

## NMR Study of Paramagnetic Properties and the Kinetics of Hydrolysis of the Dy–tris–tBu–DOTA–ester Complex

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*It was shown that Dy<sup>3+</sup> complex with tri-tert-butyl-1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid is subjected to irreversible stepwise hydrolysis with the final formation of the complex [Dy(DOTA)]<sup>-</sup> and the hydrolysis rate constants were determined. The temperature sensitivity of the paramagnetic chemical shifts of the signals corresponding to the initial complex and two intermediate hydrolysis products was estimated.*

**Keywords:** Lanthanide-induced shifts, NMR, chelate ligands, polyaminopolycarboxyl ligands, lanthanides complexes, substituted DOTA.

## ЯМР исследование парамагнитных свойств и кинетики гидролиза Dy–трис–tBu–DOTA

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*Показано, что комплекс Dy<sup>3+</sup> с три-трет-бутил-1,4,7,10-тетраазациклодекан-1,4,7,10-тетрауксусной кислотой подвергается необратимому ступенчатому гидролизу с окончательным образованием комплекса [Dy(DOTA)]<sup>-</sup>, и определены соответствующие константы скорости. Оценена температурная чувствительность парамагнитных химических сдвигов сигналов, соответствующих исходному комплексу и двум промежуточным продуктам гидролиза.*

**Ключевые слова:** Лантанид-индуцированные сдвиги, ЯМР, хелатные лиганды, полиаминополикарбоксильные лиганды, комплексы лантанидов, замещенный DOTA лиганд.

### Introduction

Polyaminopolycarboxylate anions (PAPC) as EDTA, DTPA and DOTA form very stable and water-soluble complexes with many polyvalent metals (and in particular with *d*- and *4f*-elements).<sup>[1,2]</sup> Chelate complexes of transition *d*- and *4f*-elements have been successfully used as fluorescent and luminescent reagents for bioanalytical studies (immunoanalysis, DNA analysis, etc.), isotopic labels, paramagnetic labels for studying the structure of complexes and dynamics of biopolymers, contrast reagents (in particular,

Gd<sup>3+</sup> and Mn<sup>2+</sup> complexes) for medical magnetic resonance imaging (MRI).<sup>[3–6]</sup>

The scope of complex compounds of this type is continuously expanding and deepening due to their chemical modification and functionalization. Thus, the covalent conjugation of metal cations with PAPC having various functional groups (fluorophores, surface-active groups, physiologically active substrates, in particular peptides and carbohydrates) gives them, in addition to the utilitarian role of a “container” for the metal cation, various other functions: surface properties activity, the ability to bind and penetrate

through biological membranes, photochemical properties, affinity for receptors and tissues.<sup>[6,7]</sup>

Note that in the literature there are many examples of studying the kinetics of chemical exchange processes including in paramagnetic lanthanide (Ln) complexes.<sup>[8–11]</sup>

However, there are few examples of publications devoted to NMR studies of irreversible processes in lanthanide complexes (and in particular complexes with PABC ligands). The study of the structure, reactivity, structural-dynamic processes, and various non-covalent interactions (especially with biological substrates) of such compounds in solutions is important for their further use in biochemical studies and in medical diagnostics. So, for example, recently a direction has been developing related to the use of Ln complexes for *in vivo* measurement of the local temperature of organs and tissues using MRI techniques in order to diagnose diseases.<sup>[10,12]</sup>

In particular, we have analyzed in detail the temperature dependences of paramagnetic lanthanide-induced shifts (LIS) in the <sup>1</sup>H NMR spectra of [Ho(H<sub>2</sub>O)(DOTA)]<sup>-</sup> complex.<sup>[13]</sup> It was shown that the LIS of signals in <sup>1</sup>H NMR spectra of the [Ho(H<sub>2</sub>O)(DOTA)]<sup>-</sup> complex are linearly dependent on the inverse temperature (in the studied temperature range). It turned out that one of the signals has the highest temperature sensitivity (about 1.49 ppm/K) compared to other paramagnetic complexes of lanthanides and *d*-elements. This work and several others substantiate the promising use of paramagnetic lanthanide complexes as special temperature-sensitive contrast agents for monitoring local temperature in organs and tissues in the diagnosis and treatment of cancer and inflammation. The study of chemically modified PABC ligands with lanthanide cations is of interest in connection with their ability to penetrate into cell membranes and overcome biological barriers. These complex compounds can also penetrate into organs and tissues, partially isolated from blood and lymph flows. They can also have tissue specificity and accumulate in certain organs and tissues (for example, in the tissues of the brain or intestine).<sup>[14–16]</sup>

The diagnostic range of application of the method for determining the local temperature using paramagnetic NMR thermosensors (in our opinion) can be significantly expanded.

