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## Production of gadolinium nanoparticles in a polymer matrix by a pulsed mechanical impact

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In this study, superparamagnetic elemental-gadolinium nanoparticles 2 to 12 nm in size were for the first time obtained under a pulsed mechanical impact (rheological discharge explosion). The synthesis was carried out in one stage in an environmentally friendly („green chemistry“) mode in a polymer matrix doped with the Gd(QH)<sub>3</sub> complex, where QH is a ligand based on 3,6 di-tert-butyl phenol that is an environmentally safe antioxidant. Emergence of these particles was confirmed by electron paramagnetic resonance, X-ray phase analysis and transmission electron microscopy. This synthesis may be regarded as basis for further progress in producing gadolinium nanoparticles which can be used in neutron— and photon-capture therapy of malignant neoplasms with biological targeting using magnetic resonance imaging or computed tomography.

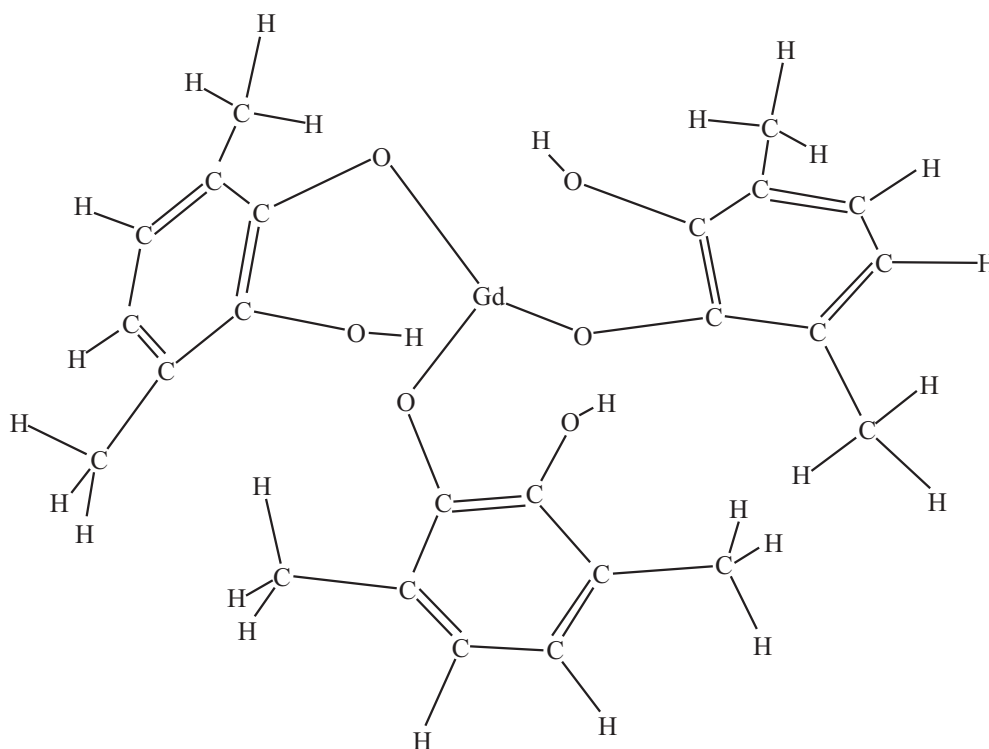
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Gadolinium and boron compounds are actively used in neutron-capture therapy (NCT) for treating malignant neoplasms [1,2]. The thermal neutron capture cross section of Gd<sup>157</sup>(*n, γ*) is  $\sigma = 254\,000$  barn, while that of B<sup>10</sup>(*n, α*) is  $\sigma = 3880$  barn. Boron exhibits more advantageous secondary  $\alpha$ -radiation whose linear energy transfer is higher than that of gadolinium  $\gamma$ -radiation [2]. However, gadolinium compounds are actively used in magnetic-resonance imaging (MRI) where the patient is exposed to high-frequency magnetic field, in computed tomography (CT) where exposure to X-rays is used, and in photon-capture therapy (PCT) where a fast-electron beam is used as an impact. Thus, Gd preparations may be used for both diagnosis and treatment by the NCT, MRI, CT and PCT methods[3–8]. The basic requirements for such preparations are as follows [4–9]: (a) the preparation should be efficiently deliverable to and removable from the tumor and ensure high contrast properties necessary for efficient monitoring of the therapeutic process, i. e. be ferromagnetic or superparamagnetic; (b) it should not be toxic, i. e. it is to be covered with a protective shell; (c) its dimensions should ensure overcoming the blood-brain barrier (the physiological barrier between the bloodstream and central nervous system); all this requires nanoparticles 2 to 10 nm in diameter, and the gadolinium local concentration in the particle should amount up to 30% of the particle mass because, being high, the gadolinium local concentration provides pointwise impact (with the impact radius around the particle of  $\sim 100\ \mu\text{m}$ ), which maximally protects healthy tissues of the body. Such particles can be positioned by magnetic field, and their motion in organs and tissues can be

