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# Prospects of paramagnetic lanthanide complexes for magnetic resonance imaging, local thermosensing and diagnosing

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**Abstract.** The features of the paramagnetic properties of lanthanide (Ln) containing complexes with crown ethers, pivaloyltrifluoroacetate, and EDTA have been studied by <sup>1</sup>H and <sup>19</sup>F NMR techniques. These complexes are of interest due to the prospect of using some of them as sensors for biology and medicine. The temperature dependencies of the lanthanide-induced shifts revealed that Ln complexes might have practical importance for <sup>1</sup>H and <sup>19</sup>F NMR temperature control in solutions. It was shown *in vitro* (using NMR spectrometers and MRI scanners) that these complexes can serve as special NMR thermo-sensitive contrast reagents.

## 1. Introduction

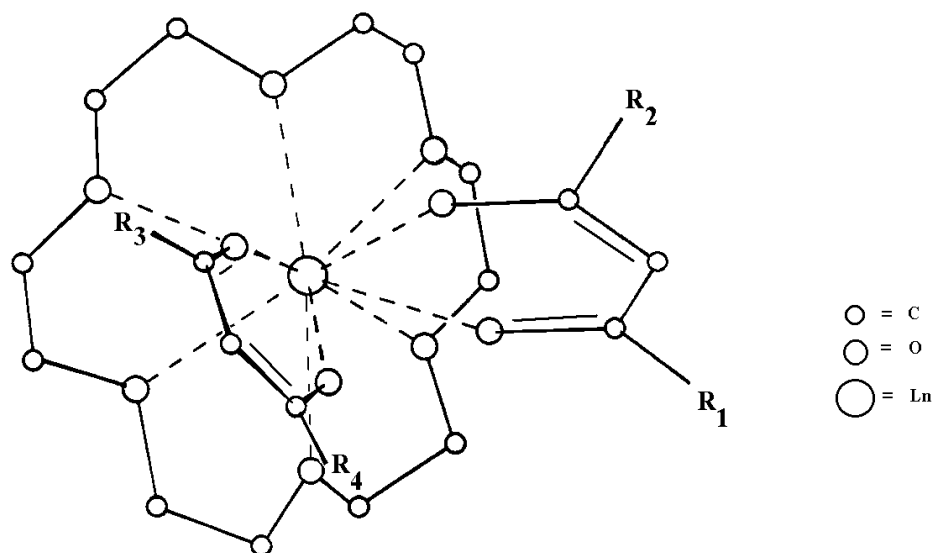
MRI is routinely used in the clinic to visualize the structure and function of organs. For tumor and cardiovascular imaging in clinic and *in vivo* studies, an enhancement in contrast is an absolute requirement to improve the sensitivity and the diagnostic contents of the images. For this, several contrast agents (CAs) have been developed earlier, most of which incorporates paramagnetic gadolinium ions (Gd<sup>3+</sup>). Currently, complexes of the different lanthanides (Ln, other than Gd), remain largely unexplored as probes for nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI).

Recent studies have demonstrated *in vitro* that MRI can be used as a tool for noninvasively assessing temperature changes in tissues associated with absorption of nonionizing radiation. As an example, we proposed the use of special NMR thermo-sensitive contrast reagents (NMR-TSCR) based on paramagnetic Ln complexes. This technique can diagnose conditions such as inflammatory reactions and cancer. The mechanism of action of NMR-TSCR is based on the substantial dependence of lanthanide-induced shifts (LIS) in NMR spectra on temperature.