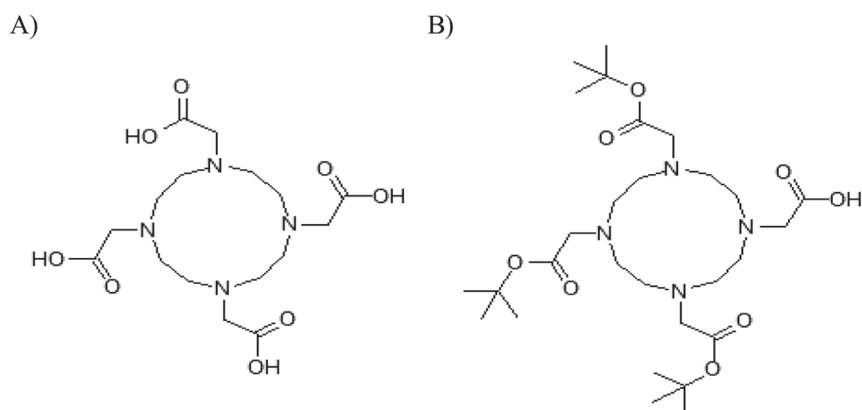
In this regard, we studied the complexes of Dy<sup>3+</sup> with tris-*tert*-butyl-1,4,7,10-tetraazacyclodecane-1,4,7,10-tetraacetic acid (*tris-t*Bu-DOTA-ester) (**I**), the structural formula of which is presented in Figure 1.

The *tris-t*Bu-DOTA-ester is a commercially available reagent, and is used in the synthesis of DOTA derivatives monosubstituted at the carboxyl group. *tert*-Butyl alcohol residues can be selectively removed with Lewis bases.<sup>[17,18]</sup>

The complex **I** is of independent interest as thermosensor reagent, despite the initially utilitarian purpose of the ligand. The assumed relative instability of the compound to hydrolysis can also have its advantages, as a result of hydrolysis, the resulting complex of Ln<sup>3+</sup> with DOTA can be more durable and easier to remove from the tissues compared to the initial one. Less toxicity of [Ln(H<sub>2</sub>O)(DOTA)]<sup>-</sup> is assumed compared to [Ln(*tris-t*Bu-DOTA-ester)]<sup>2+</sup>. Thus, the critical parameters for assessing the suitability of **I** as promising thermosensor reagents are: temperature sensitivity due to the LISs, hydrolysis rate under given conditions (for example, at a temperature of 37 °C in an aqueous solution at neutral pH values), the presence of molecular dynamics processes (complex stability and affinity for substrates).

The NMR method allows to study both reversible and irreversible processes in solutions.<sup>[9,10]</sup> For irreversible reactions in solutions, it is important to determine the process parameters as accurately as possible: reaction time and component concentration. One can note modern studies on this subject, for example, work,<sup>[18]</sup> where the use of a flow reactor with NMR detection allows monitoring reactions at time intervals from several seconds to several minutes. A review of modern NMR methods for studying the kinetics of reversible and irreversible processes is given in.<sup>[8,9,19–21]</sup> In particular, the technique (named the homonuclear double-resonance transfer of local nuclear spin population inversion) was proposed for a qualitative and quantitative study of the kinetics of reversible and irreversible processes.<sup>[22]</sup> Although these studies have been published in specialized literature.<sup>[8,9,22]</sup> Recently, a similar technique (for the qualitative determination of reversible and irreversible chemical processes) was published in a general chemical journal.<sup>[23]</sup> A detailed discussion of this issue is published in Ref.<sup>[24]</sup>

The main aim of this work is to assess the kinetic instability of the complex [Dy(*tris-t*Bu-DOTA-ester)]<sup>2+</sup> in



