detectors is θ and the time delay between the two gamma rays γ_1 and γ_2 is t:

$$N(\theta, t) = \varepsilon \left[Acc(\theta) + w(\theta, t)e^{-\lambda t} \right] \qquad (1)$$

The accidental coincidences per unit of time $Acc(\theta)$ represent the detection of two gamma rays, γ_1 and γ_2 from different nuclei, $w(\theta, t)$ is the probability per unit of time of detecting γ_1 and γ_2 from the same nucleus separated by a θ angle and a time t and ε is a factor that depends on the measurement time, the detector's efficiency and the sample-detector geometry (precautions were taken to have equal ε for all spectra).

The time differential anisotropy $R(t)$ is calculated using the coincidence spectra after discounting the accidental background as follows:

$$R(t) = 2\frac{w(180°, t) - w(90°, t)}{w(180°, t) + 2w(90°, t)} = A_{22}G_{22}(t) \qquad (2)$$

where $G_{22}(t)$ is the perturbation function and has the following form for a static quadrupole interaction:

$$G_{22}(t) = \sum_{n=0}^{3} S_{2n}e^{-\delta\omega_n t}\cos(\omega_n t) \qquad (3)$$

The frequencies ω_n are related to the quadrupole frequency $\omega_Q = \pi eQV_{zz}/20h$ by $\omega_n = g_n(\eta)\omega_Q$. The coefficients $g_n(\eta)$ are known functions of the asymmetry parameter $\eta = (V_{xx} - V_{yy})/V_{zz}$, where V_{kk} ($k = x, y, z$) denotes the

principal components of the EFG tensor. The exponential function accounts for a Lorentzian frequency distribution of width δ around ω_Q. We fitted the experimental ratio $R(t)$ by using

$$R(t) = A_{22} \sum f_i G_{22}^i(t) \qquad (4)$$

where f_i is the relative fraction of nuclei that experiences a given perturbation $G_{22}^i(t)$.

3 Results and discussion

The X-ray powder pattern recorded from the synthesized solid is plotted in Figure 1. The diffractogram verifies that the chemical synthesis resulted in KHfDTPA·3H$_2$O. Extra lines with intensity lower that 20% correspond to diethylenetriaminepentaacetic acid that didn't react.

The Time Differential Perturbed Angular Correlations spectrum and its Fourier transform for the as-prepared ^{181}Hf-KHfDTPA·3H$_2$O are shown in Figure 2b. In the same figure the results for the reactant HfOCl$_2$·8H$_2$O are displayed, in order to make evident its absence in the final as-prepared sample. The spectrum for ^{181}Hf-HfOCl$_2$·8H$_2$O can be fitted assuming the existence of a principal quadrupole interaction:

$$^{181}\text{Hf-HfOCl}_2\cdot 8\text{H}_2\text{O}: \quad \omega_Q = 113\,(0)\ \text{Mrad/s}$$
$$\eta = 0.54(1) \quad \delta = 6(0)\ \%$$

in accordance with the literature [12].

On the other hand, the room temperature spectrum of the compound of interest can be fitted with only one quadrupole interaction,

$$^{181}\text{Hf-KHfDTPA}\cdot 3\text{H}_2\text{O}: \quad \omega_Q = 141\,(0)\ \text{Mrad/s}$$
$$\eta = 0.97(0) \quad \delta = 1(0)\ \%$$

This result is consistent with the existence of a unique site for hafnium atoms in the crystal [13]. A simple calculation, by assuming all the ions as point charges and taking into account only the nearest neighbours (at distances closer than 3.3 Å) yields a quadrupole frequency ω_Q of 137 Mrad/s and a asymmetry parameter of 0.88, values that are in good agreement with the experimental results. However, more realistic *ab initio* calculations of the electric field gradients at hafnium sites in KHfDTPA·3H$_2$O are underway. A very low frequency distribution (less than 1%) was found, revealing that the chemical synthesis resulted in a compound with minimum crystallographic defects. In addition, all ^{181}Hf are located in KHfDTPA·3H$_2$O sites thus supporting the idea that the compounds contributing to the extra peaks in the diffractogram do not contain hafnium atoms.

