Time Differential Perturbed Angular γγ-Correlation Studies of Diethylenetriaminepentaacetic Acid Complexes with ^{111}In and ^{111m}Cd

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Static and dynamic electric quadrupole interactions of ^{111}Cd in complexes with diethylenetriaminepentaacetic acid were studied by the time differential perturbed angular γγ-correlation technique using two parent isotopes, ^{111}In(EC)^{111}Cd and ^{111m}Cd. The measurements were carried out using neutral aqueous solutions of the diethylenetriaminepentaacetic-acid-complexes with initial isotopes at 293 K and 77 K. It was shown that the ^{111}Cd-diethylenetriaminepentaacetic-acid-complex in aqueous solutions at pH = 7.0 is characterised by the re-orientational correlation time of 7.7×10^{-11} s and an electric field gradient $V_{zz} = 6.7(2) \times 10^{21}$ V/m^2 with an asymmetry parameter $\eta = 0.75(5)$. A direct comparison of the electric quadrupole interaction parameters for diethylenetriaminepentaacetic- acid-complexes with ^{111}In and ^{111m}Cd confirmed the proposal about the fragmentation of the complexes caused by the after-effects of electron capture in ^{111}In. An observed difference in the electric quadrupole interaction parameters obtained for the solutions with ^{111}In and ^{111m}Cd complexes reflects a process of a chemical rearrangement of the complex structure after the In decay into Cd.

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1. Introduction

Complexes of radioactive metals with organic ligands are widely used in nuclear medicine for diagnostics and therapy. The most common diagnostic modality

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is the gamma-scintigraphy, which requires an isotope emitting gamma-rays with an energy of about one hundred keV. A radioactive isotope is to be bound to an organic compound forming a stable complex that reduces the metal toxicity and changes its biochemical behaviour. The complexes used in radiopharmaceuticals (RPH) designing are characterised by a number of parameters including the *in vivo* stability. *In vitro* stability is usually a good indication that the complex is to be stable *in vivo* and it can be regarded as a candidate for designing new RPH [1].

One of the gamma-emitting isotopes used in the modern nuclear medical practice is ^{111}In with a half-life of 2.7 days. ^{111}In-complex with diethylenetriamine-pentaacetic acid (DTPA) is used as RPH itself and for preparation of RPH specific to a particular organ or tissue, when bound to a receptor targeted agent.

^{111}In is also one of the most convenient isotopes used in the time differential perturbed angular $\gamma\gamma$-correlation (TDPAC) method. The TDPAC technique allows getting information about electric quadrupole interactions (EQI) of a probe nucleus with its local environment in samples with extremely low concentration of probe atoms ($10^{11}-10^{12}$ atoms per one preparation). The theory and the method of TDPAC are described in detail in [2]. TDPAC offers a number of possibilities for studying ^{111}In-containing complexes, including assessing the mobility and radius of complexes and their stability in solutions in conditions simulating the "*in vivo*" situation or even *in vivo* using small laboratory animals [3].

It is necessary to take into account that the EQI parameters, extracted from the TDPAC measurements using ^{111}In as a parent isotope, are actually related to ^{111}Cd, i.e. to a complex after a chemical transmutation of the metallic ion. It is still an open question whether the rearrangement of the entire complex takes place within the time window available in the TDPAC experiments (about 500 ns for ^{111}In) or daughter ^{111}Cd remains in the environment typical of indium and the obtained parameters can characterise the initial complex. Another problem concerns the so-called after-effects, since ^{111}In transforms to ^{111}Cd by electron capture decay followed by an emission of Auger-electrons and a shock ionization of Cd and its nearest neighbours. In particular, there is a possibility of a complex to disintegrate due to the Coulomb repulsion between the positively charged Cd ion and its environment [4].

