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Magnetic properties of Gd^{3+} ions in the spatially distributed DNA molecules

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Abstract

The magnetic moment in DNA liquid-crystal dispersions experimentally was measured by SQUID magnetometer. The magnetic susceptibility of DNA, DNA with La, and DNA with Gd at 4.2 - 300 K versus temperature was obtained. The total magnetic moment is represented by two parts, i.e. the positive paramagnetic part, caused by Gd^{3+} ions, radicals, and the negative diamagnetic part. The number of paramagnetic centers was calculated also. The number of Gd^{3+} ions is in a good accordance with number of phosphate complexes, so we assume that Gd is bound to phosphate groups. We propose new magnetic method for the evaluation of Gd content in DNA – Gd construction.

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1. Introduction

^{157}Gd is a potential perspective agent for neutron capture cancer therapy (NCT). The microdistribution of Gd in cultured human glioblastoma cells exposed to Gd-diethylenetriaminepentaacetic acid (Gd-DTPA) was observed recently [1]. The Gd-DTPA penetrates the plasma membrane, and no deleterious effect on cell survival was observed. An analysis revealed a higher Gd accumulation in cell nuclei compared with cytoplasm. This is significant for prospective NCT because the proximity of Gd to DNA increases the cell-killing potential of the short-range, high-energy electrons emitted during the neutron capture reaction. Gd-containing cells bombarded by the thermal neutrons demonstrate reaction in inducing cell death. Gadolinium neutron capture therapy (Gd-NCT) utilizes the following nuclear capture reaction (NCR) of ^{157}Gd, nonradioelement, by thermal neutron irradiation: $^{157}Gd + n_{th} \rightarrow {}^{158}Gd + \gamma$-rays + internal conversion electrons -> Auger electrons + characteristic X-rays.

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The success of Gd-NCT depends on a high accumulation of Gd in the tumor. Therefore, the first problem is a sufficient concentration of gadolinium should be retained in the tumor tissue during neutron irradiation after intratumoral injection. The second problem is the toxicity of free gadolinium to tissues [2,3]. To avoid the toxicity, it is necessary to link the ^{157}Gd-ion to biopolymeric molecules. Therefore, gadolinium complexes that can be efficiently accumulated in tumor have been sought. The chelate complexes of gadolinium, nanoparticles of various origins have received considerable attention as potent molecular constructions for targeting a site and controlled release gadolinium in the tumor tissue during a Gd-NCT trial. In the present paper, novel highly rare earth elements loaded dsDNA (dsRNA) liquid-crystalline particles were prepared as a potential platform for Gd-NCT. We propose new magnetic method for evaluation of the Gd content in DNA – Gd construction.

2. Materials and methods.

In the samples presented in work, molecules of DNA formed cholesteric phase were investigated. The presence of cholesteric phase of molecules of DNA in the sample was detected by means of a circular dichroism spectrum and it is essential direct experimental acknowledgement. X-ray analysis confirms presence in the sample of the ordered phase and gives DNA concentration value corresponds to cholesteric phase. The samples of DNA, DNA with La, DNA with Gd were investigated. Constructions DNA with La, DNA with Gd were synthesized from pure DNA by $LaCl_3$ and $GdCl_3$ water solution treatment correspondingly.

The temperature dependence of magnetic moment, Pm, in liquid-crystal dispersions were experimentally measured by SQUID magnetometer [4]. The total magnetic moment is represented by two parts, i.e. the positive paramagnetic part, caused by Gd^{3+} ions, magnetic residues (terminal and other residues), and the negative diamagnetic part, caused both the presence of the „rest“ water (and La^{3+} ions in DNA with La case). Two contributions into the total magnetic moment have been separated by mathematical processing of experimental temperature dependence of magnetic susceptibility $\chi = P_m/(H\ m)$ using the Curie-Weiss equation with constant value of χ_0 , namely $\chi = \chi_0 + C/(T - \Theta)$, where C is Curie constant, Θ – paramagnetic Curie temperature. Curie constant C is equals $N^*\cdot\mu^2/3\ k$, where μ is effective magnetic moment per magnetic ion, k is Boltzmann constant. The number of paramagnetic centers (N*) was calculated because value of μ for paramagnetic center can be obtained from the expression: $\mu = g\cdot\mu_B\cdot(J\cdot(J+1))^{1/2}$ as well. Bohr magneton μ_B and J moment are well known. g – factor was obtained from ESR experiment.