**Figure 1.** The structural formula of the ligands: H<sub>4</sub>DOTA (A) and *tris-t*Bu-DOTA-ester (B).

aqueous solution using NMR methods. An additional purpose of the work was to assess the temperature sensitivity of the signals of the studied complexes. The advantage of complex **I** in comparison with the compounds of  $[\text{Ln}(\text{H}_2\text{O})(\text{DOTA})]^-$  is that this complex has tertiary butyl groups, the signals in the NMR spectra of which are almost an order of magnitude more intense than other signals. This property makes compound **I** to be more preferred as an NMR temperature probe compared to the  $[\text{Ln}(\text{H}_2\text{O})(\text{DOTA})]^-$  complexes.

## Experimental

To prepare  $\text{Dy}^{3+}$  complexes  $\text{C}_{28}\text{H}_{52}\text{N}_4\text{O}_8$  (*tris-tert*-butyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate, *tris-tert*-Bu-DOTA-ester, "Sigma Aldrich"), and  $[\text{DyCl}_3(\text{H}_2\text{O})_6]$ , obtained by dissolving the corresponding oxide in hydrochloric acid, were used. The salt purification of  $[\text{DyCl}_3(\text{H}_2\text{O})_6]$  was carried out by recrystallization from hydrochloric acid. The solvent was  $\text{D}_2\text{O}$  heavy water (99.8 %) produced by the Cherkasy Isotope Plant (TU 95.669-79). Stock solutions in  $\text{D}_2\text{O}$  had concentrations for both components  $C_1 = C_{\text{Ln}} = 0.020 \pm 0.001$  M.

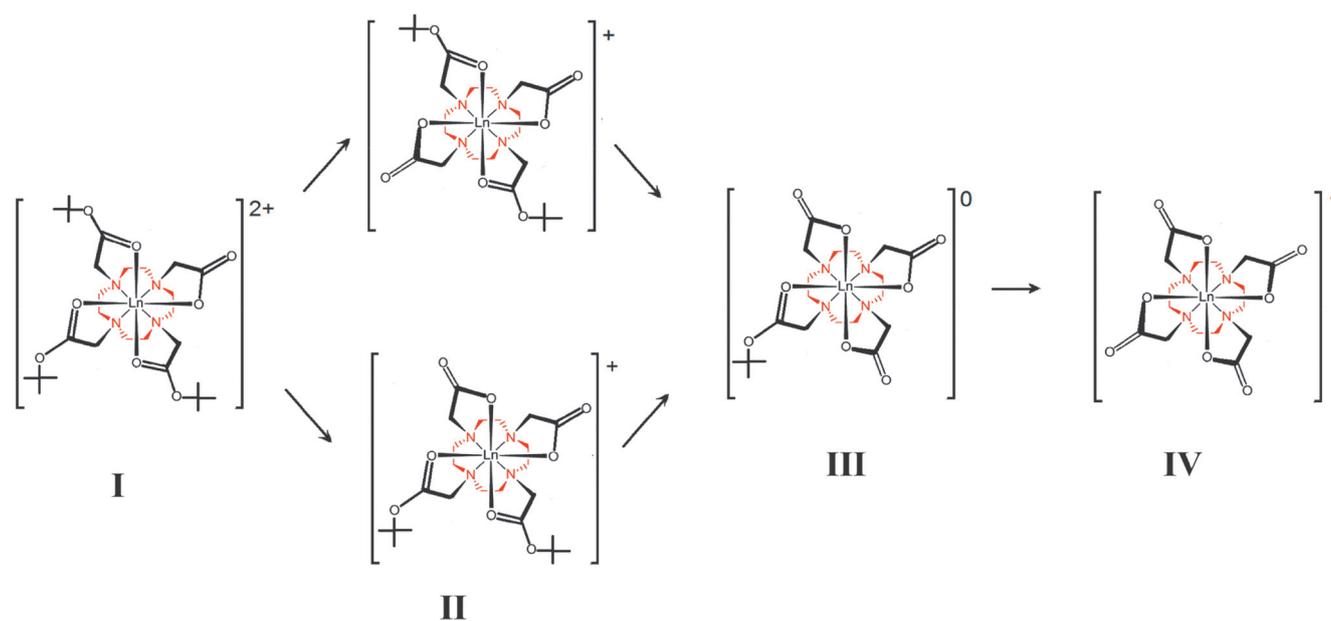
NMR spectra were recorded on a Bruker Avance-III-500 serial pulse spectrometer (operating frequency of  $^1\text{H}$  NMR was 500.13 MHz). The constant magnetic field was stabilized by using NMR signals on deuterium nuclei from  $\text{D}_2\text{O}$ . The error and stability  $\pm 0.3$  K of the functioning of temperature controller was operated by using standard samples with known temperature dependence of chemical shifts in the  $^1\text{H}$  NMR spectrum.