controlled in the non-contact manner with the aid of external magnetic field. By now, a great number of Gd preparations have been synthesized based on nanoparticles of different chemical compositions. Attempts to obtain nanocomposites containing small (10–15 nm) particles of Gd<sub>2</sub>O<sub>3</sub>, GdBO<sub>3</sub> stabilized with polysaccharides have been successfully implemented [9–11]; water-soluble magnetically active nanobiocomposites of gadolinium complexes have been created [2]. However, formation of such nanosized particles is a complex multi-stage process. To date, there has been performed a countable number of studies devoted to direct synthesis of elemental Gd nanoparticles. Nanoparticles of elemental Gd in paraffin 18 to 89 nm in diameter were obtained by evaporating the metal in a flow of pure helium or with adding 0.5% of oxygen [12]; particles with the size of 20 to 40 nm were also obtained by depositing Gd vapor onto a quartz substrate [13]. By mechanical co-grinding of gadolinium and potassium chloride, elemental Gd particles 100–500 nm in size were obtained [13], while co-grinding with silicon oxide and polystyrene gave particles of up to 80–200 nm [14]. No direct one-stage synthesis of elemental Gd nanoparticles in a polymer matrix has been performed by now. Therefore, it is important to propose an original and „green“ (environmentally safe) method for producing superparamagnetic nanoparticles of elemental gadolinium stabilized by a polymer matrix. This will improve their pharmacological and therapeutic properties by ensuring control over pharmacokinetics and biodistribution.

In this work, we have considered a mechanochemical method for synthesizing superparamagnetic nanoparticles of elemental Gd in a polystyrene matrix from semiquinone



**Figure 1.** Structure of the  $\text{Gd}(\text{QH})_3$  complex.

complex  $\text{Gd}(\text{QH})_3$ . To synthesize this complex, we used anhydrous gadolinium chloride  $\text{GdCl}_3$  and anhydrous powder of 3,6-di-tert-butyl pyrocatechol (Gadolinium (III) chloride, and also 3,6-di-tert-butyl catechol produced by Aldrich. The synthesis was performed according to the standard procedure [15]: solid-phase mixing of stoichiometrically weighed portions, putting the mixture in chloroform and stirring with a magnetic agitator until complete disappearance of the sediment, evaporation, rinsing, and drying. The structure of the complex (Fig. 1) was calculated and optimized by using code Gaussian 98, Rev. A.5 [16]; QH is an antioxidative biologically harmless 3,6-di-tert-butyl ligand easily removable mechanically in order to obtain Gd ions from which the metal nanoparticle is formed.

The one-stage fabrication of elemental Gd nanoparticles was performed in the mode of the below-described impact on the sample (Fig. 2, *a* demonstrates the setup used for this purpose). First, a uniaxial load is applied (for 3 s at the compression rate of 1.0 GPa/s); it is followed by a rapid pressure release (for  $\sim 5 \cdot 10^{-7}$  s) at the preset pressure of 3 GPa, which initiates a rheological discharge explosion (ultra-fast destruction). In the absence of the rapid release of pressure, the samples did not experience the rheological explosion under uniaxial compression up to 5 GPa. The setup is capable of recording alternating current  $J(t)$  generated by the proceeding physical and chemical processes. Thus, the oscilloscope records voltage  $U(t) = RJ(t)$  (resistance is 50  $\Omega$ ). Fig. 2, *b* demonstrates typical signal  $U(t)$  from composite PS (polystyrene) + 10 mass% of  $\text{Gd}(\text{QH})_3$  displayed on the digital oscilloscope screen. This figure

also presents the signal from the rheological explosion of the PS polymer matrix, which is an order of magnitude lower than the pulse from the composite. This difference in the intensities of recorded signals clearly evidences that introducing the organoelement gadolinium complex promotes in the polymer matrix additional physicochemical processes associated with the introduced complex.