In order to assess the influence of the chemical rearrangement of the complex due to In$\rightarrow$Cd transmutation and of the electron capture after-effects on the EQI parameters obtained in the TDPAC experiments, we studied the static and dynamic EQI in In(Cd) complexes with DTPA using two parent isotopes, ^{111}In and ^{111m}Cd. The latter is an isomeric state of ^{111}Cd with the half-life of 48 minutes and no problems with after-effects and chemical process are involved. The suitable for TDPAC measurements $\gamma\gamma$-cascade 150–245 keV, discharging the ^{111m}Cd, proceeds via the same intermediate exited state 245 keV ($I = 5/2, T_{1/2} = 84$ ns, $Q = 0.8$ barn) as the $\gamma\gamma$-cascade 172–245 keV used with the parent ^{111}In isotope.

2. Experimental

[111m]Cd was produced by neutron irradiation of 1 mg of natural metallic cadmium in the 5 MW-swimming pool type reactor at IPEN-CNEN/SP in a neutron flux of 2×10^{13} neutron/(cm^2 s) for 2 hours. The other radioactive isotopes activated by irradiation of natural cadmium in reactor, such as [117]Cd and [117m]Cd, do not hamper the TDPAC measurements, since they contribute only to the prompt and random coincidences.

After the irradiation, 1 mg of Cd was dissolved in 0.3 ml of 1 M nitric acid, which was evaporated to dryness. The residue was dissolved in 0.3 ml of 1 M hydrochloric acid, which was also evaporated. Finally, the activity was dissolved in 0.5 ml of hydrochloric acid. For preparation of samples with ^{111}In, a commercially available (Nordion, Canada) carrier free solution of [111]InCl$_3$ with a high specific radioactivity was used.

The initial radioactive solutions (0.1–0.2 ml, depending on the activity, in the case of [111m]Cd and several microliters in the case of ^{111}In) were added to the 2 mM solution of DTPA in 0.5 M HCl. The ratio of molar concentrations [Cd]:[DTPA] was always kept to about 1 (with a slight excess of the ligand), the concentration ratio [In]:[DTPA]=1:∞. Thus, the excess of DTPA and high stability constants of DTPA complexes with Cd and In ($\log K = 9.0$ and 29.0, respectively [5]) ensure a formation of expected complexes, since there are no other ligands or ions, which can compete with DTPA. Sodium hydroxide solution was used for adjusting the pH value to 7.0. The samples were kept in sealed plastic tubes. The TDPAC measurements were performed with liquid samples at 293 K and with frozen solutions at 77 K.

The angular correlations of the 172–245 keV and 150–245 keV γ-ray cascades in [111]Cd were measured using a conventional slow-fast TDPAC spectrometer at IPEN-CNEN/SP equipped with 4 BaF$_2$ scintillators and XP2020Q PMT. The resolution time was 0.8 ns.

12 coincidence spectra $N_i(\Theta, t)$ were accumulated simultaneously at the angles $\Theta = 90°$ and $180°$ between the detectors. The anisotropy spectra of angular correlations were obtained by the standard formula:

$$R(t) = 2\frac{N(180°, t) - N(90°, t)}{N(180°, t) + 2N(90°, t)} \cong A_{22}Q_2G_2(t),\tag{1}$$

where $N(180°, t) = \sqrt[4]{\prod_{i=1}^{4} N_i(180°, t)}$, $N(90°, t) = \sqrt[8]{\prod_{i=1}^{8} N_i(90°, t)}$, A_{22} is the correlation coefficient (-0.18 for the 172–245 keV cascade and $+0.16$ for the 150–245 keV cascade in [111]Cd); Q_2 is the solid angle and sample size correction and $G_2(t)$ is a perturbation coefficient containing information about EQI. The anisotropy spectra were obtained taking into consideration the finite time resolution, a random coincidence background and a prompt curve. Spectra $R(t)$ were fitted using the least square method.

In case of a static quadrupole interaction (frozen solutions), the data were fitted by the following equation:

$$R(t) = \sum_i p^i \sum_{l=0}^{3} a_l(\eta^1) \cos(\omega_l^i(\eta^i)t) \exp(-\Lambda^i \omega_l^i(\eta^i)t), \tag{2}$$

where p^i are the relative populations of i inequivalent sites of the probe atoms, a_l are the amplitude coefficients and ω_l are the frequencies, which are the functions of the asymmetry parameter η of an electric field gradient (EFG) and the quadrupole frequency $\nu_Q = eQV_{zz}/h$ (Q is the nuclear quadrupole moment, and V_{zz} is the main component of EFG tensor). Λ is a relative half width at half-maximum of the ν_Q distribution around the mean value assuming that it is a Lorentzian. Such distributions arise due to variations of the charge environment of the probe nuclei. This is typical of frozen solutions, where EFG is determined not only by the regular charge distribution in a given molecule, but also by a random arrangement of the other molecules.