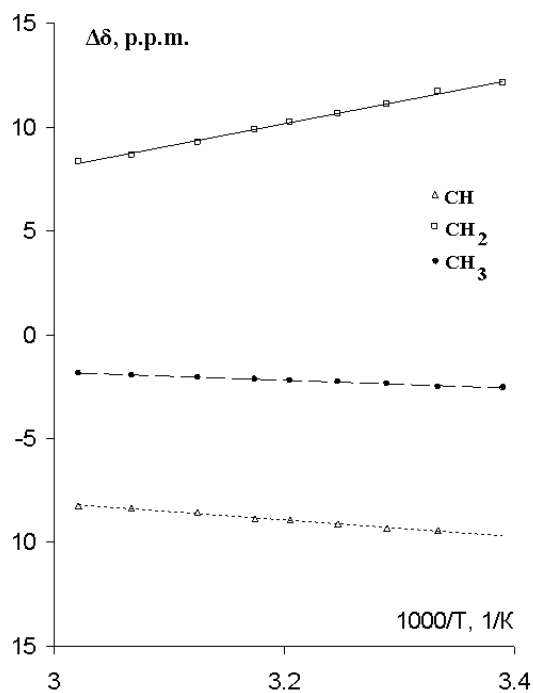
Coordination compounds of lanthanides (Ln) with  $\beta$ -diketones have been considered as photoluminescence devices and photoresists as well as precursors for producing covers by the MO CVD method [1,2]. The pivaloyltrifluoroacetate ion, (ptf)<sup>-</sup>, is among interesting ligands of  $\beta$ -diketone anions. The ligand involves fluorine atoms usable for NMR-sensors. Metal chelates with this ligand are thermostable and volatile. We previously researched by <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR (in solution) and by X-ray diffraction (in the crystal state) the starting compound [Ln(H<sub>2</sub>O)(ptf)<sub>3</sub>] and the products formed by reacting with different ligands [3,4]. Furthermore, the temperature dependence of the signals of <sup>19</sup>F NMR of paramagnetic lanthanide complexes previously has rarely been studied in detail.



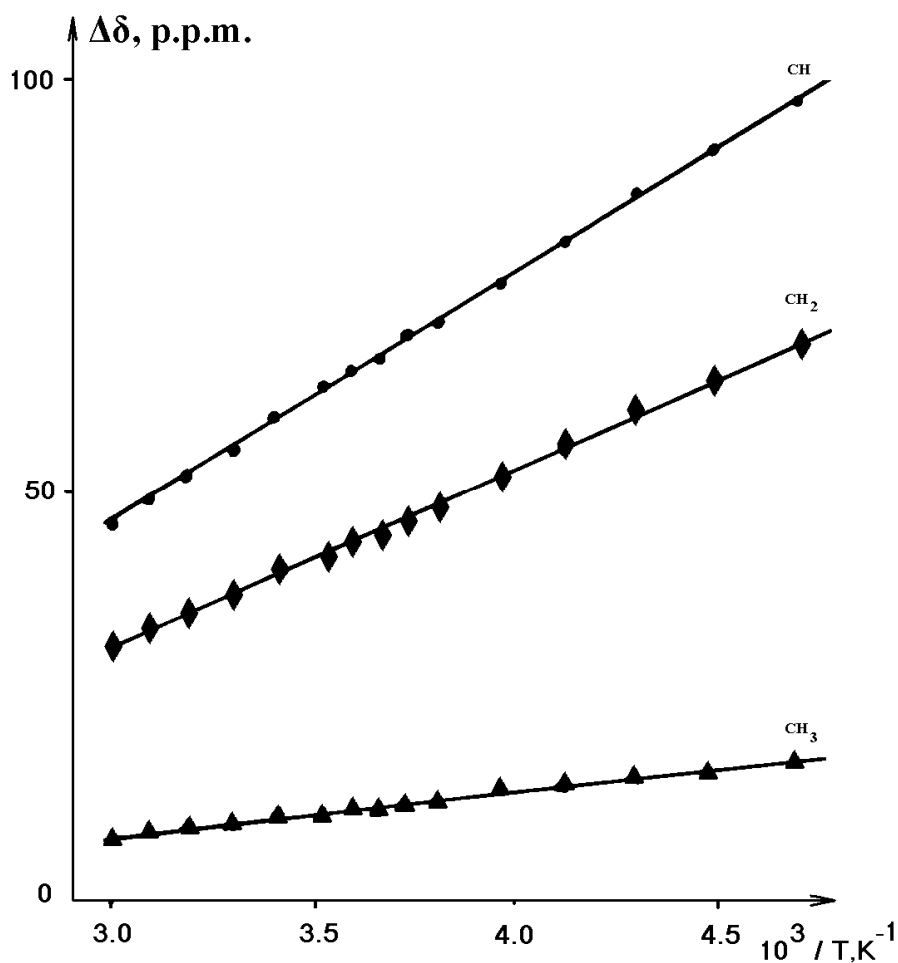
The aim of this work was  $^1\text{H}$  and  $^{19}\text{F}$  NMR investigation of  $[\text{Ln}(\text{PTA})_2(18\text{-crown-6})]^+$  ( $\text{Ln} = \text{La}, \text{Nd}, \text{Pr}$  and  $\text{Eu}$ ; Figure 1) and  $[\text{Ho}(\text{EDTA})]^+$  (Figure 6) as NMR thermo-sensitive contrast reagents (NMR-TSCR). We also studied the substantial temperature dependence of the paramagnetic lanthanide-induced shifts (LIS) in *tris*-pivaloyltrifluoroacetate lanthanides(III) (in  $\text{CDCl}_3$  and  $\text{CD}_3\text{C}_6\text{D}_5$ ; Figure 2 and 3) and  $[\text{Ho}(\text{EDTA})]^+$  (in  $\text{D}_2\text{O}$ ; Figure 5) [3-5].