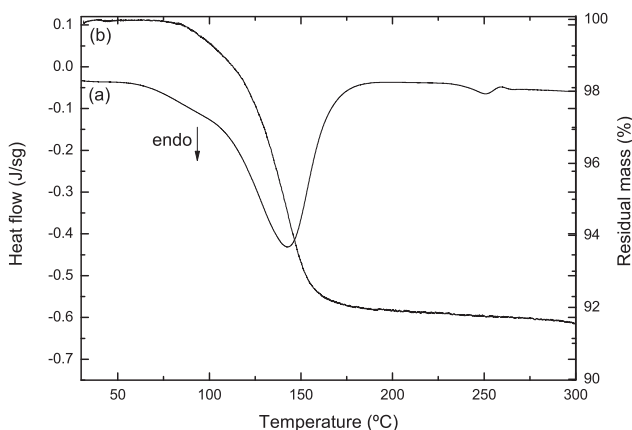Thermogravimetric and differential scanning calorimetric results for KHfDTPA·3H$_2$O are plotted in Figure 3. The DSC curve (3a) exhibits two endothermic changes,
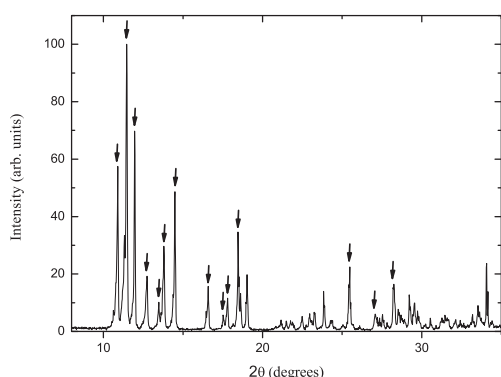
Fig. 1: XRD result for the as-prepared sample. Arrows point to the characteristic diffraction lines of KHfDTPA·3H$_2$O.
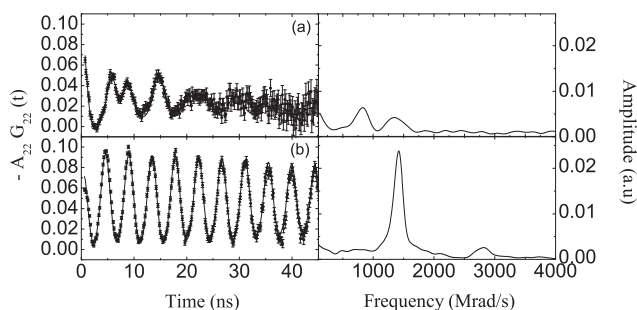
Fig. 2: Spin rotation curves and their corresponding Fourier analyses determined at room temperature for (a) the reactant ^{181}Hf-HfOCl$_2$·8H$_2$O and (b) the as- prepared sample. Full lines in the spin rotation curves indicate the fitting result.


Fig. 3: Thermograms for the as-prepared sample performed at 5 °C/min under dynamic nitrogen atmosphere: (a) differential scanning calorimetry curve and (b) thermogravimetric curve.
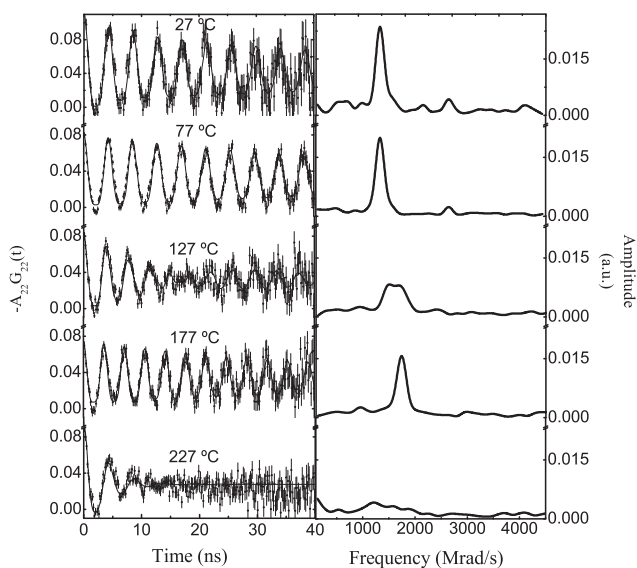
Fig. 4: Spin rotation curves obtained at different temperatures for the as-prepared sample and their corresponding Fourier analyses. Full lines in the spin rotation curves indicate the fitting result.

the biggest centred at 142 °C (corresponding to $\Delta H = 190 \, J/g$) and a small one at 250 °C. The thermogravimetric curve (3b) shows a one-step loss of mass between 80 °C and 180 °C that is in good agreement with the first endothermic peak of the DSC curve. A simple calculation of the residual mass yields a loss of 2.95 mole of water per mole of $KHfDTPA \cdot 3H_2O$, fact that allows assigning this peak to the dehydration of $KHfDTPA \cdot 3H_2O$ to produce $KHfDTPA$. No loss of mass occurs over 180 °C, indicating that the DSC peak around 250 °C might correspond to a molecular reorganization or to a phase transition.