For a dynamic perturbation, in accordance with the Abragam and Pound theory [6] for dilute solutions with low viscosity, the angular correlation anisotropy has an exponential form

$$R(t) = \sum_i a_i \exp(-\lambda_i t), \tag{3}$$

where i refers to different inequivalent molecules containing the probe atoms and a_i are the amplitudes proportional to their abundance, λ_i are the relaxation constants (for nuclear spin 5/2, $\lambda \approx 2.53\nu_Q^2\tau_c$, where τ_c is the re-orientational correlation time [6] describing the mobility of molecules in a solution).

3. Results and conclusions

At room temperature, the TDPAC measurements were carried out for neutral aqueous solutions of ^{111}In-DTPA (2 samples) and [111m]Cd-DTPA (5 samples). The results were reproducible and the summarised spectra are given in Fig. 1. Both spectra are typical examples of dynamic interaction and they can be fitted using the model (3). The spectrum for [111]Cd-DTPA (without several first channels which were not used in the fitting procedure) could be fitted assuming only one exponential function with the relaxation constant $\lambda = 3(1) \times 10^6$ s^{-1}. This value is comparable with 2.5×10^6 s^{-1} for In-DTPA solution at pH = 1.4 [7], but is much smaller than the value obtained in [8, 9] for In-DTPA complexes in neutral aqueous solutions, 11×10^6 to 19×10^6 s^{-1}.

The spectrum for ^{111}In-DTPA could be satisfactorily fitted only assuming three fractions populated as 2:5:4 with essentially different relaxation constants, namely: $44(3) \times 10^6$, $4.2(5) \times 10^6$ and 0 s^{-1}. The latter fraction can be defined as a constant term a_0. It was initially observed in [4, 8, 9] and assigned to the light fragments of disintegrated complexes formed as a result of Auger-process
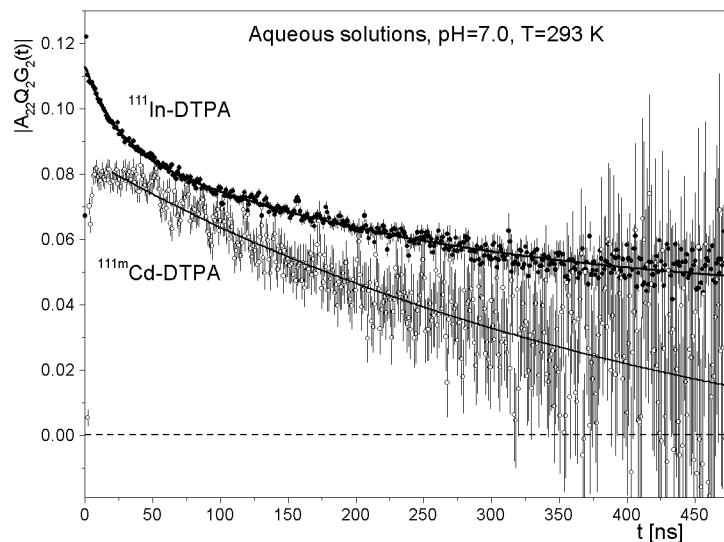
Fig. 1. TDPAC spectra measured at room temperature for neutral aqueous solutions of complexes ^{111}In-DTPA and [111m]Cd-DTPA. The approximation functions obtained in accordance with Eq. (3) are shown by solid curves.

and Coulomb repulsion in the daughter complex Cd-DTPA. As no such fraction was found for the sample with [111m]Cd, this fact confirms the proposal about the influence of electron capture after-effects on fragmentation of ^{111}In-complexes with organic ligands.