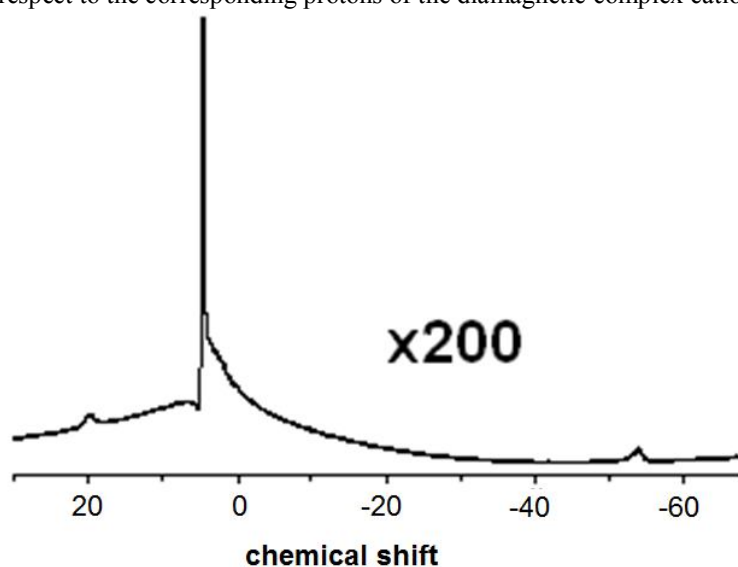
**Figure 1.** The proposed structure of the complex ions  $[\text{Ln}(\text{PTA})_2(18\text{-crown-6})]^+$ , where  $\text{Ln} = \text{La}, \text{Ce}, \text{Pr}, \text{Nd}$ ;  $\text{R}_1 = \text{R}_3 = -\text{Bu}^t$ ;  $\text{R}_2 = \text{R}_4 = -\text{CF}_3$ .