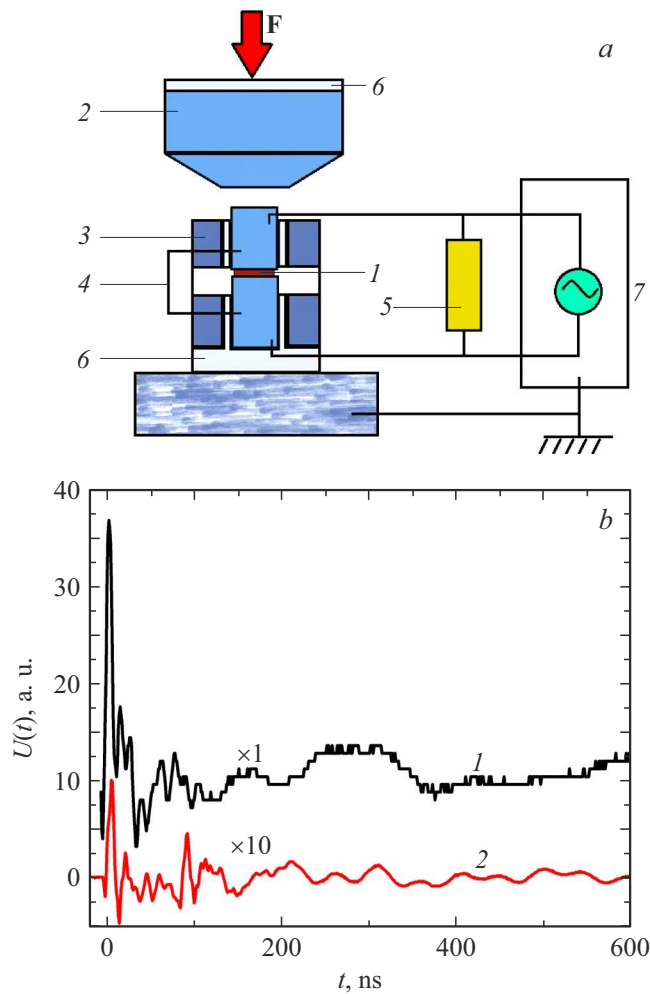
After exposure to the pulsed mechanical impact, samples of the PS + 10 mass% of  $\text{Gd}(\text{QH})_3$  composite were studied by X-ray phase analysis using a DRON-3M diffractometer, BSV-29 tube ( $\text{CuK}_\alpha$ -radiation), and Ni filter. The X-ray reflection/diffraction spectrum (Fig. 3, *a*) clearly shows the presence of bands with maxima at scattering angles  $2\theta = 26.92, 33.43, 49.31^\circ$ . As per the diffractometer database, the bands at  $2\theta = 28.02, 32.47, 46.58^\circ$  are related to the face-centered cubic (fcc) lattice of metallic Gd. This means that the obtained Gd nanoparticles have an almost fcc lattice. Calculation of crystallite sizes  $d$  via Scherrer formula  $d = \lambda/\beta \cos \theta$  [17] ( $\lambda$  is the X-ray wavelength in  $\text{\AA}$ ,  $\beta$  is the half-width of the observed diffraction band in radians,  $\cos \theta$  for  $2\theta/2$ ) shows, taking into account that mean  $\beta$  is

$$\beta = (\beta_1 + \beta_2 + \beta_3)/3 = 1.5 \pm 0.2^\circ, \quad 1^\circ = 0.0175 \text{ rad},$$

while mean  $\cos \theta$  is

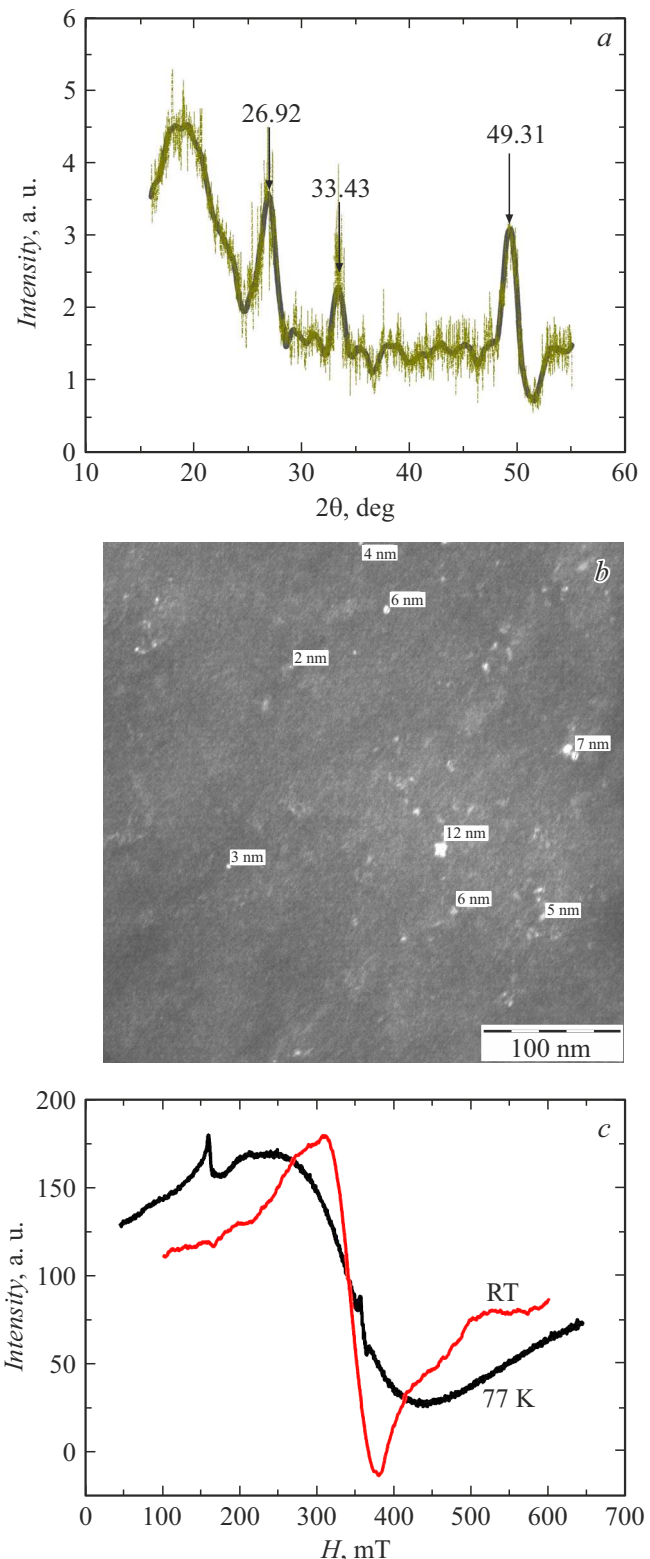
$$\cos \theta = (\cos \theta_1 + \cos \theta_2 + \cos \theta_3)/3 = 0.9 \pm 0.1,$$