Within the experimental errors, the second relaxation constant, $4.2(5) \times 10^6$ s^{-1}, is equal to the parameter λ found for the Cd-DTPA complex. Thus, we can ascribe this fraction to the complexes Cd-DTPA survived the Auger-process or formed after a full disintegration of initial complex after electron capture in ^{111}In with the subsequent binding of Cd to a new ligand molecule. It is questionable if the latter process can occur in such short time as < 100 ns, though the studies of the "survival" fraction dependence on the ligand concentration [9] are in favour of the re-chelating process.

The origin of the less abundant fraction with the high relaxation constant is unclear. Considering that λ is proportional to the re-orientational correlation time and to the squared quadrupole frequency, the ν_Q values for two fractions (with $\lambda = 44 \times 10^6$ and 4×10^6 s^{-1}) should differ by a factor of 3 or τ_c values — by a factor of 10. Obviously, this fraction is related to some clusters with much lower mobility in comparison with the In(Cd)-DTPA complexes or to high transient EFG occurred in the complexes during a chemical rearrangement.

The TDPAC measurements for the frozen solutions kept at the liquid nitrogen temperature allowed determining the average quadrupole frequency for DTPA complexes with both parent In and Cd. The spectra are given in Fig. 2.
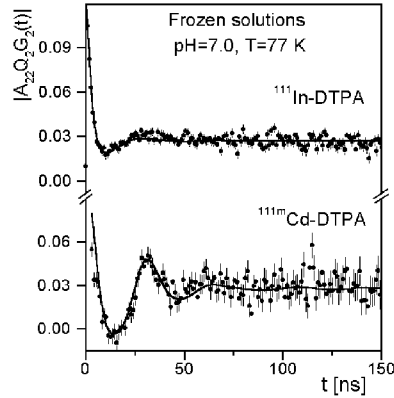
Fig. 2. TDPAC spectra measured for frozen neutral aqueous solutions of complexes ^{111}In-DTPA and [111m]Cd-DTPA. The approximation functions obtained in accordance with Eq. (2) are shown by solid curves.

A very broad distribution ($\Lambda \approx 50\%$) of the quadrupole frequency 170(30) MHz was observed for the sample containing DTPA complexes with the parent [111]In. For the complexes [111m]Cd-DTPA, the following parameters were obtained: $\nu_Q = 125(2)$ MHz, $\eta = 0.75(5)$ and $\Lambda = 17(3)\%$. The much broader distribution of ν_Q around the average value for ^{111}In sample than that for the [111m]Cd sample is reasonable to be connected with the influence of after-effects, which create additional disorder in the frozen solution. Using the values of ν_Q and λ for both parent complexes, one can calculate the re-orientational correlation time, which is 7.7×10^{-11} s and 5.8×10^{-11} s for Cd-DTPA complexes originated from initial complexes [111m]Cd-DTPA and ^{111}In-DTPA, respectively.

The results obtained for the dynamic and static EQI for the solutions of DTPA complexes with parent ^{111}In and [111m]Cd allow deriving the following conclusions:

1. The Cd-DTPA complex in a neutral aqueous solution is characterised by the re-orientational correlation time 7.7×10^{-11} s, the main EFG component $V_{zz} = 6.7(2) \times 10^{21}$ V/m^2 and $\eta = 0.75(5)$.

2. A direct comparison of the results obtained at 293 K with neutral solutions of parent complexes [111m]Cd-DTPA and ^{111}In-DTPA confirms the proposal [4] about a disintegration of complexes after ^{111}In electron capture decay as a result of the Auger-process and the following Coulomb fragmentation.

3. The EQI parameters for neutral solutions of DTPA complexes with parent ^{111}In and [111m]Cd are close to each other, though not identical, meaning an existence of dynamic effect of the chemical rearrangement in the complex caused by the nuclear transmutation In→Cd and electron capture after-effects. The closeness of the EQI parameters adds to a possibility of

studying ¹¹¹In-containg RPH by the TDPAC method, since the results, which are reflected by the characteristics of the integral complexes, could be extracted from the ¹¹¹In-TDPAC experiments.

Acknowledgments

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