With the aim to study the thermal evolution of the hyperfine interactions at hafnium sites in the crystal lattice of the as-prepared solid, TDPAC experiments were performed from room temperature to 277 °C. Selected TD-PAC spectra and their Fourier transforms are shown in Figure 4. All spectra, except that corresponding to 127 °C, can be well fitted by assuming the existence of a unique quadrupole interaction. On the other side, two interac-
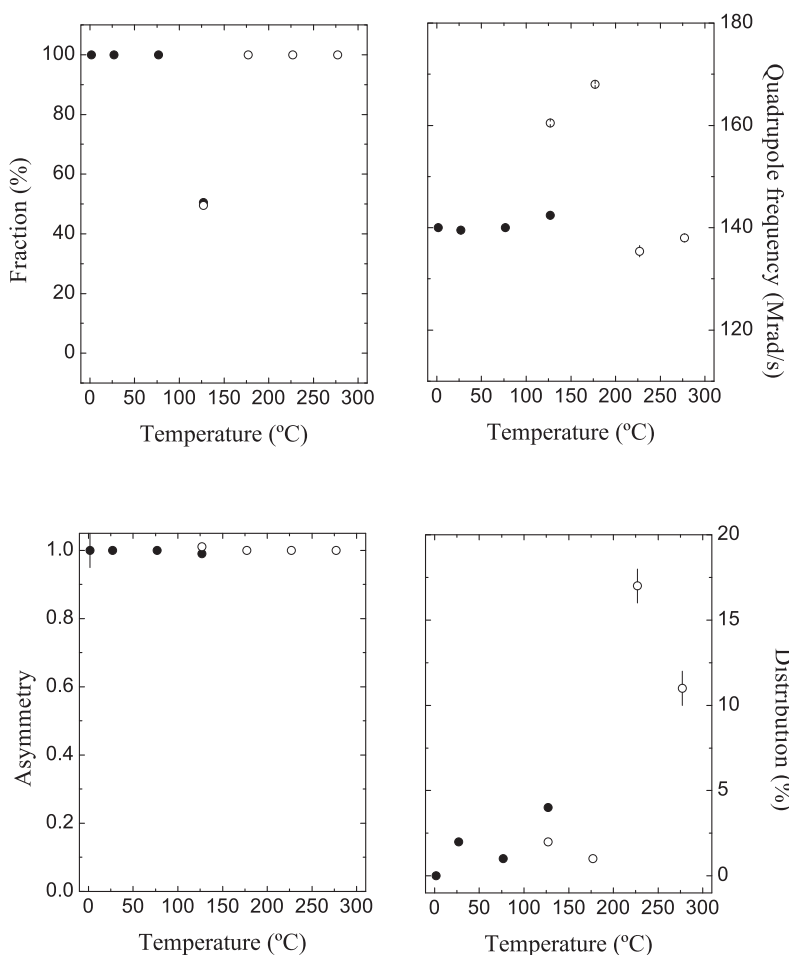
Fig. 5: Hyperfine parameters for the as-prepared sample measured at different temperatures.

tions are necessary to fit the spectrum at 127 °C. The resulting quadrupole parameters are plotted in Figure 5.

Spectra for 27 °C and 77 °C are characterized by a well defined and highly asymmetric interaction with average quadrupole frequency ω_Q of 141 (0) Mrad/s. A higher quadrupole frequency ω_Q of 168 (0) Mrad/s also well defined and fully asymmetric describes the compound at 177 °C. An intermediate situation is found at 127 °C, where equal amounts of two hyperfine interactions are found, one of them with quadrupole frequency $\omega_Q =$ 142 (0) Mrad/s and the other 160(0) Mrad/s (full circles and open circles in Figure 5 respectively), both of them rather defined ($\delta < 4\%$) and fully asymmetric. Finally, at 227 °C a poorly defined fully asymmetric interaction ($\delta >$ 15%) of quadrupole frequency $\omega_Q = 140$ Mrad/s replaces the well defined interactions evident at lower temperatures.

According to the thermogravimetric analysis no significant dehydration occurs before 80 °C, thus the quadrupole interactions characterizing the spectra at 27 °C and 77 °C can be assigned to KHfDTPA·3H$_2$O. On the other side, the loss of three water molecules achieved around 180 °C corresponding to the TDPAC spectrum at 177 °C, allows us to unambiguously associate the 168 Mrad/s fully asymmetric quadrupole interaction to the anhydrous compound KHfDTPA. In this way, the water vacancies in the hafnium coordination sphere originate a higher electric field gradient in the hafnium site without loss of asymmetry. In addition, the partial dehydration accomplished at 127 °C, evident from the thermogram, is in agreement with the existence at such temperature of a mixture of quadrupole interactions corresponding to hydrated and anhydrous hafnium diethylenetriaminepentaacetate. The change in the characteristic quadrupole parameters of KHfDTPA at temperatures over 200 °C is explained in terms of a reorganization of the coordination sphere of hafnium towards configurations that do not include the water vacancies. Thus the variety of possible steric relaxations gives place to a poor defined interaction characterized by quadrupole frequency and asymmetry parameter comparable to those of KHfDTPA·3H$_2$O. The presence of a dynamic effect associated with this reorganization cannot be excluded.

4 Conclusions

The obtaining of crystalline KHfDTPA·3H$_2$O was achieved by chemical synthesis from hafnium oxychloride octahydrated, diethylenetriaminepentaacetic acid and potassium carbonate. A unique hyperfine interaction of quadrupole frequency $\omega_Q = 141$ Mrad/s and asymmetry parameter of 0.97 characterizes this compound at room temperature, fact that is consistent with the existence of only one site for hafnium atoms in the crystal lattice. Simple point charge model calculations of the electric field gradient at hafnium sites are in good agreement with this experimental TDPAC results. However, more realistic *ab initio* calculations of the electric field gradients at hafnium sites are underway.

Calorimetric studies revealed that KHfDTPA·3H$_2$O losses all the hydration water molecules in one step. The Time Differential Perturbed Angular Correlation technique senses this dehydration as an increasing in the quadrupole frequency ω_Q to 168 Mrad/s without loss in the asymmetry.

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