**I.**  $^1\text{H}$  NMR (308 K)  $\delta_{\text{H}}$  ppm:  $-113.9$  (*ring*  $\text{CH}_2$ ),  $-60.3$  (*t*-Bu ester  $\text{CH}_3$ ),  $-53.3$  (*t*-Bu ester  $\text{CH}_2$ ),  $-19.0$  (*t*-Bu ester  $\text{CH}$ ),  $-9.1$  (*t*-Bu ester  $\text{CH}_2$ ),  $41.9$  (*t*-Bu ester  $\text{CH}_3$ ),  $64.8$  (*t*-Bu ester  $\text{CH}_3$ ),  $89.1$  (*acetic*  $\text{CH}_2$ ).

**II.**  $^1\text{H}$  NMR (308 K)  $\delta_{\text{H}}$  ppm:  $-110.1$  (*ring*  $\text{CH}_2$ ),  $-57.7$  (*t*-Bu ester  $\text{CH}_3$ ),  $-8.2$  (*t*-Bu ester  $\text{CH}_2$ ),  $101.0$  (*acetic*  $\text{CH}_2$ ).

**III.**  $^1\text{H}$  NMR (308 K)  $\delta_{\text{H}}$  ppm:  $-98.0$  (*ring*  $\text{CH}_2$ ),  $-64.2$  (*t*-Bu ester  $\text{CH}_2$ ),  $112.0$  (*acetic*  $\text{CH}_2$ ).

**IV.**  $^1\text{H}$  NMR (302 K, SAP-isomer)  $\delta_{\text{H}}$  ppm:  $300.3$  (*ac*2),  $159.2$  (*ax*2),  $107.22$  (*ac*1),  $-95.9$  (*el*),  $-103.1$  (*e*2).



**Figure 2.** Step hydrolysis of the compound  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$  (**I**) to  $[\text{Dy}(\text{bis-}t\text{Bu-DOTA-ester})]^{2+}$  (**II**),  $[\text{Dy}(t\text{Bu-DOTA-ester})]$  (**III**) and  $[\text{Dy}(\text{DOTA})]^-$  (**IV**).

## Kinetic Data Getting

The hydrolysis of complex **I** can be formally described by a system of kinetic equations (1).

$$\begin{cases} \frac{d[\text{I}]}{dt} = -k_1[\text{I}] \\ \frac{d[\text{II}]}{dt} = k_1[\text{I}] - k_2[\text{II}] \\ \frac{d[\text{III}]}{dt} = k_2[\text{II}] - k_3[\text{III}] \\ \frac{d[\text{IV}]}{dt} = k_3[\text{III}] \end{cases} \quad (1)$$

where  $k_1$ ,  $k_2$  and  $k_3$  are effective (observed) rate constants of the pseudo-first order (due to the fact that the concentration of  $\text{D}_2\text{O}$  is constant).

The intensity of a particular NMR signal (*e.g.*, ester  $\text{CH}_3$  protons or  $\text{CH}_2$  protons of a macrocycle) is related to the concentration of the component by the ratio

$$I_j = A \cdot C_j \quad (2)$$

where  $I_j$  is the signal intensity of the protons of component  $j$ ,  $A$  is the experimentally determined constant,  $C_j$  is the concentration of component  $j$ .

