

# Investigation of the kinetics of the In(III)-DOTA complex formation by a $\gamma\gamma$ -perturbed angular correlation method

K.P. Zhernosekov<sup>2</sup>, D.V. Filossofov<sup>1</sup>, N.A. Korolev<sup>1</sup>, A.F. Novgorodov<sup>1</sup>, N.A. Lebedev<sup>1</sup>, A. Velichkov<sup>1</sup>, F Rösch<sup>2</sup>  
<sup>1</sup>Joint Institute of Nuclear Research, LNP, RUS-141980 Dubna, Russian Federation;  
<sup>2</sup>Institut für Kernchemie, Johannes Gutenberg-Universität Mainz, Germany

<sup>111</sup>In complexes with the macrocyclic ligand DOTA and its derivatives represent promising radiopharmaceuticals, because the kinetic stability of these complexes is most relevant. In this work the perturbed angular  $\gamma\gamma$ -correlation (PAC) method was used to investigate the kinetics of In(III)-DOTA complex formation in chloride solutions at room temperature.

The time-integrated angular correlation of cascade  $\gamma$ -rays is given by  $W(\theta, \infty) = 1 + A_{22}G_2(\infty)Q_2P_2(\cos(\theta)) + \dots$ , where  $A_{ii}$  are the angular correlation coefficients,  $P_i(\cos\theta)$  are the Legendre polynomials,  $Q_i$ -solid angle correlation factors and  $G_i(\infty)$  are the time-integrated angular correlation (TIAC) perturbation factors. TIAC perturbation factors reflect information about hyperfine interactions due to the chemical environment and in that way about chemical speciation. For  $[\text{In}(\text{H}_2\text{O})_6]^{3+}$  ("liquid state")  $G_2(\infty)$  is equal 1 while for  $\text{In}(\text{OH})_3(\text{c})$  "solid" it is 0.2.

Measurements were performed on the four-detector PAC spectrometer (JINR) [1].  $A_2G_2(\infty)Q_2$  values were calculated as

$$A_2G_2(\infty)Q_2 = 2 \frac{N(180^\circ) - N(90^\circ)}{N(180^\circ) + 2N(90^\circ)} \quad (1)$$

where  $N(180^\circ)$  and  $N(90^\circ)$  are average counts of coincidences at  $180^\circ$  and  $90^\circ$ , respectively.

No-carrier-added <sup>111</sup>In ( $T_{1/2} = 2.83$  d) was produced by irradiation of a natural silver target with 30 MeV  $\alpha$ -particles with subsequent separation and purification [2]. The activity of the probes was 100 kBq, the volume 0.5 ml. For the samples preparation polyethylene vials of 1.5 ml volume were used. Aqueous solutions of type NaCl/H<sup>+</sup>/DOTA with an overall ionic strength  $\mu = 0.1$  and pH = 2-4 were used for the investigations, with constant concentration of DOTA of  $10^{-5}$  M. Aliquots of the isotope in  $2 \cdot 10^{-3}$  M HCl were added directly before measurements. After measurements, the pH of the samples was determined by means of a pre-calibrated glass electrode using standard buffer solutions. One of the obtained dependencies of  $A_2G_2(\infty)Q_2$  -values on the time at room temperature, reflecting transition of the radionuclide form from the aqua complexes of indium to the In-DOTA-complexes at room temperature, is illustrated in Figure 1.

For trivalent cations  $\text{Me}^{3+}$  the thermodynamically stable complexes of type  $[\text{Me-DOTA}]$  are known to exist in aqueous solutions [3-4]. These species are forming through different deprotonated intermediates of  $\text{Me}^{3+}$ -DOTA complexes:



with subsequent deprotonation of intermediates:



At time  $t = 0$ ,  $A_2G_2(\infty)Q_2$  is equal to  $-0.13$  corresponding to the aqua complex of indium. With time, it is approaching  $-0.1$ , thus reflecting formation of In(III)-DOTA complexes.

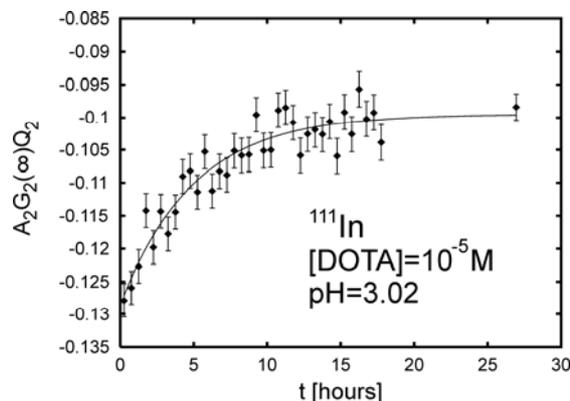


Fig.1.  $A_2G_2(\infty)Q_2$  -values versus time, NaCl  $\mu = 0.1$ , room temperature. Fit of the experimental data (solid line Eq.(4)).

In the case of <sup>111</sup>In labelled compounds, the value of  $A_2G_2(\infty)Q_2$  also depends on the size of the molecules and is sensitive for any  $[\text{InH}_{n-m}\text{DOTA}]^{n-m-1}$  complexes forming. Our data are described for an excess of ligand:

$$\frac{d \sum_{n,m} [\text{InH}_{n-m}\text{DOTA}]^{n-m-1}}{dt} = k_{f,\text{obs}} [\text{In}^{3+}], \quad (4)$$

where  $k_{f,\text{obs}}$  is observed for pseudo-first-order constants of In(III)-DOTA complex formation.

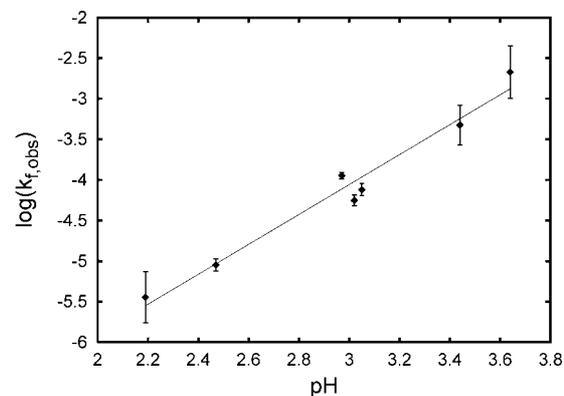


Fig.2.  $\log k_{f,\text{obs}}$  ( $k_{f,\text{obs}}$ ,  $[\text{s}^{-1}]$ ) versus pH.

A linear dependency of  $\log k_{f,\text{obs}}$  on pH (Fig.2) with a proportionality coefficient 1.86, is observed in the range pH = 2 – 4. It can be interpreted on base of equilibrium (2).  $\text{In}^{3+}$  interacts mainly with  $\text{H}_2\text{DOTA}^{2-}$ , whose concentration is proportional to  $[\text{H}^+]^{-2}$ .

**Acknowledgements** This work was supported by grant of RFFI 03-03-32120a.

- [1] O.I. Kochetov et. al., P13-2002-265 JINR Dubna, 2002.
- [2] D.V. Filossofov et. al., Appl. Radiat. Isot. 55, 293 (2001).
- [3] É. Tóth et al., Inorg. Chem. 33, 4070 (1994).
- [4] L. Shuang, D.S. Edwards, Bioconjugate Chem. 12, 7 (2001).