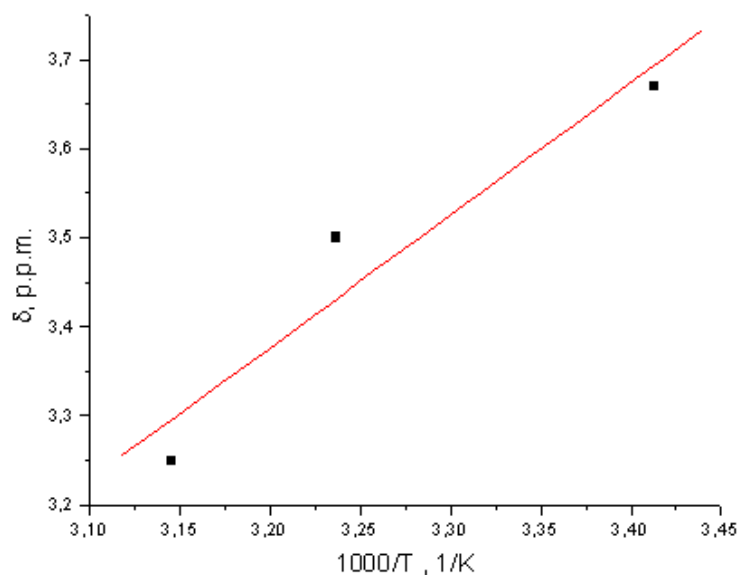
**Figure 2.** The temperature dependence of the paramagnetic lanthanide-induced shifts in the spectra of the 200 MHz  $^1\text{H}$  NMR of the complex cation  $[\text{Eu}(\text{PTA})_2(18\text{-crown-6})]^+$  in the solvent  $\text{CDCl}_3$  (taken with respect to the corresponding protons of the diamagnetic complex cation  $[\text{La}(\text{PTA})_2(18\text{-crown-6})]^+$ ).



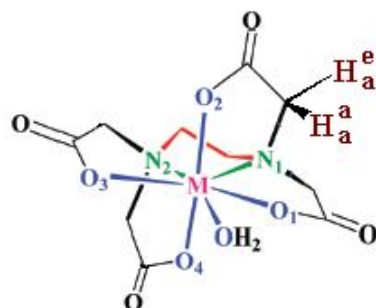
**Figure 3.** The temperature dependence of the paramagnetic lanthanide-induced shifts in the spectra of the 100 MHz  $^1\text{H}$  NMR of the complex cation  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^+$  in the solvent  $\text{CDCl}_3$  (taken with respect to the corresponding protons of the diamagnetic complex cation  $[\text{La}(\text{PTA})_2(18\text{-crown-6})]^+$ ).



**Figure 4.** 300 MHz  $^1\text{H}$  NMR of the complex  $[\text{Ho}(\text{EDTA})]^+$  in the solvent  $\text{D}_2\text{O}$  (used the sensor for microtomography, a diameter of 5 mm).



**Figure 5.** The temperature dependence of the paramagnetic lanthanide-induced shifts in the spectra of the 470.59 MHz  $^{19}\text{F}$  NMR of the complex cation  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^+$  in the solvent  $\text{CDCl}_3$  (taken with respect to the corresponding protons of the diamagnetic complex cation  $[\text{La}(\text{PTA})_2(18\text{-crown-6})]^+$ ); by BRUKER BioSpec 117/16 scanner.



**Figure 6.** The proposed structure of the  $[\text{Ho}(\text{EDTA})]^+$  complex.

## 2. Results and discussion

It was found by  $^{19}\text{F}$  NMR that the experimental paramagnetic LIS values ( $\delta_{\text{LIS}}$ ) of  $[\text{Ln}(\text{PTA})_2(18\text{-crown-6})]^+$  {for the signals of  $\text{CF}_3$ } are well fitted by linear dependence on  $1/T$  (Figure 5). This result correlates well with  $^1\text{H}$  NMR studies of many other paramagnetic compounds of Ln cations.