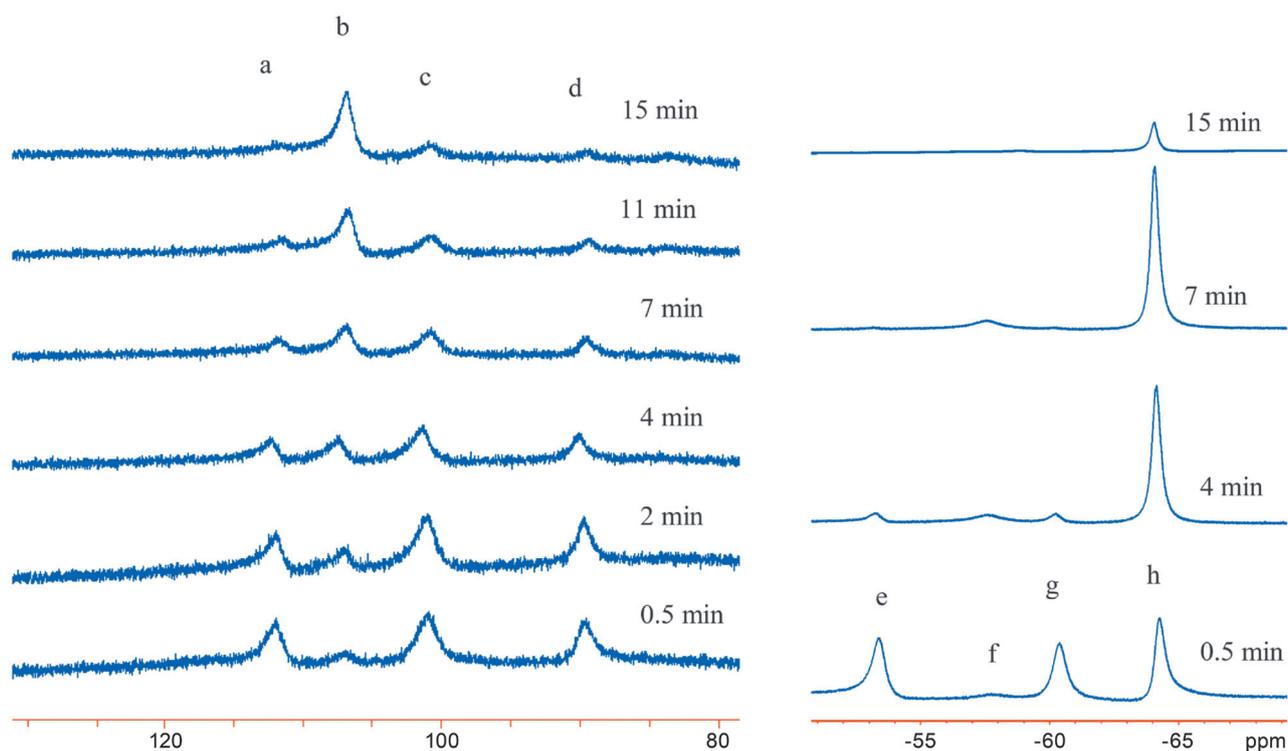
Substitution of (2) in (1) gives a similar kinetic scheme, which is solved by numerical methods.

The current signal intensities (concentrations), the reaction time are established experimentally.

The concentrations of the components were evaluated by analyzing the NMR spectra recorded at different time intervals after mixing the components and the start of the NMR-scanning, with continuous timing (with  $\pm 30$  sec error taking into account the average time for a single NMR-scan).

## Results and Discussion

The hydrolysis of the  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$  complex is almost irreversible (Figure 2), while the interme-



**Figure 3.** 500 MHz  $^1\text{H}$  NMR spectra of  $[\text{Dy}(\text{tris-tBu-DOTA-ester})]^{2+}$  at different reaction times (308K). Signals “a”, “b”, “c”, “d” correspond to acetic  $\text{CH}_2$  protons, and signals “e”, “f”, “g”, “h” correspond to  $\text{CH}_3$  protons of *isobutyl* ester.

diate formed complexes  $[\text{Dy}(\text{bis-tBu-DOTA-ester})]^{2+}$  (**II**) with a charge “+1” can exist in the form of isomers with different orientations of ester and carboxyl groups.