that the possible size of the obtained nanoparticles is  $5.5 \pm 0.7$  nm. Examination with transmission electron microscope LEO 912 AB OMEGA at the accelerating voltage



**Figure 2.** *a* — schematic diagram of the high-pressure cell. *1* — sample, *2* — Bridgman anvil, *3* — steel bushing, *4* — punches, *5* — load resistance  $R = 50 \Omega$ , *6* — insulation, *7* — digital oscilloscope. *b* — time sweeps of signals from composite PS + 10 mass% of  $\text{Gd}(\text{QH})_3$  (*1*) and matrix polymer (PS) (*2*).

of 100 kV confirmed formation of metallic gadolinium nanoparticles 2 to 12 nm in size (light contours in Fig. 3, *b*). Analysis of the data presented in the microphotograph (Fig. 3, *b*) provided rough estimation of the depth of the  $\text{Gd}(\text{QH})_3$  complex chemical transformation into Gd nanoparticles under the mechanical impact described above. Fig. 3, *b* shows that the sample under study, which is a square with the side of 350 nm and thickness of 50 nm (we have selected the 50 nm thickness because the diamond knife cuts from the initial sample test films  $50 \pm 10$  nm thick), contains  $\sim 3 \cdot 10^4$  Gd atoms in the form of spherical nanoparticles of different sizes, since the volume of the observed nanoparticles is  $\sim 5000 \text{ nm}^3$ , while [17] shows that the Gd atom volume in the fcc lattice is  $\sim 0.147 \text{ nm}^3$ . Thus, obtain that, after the mechanical impact, in  $1 \text{ cm}^3$  of the sample there emerge  $\sim 6 \cdot 10^{18}$  Gd atoms forming an ensemble of nanoparticles. The initial samples contained 10 mass% of  $\text{Gd}(\text{QH})_3$  ( $\sim 6 \cdot 10^{19}$  complexes in  $1 \text{ cm}^3$ );



**Figure 3.** Results of studying the PS+10 mass% of  $\text{Gd}(\text{QH})_3$  composite after mechanochemical treatment with the rheological discharge explosion at 3 GPa. *a* — X-ray reflection/diffraction spectrum; *b* — microphotograph of the room-temperature sample; *c* — EPR spectra measured at 77 K and room temperature (RT).

this means that the chemical transformation depth was about 10%.

Using the EPR method, it was established that nanoparticles of elemental gadolinium arising under the rheological explosion are superparamagnetic molecular formations. Indeed, the width of EPR spectra for these particles (obtained with EPR spectrometer Bruker EMX, Germany) decreases from 210 to 70 mT with temperature increasing from 77 K to RT (Fig. 3, c). This property of superparamagnetic particles is well known and testifies their distinction from paramagnetic particles whose spectra get wider with increasing temperature [18].

Thus, in this study there was implemented for the first time a one-stage „green chemistry“ method for obtaining elemental Gd superparamagnetic nanoparticles 2 to 12 nm in size which can be used in neutron — and photon-capture therapy of malignant neoplasms with using biological targeting by the MRI and CT methods. Obviously, it is necessary to develop in future a method for withdrawing elemental Gd nanoparticles from the polymer matrix and also to conduct a search for polymer shells more promising in view of using them for therapeutic purposes.

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## Conflict of interests

The authors declare that they have no conflict of interests.

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