We investigated experimental  $^1\text{H}$  and  $^{19}\text{F}$  NMR paramagnetic LISs versus  $T$  for the system in order to compare with analogous literature data. The derivative of  $\delta_{\text{LIS}}(T)$  was calculated for the signals. These values appeared to be 0.021 for  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^+$  (in case of  $^{19}\text{F}$  NMR). The value of  $\partial\delta/\partial T$  for the CH signal of  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^+$  is 0.46 p.p.m./K (in case of  $^1\text{H}$  NMR). The value of  $\partial\delta/\partial T$  for the  $\text{CH}_2$  signal of  $[\text{Ho}(\text{EDTA})]^+$  is 0.9 p.p.m./K (in case of  $^1\text{H}$  NMR). 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 LIS temperature sensitivity in the range from 0 to 1.17 p.p.m./K [4,6-12]. The obtained results indicate that the coordination compound  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^+$  may be considered as sensitive  $^1\text{H}$  and  $^{19}\text{F}$  NMR lanthanide paramagnetic probe for *in situ* temperature control in organic solutions. It should be noted that this is a second determination of the temperature sensitivity of LIS in  $^{19}\text{F}$

NMR spectra of paramagnetic complexes of lanthanides. The compound  $[\text{Ho}(\text{EDTA})]^{+}$  may have a medical use for determining the local temperature of the body using MRI. The compound  $[\text{Pr}(\text{PTA})_2(18\text{-crown-6})]^{+}$  may also have a medical use for determining the local temperature of the body using MRI [7] in the case of application of coating technology (for example similarly to the publication [13]).

### 3. Experimental section

*General.* All reagents and solvents were commercially available and were used without additional purification. Elemental analysis was performed on a EuroEA 3000 analyzer. The melting points were determined on a Boëtius hot stage. The IR spectra were measured on a Scimitar FTS 2000 spectrometer in KBr in the range 375–4000  $\text{cm}^{-1}$ . Thermogravimetry was performed using a NETZSCH TG 209 F1 Iris thermomicrobalance (sample weight  $\sim 7$  mg, aluminum crucible) in a helium atmosphere, gas flow rate 60 mL/min, heating rate 10 deg/min. The results were treated using Proteus Analysis software.

*NMR spectroscopy.* Solutions in  $\text{CDCl}_3$  and  $\text{CD}_2\text{Cl}_2$  had the concentration of complexes  $C = 5 \cdot 10^{-3}$  M. The  $^1\text{H}$  NMR spectra were measured with MSL-300, Avance-300, Avance-500 spectrometers and 500 MHz BioSpec 117/16 scanner (all produced by Bruker, Germany). The residual proton signal in  $\text{CDCl}_3$  (7.23 p.p.m. at 298 K) was used for chemical shift referencing. Through all the measurements the magnetic field was stabilized, using deuterium lock of the solvent. The spectra were measured in the tubes with an outer diameter of 5 mm. A B-VT-1000 temperature unit with the accuracy of 0.5 K and stability of  $0.2 \text{ K h}^{-1}$  was used for temperature control. The unit was calibrated, using standard samples with known temperature dependence of chemical shifts. Paramagnetic LISs were determined relative to the diamagnetic complex, which served as a reference. As it can be seen in Fig. 2, 3 and 5, experimental LIS values are well fitted, assuming their linear dependence on  $1/T$ .

### 4. In conclusion

According to our evaluations, temperature determination error ( $\Delta T$ ) is  $\sim 0.4$  K and 3D resolution ( $\Delta L$ ) is 100  $\mu\text{m}$  (see Fig. 7). To solve the main problem requires answers to a number of interrelated issues: (1) development of the method of the molecular structure determination of paramagnetic Ln complexes in solution according to the combined analysis of LIS and of the paramagnetic spin-lattice relaxation enhancement; (2) the information about the molecular structure and the dynamics of Ln coordination compounds with macrocyclic (crown-ethers) and acyclic (EDTA-like) ligands in solutions. The temperature dependencies of LISs revealed that Ln complexes might have practical importance for  $^1\text{H}$  and  $^{19}\text{F}$  NMR temperature control in solutions. It was shown *in vitro* (using NMR spectroscopy and MRI scanners) that these complexes can serve as NMR-TSCR and CAs.



**Figure 7.** The proposed image of temperature gradient at cancer and inflammation.

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