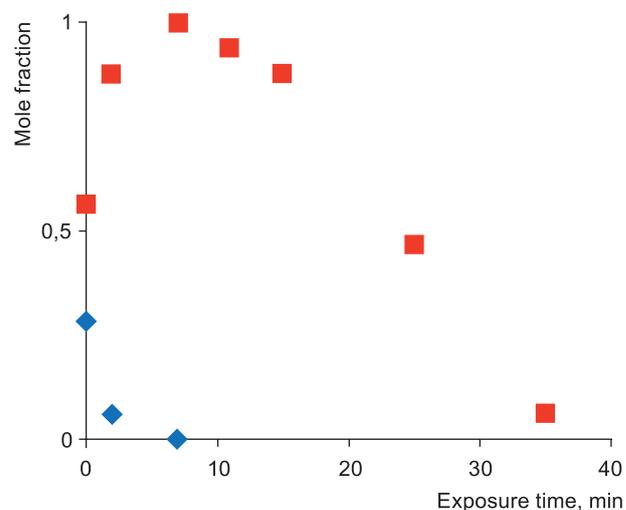
The kinetics of the process can be described as a sequence of irreversible reactions of the first order, considering the concentration of the second reagent  $\text{D}_2\text{O}$  is constant. The hydrolysis rate may depend on the *pH*, temperature, concentration of components, *etc.* In this work, an NMR study of the hydrolysis of  $[\text{Dy}(\text{tris-tBu-DOTA-ester})]^{2+}$  was carried out with the following parameters: temperature 308 K (35 °C); *pH* 7.0; the concentration of the complex is 0.02 M; solvent  $\text{D}_2\text{O}$ .

In the 500 MHz  $^1\text{H}$  NMR spectra of  $[\text{Dy}(\text{tris-tBu-DOTA-ester})]^{2+}$ , the signals of the groups of  $\text{CH}_2$  protons of the macrocycle (“a”, “b”, “c”, “d”) and  $\text{CH}_3$  protons of *isobutyl* ester (“e”, “f”, “g”, “h”) are distinguishable. The signals “e”, “g” and “f” (related to the “SAP-isomers” of complexes **I** and **II**) gradually disappear with some short exposure, while the relative intensity of the signal “h” (related to complex **III**) first increases in proportion to the decrease in the intensity of “e”, “f” and “g”, then gradually decreases.

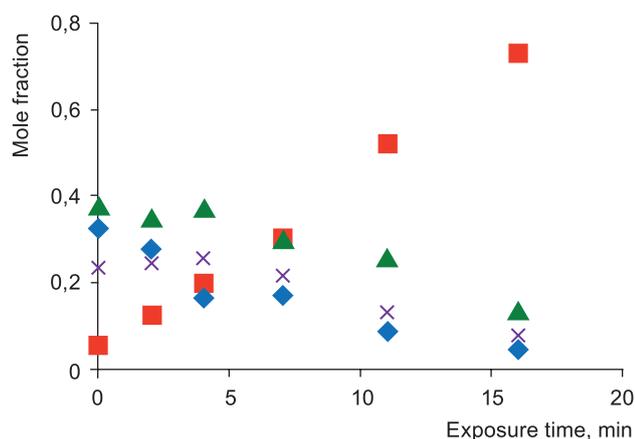
A similar behavior is observed for signals “a”, “b”, “c” and “d”, when with increasing reaction time (with an interval of several minutes), the signal “b” (related to complex **IV**) gradually increases in intensity, while the intensities of the signals “a”, “c” and “d” (relating to complexes **II**, **III** and **I**, respectively) are continuously decreasing.

The mole fractions of  $\text{CH}_3$  and  $\text{CH}_2$  proton signals change in accordance with the gradual hydrolysis of the initial complex and intermediates and the accumulation of the  $[\text{Dy}(\text{DOTA})]^-$  complex (see Figures 3, 4 and 5).

From the change in the spectral integrated intensities of the signals belonging to different complexes, the hydrolysis rate constants are shown in Table 1. Almost complete hydrolysis of  $[\text{Dy}(\text{tris-tBu-DOTA-ester})]^{2+}$  to  $[\text{Dy}(\text{DOTA})]^-$  passed in 35 minutes at a physiological temperature of 308 K (+35 °C). It can be noted that the rate of hydrolysis of mono-substituted complex (**III**) is several times lower than that of two- and three-substituted complexes, and therefore, form **III** with zero charge prevails among all intermediate partially substituted complexes in the solution.



**Figure 4.** Kinetic curves of the hydrolysis of  $[\text{Dy}(\text{tris-tBu-DOTA-ester})]^{2+}$  in  $\text{D}_2\text{O}$ , measured by the change in the integral intensity of the  $\text{CH}_3$  signals of groups of the complexes **III** (■) and **II** (◆).



**Figure 5.** Kinetic curves of the hydrolysis of  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$ , measured by the change in the integrated intensity of the signals of  $\text{CH}_2$  groups of complexes I (♦), II (×), III (▲) and IV (■).

The experimentally found values of the rate constants of the ester hydrolysis reaction are of the order of the units of 1/s, which corresponds, for example, to the literature data for ester hydrolysis reactions in aqueous media.<sup>[25,26]</sup>

**Table 1.** The rate constants  $k$  of the hydrolysis of reagents at 308 K.

Complex	Rate constant $k_{308}$ 1/s
$[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$	$11.8 \pm 1.3$
$[\text{Dy}(\text{bis-}t\text{Bu-DOTA-ester})]^+$	$12.8 \pm 1.3$
$[\text{Dy}(t\text{Bu-DOTA-ester})]$	$3.0 \pm 0.7$

In the NMR spectra of lanthanide complexes, the values of paramagnetic chemical shifts linearly depend on the inverse temperature. It was experimentally found that in the  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$  NMR spectra, paramagnetic CSs vary significantly with temperature.<sup>[27,28]</sup> The temperature sensitivity of the LIS observed for  $\text{CH}_3$  signals in the spectra of the complex  $[\text{Dy}(t\text{Bu-DOTA-ester})]$  amounted to  $d(\Delta\delta_{\text{ex}})/dT = 0.38$  ppm/K. Analogically, found temperature sensitivities of the complexes  $[\text{Dy}(\text{bis-}t\text{Bu-DOTA-ester})]^+$  and  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$  are 0.28 and 0.34 ppm/K, respectively. The found values of the temperature sensitivity  $d(\Delta\delta_{\text{ex}})/dT$  are orders of magnitude greater than for the temperature sensitivity of the chemical shift of pure water (of the order of 0.01 ppm/K). It should be noted that other complex compounds, which were earlier investigated by  $^1\text{H}$  NMR in both organic and aqueous media are characterized by the paramagnetic CS temperature sensitivity in the range from 0 to 1.5 ppm/K.<sup>[8,10–13,29–31]</sup> The obtained result indicate that the coordination compounds I, II and III may be considered as the middle sensitive  $^1\text{H}$  NMR lanthanide paramagnetic probes for *in situ* temperature control in solutions. Therefore, complexes I, II and III can be considered as potential reagents for determining the temperature in liquid samples installed in an NMR spectrometer, either directly in reaction media, or for *in situ* studies of exothermic or endothermic processes. It can be assumed that the compound III could serve as a

temperature probe for assessing the local temperature in the body of mice using 3D MRI at injection of the initial complex I.

## Conclusion

Thus, the  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$  complex undergoes almost complete hydrolysis to  $[\text{Dy}(\text{DOTA})]^-$  in about half an hour at physiological temperature (308 K). The dominant intermediate hydrolysis product is the neutral monosubstituted complex  $[\text{Dy}(t\text{Bu-DOTA-ester})]$  with the lowest hydrolysis rate. The coordination compounds  $[\text{Dy}(\text{tris-}t\text{Bu-DOTA-ester})]^{2+}$ ,  $[\text{Dy}(\text{bis-}t\text{Bu-DOTA-ester})]^+$  and  $[\text{Dy}(t\text{Bu-DOTA-ester})]$  may be considered as the middle sensitive  $^1\text{H}$  NMR lanthanide paramagnetic probes for *in situ* temperature control in solutions. The NMR method reveals its effectiveness for studying the kinetics of not only reversible, but also irreversible processes in solutions.

**Acknowledgements.** The research was supported by the Russian Science Foundation (the research project No. 20-63-46026).

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Received 06.06.2020

Accepted 11.08.2020