3. Results and discussion

Magnetic properties of DNA with Gd and DNA with La are investigated. Also magnetic properties of pure DNA were investigated. Nevertheless it is interesting what the origin of paramagnetic propertied of DNA and DNA La samples is. An unambiguous accuracy of SQUID magnetometer (part of nanoemu) supports the conclusion that a paramagnetism of pure DNA (see Table 1) exists definitely and relatively close to DNA with La. The calculated value of χ_0 , C and Θ for samples obtained from $\chi = \chi_0 + C/(T - \Theta)$ approximation are represented in Table 1.

Table 1. Table of samples with measured χ_0 , C - Curie constant and Θ – paramagnetic Curie temperature.

	χ_0, • 10^{-6} emu/gOe	C, •10^{-4} emu K/g Oe	Θ, K
DNA	3.5	0.8	-0.35
DNA La	1.3	1.5	-2.0
DNA Gd ZFC >77 K	8.8	236	4.2
DNA Gd ZFC 4-300K	2.5	254	-0.13
DNA Gd FC >77 K	7.2	245	2.6
DNA Gd FC 4-300K	-29	307.3	-2.6
DNA Cu[4]	-9.4	3.54	-0.75

We can suppose that La interacts with magnetic residuals (the phosphate complex, the terminal

residuals and so on). The less paramagnetic issue in pure DNA is likely deal with La that possibly can "heals" the magnetic residuals. One can see, that the magnetic properties of DNA Gd samples are represented more rigidly relative to DNA, DNA La and early measured [4] DNA Cu (table 1). Really, on the Fig 1 is shown that magnetic properties of DNA, DNA with La are weak relative to DNA with Gd ones.

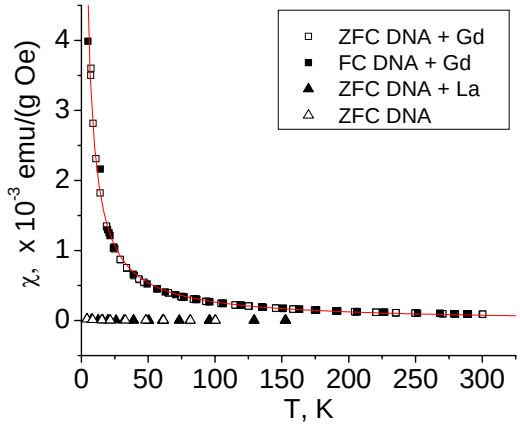

Fig. 1 Temperature dependence of the magnetic susceptibility of the samples Gd DNA (square, □-ZFC ■- FC), La DNA (▲- triangle) and GNA (Δ - triangle) at the field 526 Oe. Mass of each sample is 4 mg.

Magnetic moment of DNA with Gd includes a few contributions into the total magnetic moment. They have been separated by mathematical processing of experimental temperature dependence of magnetic susceptibility using the Curie-Weiss equation with constant value of χ_0. The calculated value of χ_0 was positive, in all experiments (see Table 1), except the low temperature (from liquid helium 4 K up to room 300K temperatures) field cooling (FC) experiment.

The number of paramagnetic centers (N*), namely number of Gd^{3+} was calculated from the temperature dependence of the magnetic susceptibility in range 77-300K. We use ZFC and FC parts of data in this range. The value of the effective magnetic moment was estimated from ESR experiments (g-factor at ambient temperature makes 1.99). One can calculate the effective magnetic moment of one Gd^{3+} ion in a sample: $\mu_{eff} = g\cdot\mu_B\cdot(J\cdot(J+1))^{1/2} = 7.9\ \mu_B$. From high-temperature part of magnetic susceptibility curves (Fig. 1, 2) it is possible to evaluate the number of Gd^{3+} ions per gram of the sample, being in $4f^7$-state, namely $N_{Gd(4f7)}$, as: $N_{Gd(4f7)} = 3\cdot k\cdot C_{CW} / (\mu_{eff})^2 = 1.86\cdot10^{21}\ g^{-1}$, where: $C_{CW} = 0.02413$ – is the constant obtained from an approximation of the temperature dependence of magnetic susceptibility according to the Curie-Weiss law. In the sample used the value of mass of one DNA molecule of as m_{DNA} mDNA is about $8\cdot10^5$ Da, or $m_{DNA} = 1.34\cdot10^{-18}$ g. The concentration of DNA in a solution, $C_{DNA} = 0.00005$ g/см^3; the volume of solution, from which a sample of DNA nanoconstruction was formed, is 80 см ^{3}. From these data, the total mass of DNA, M_{DNA}, is 0.004 g. This means that the number of DNA molecules in a sample, N_{DNA}, equals to: $N_{DNA} = M_{DNA}/ m_{DNA} = 2.98\cdot10^{15}$. The number of Gd^{3+} ions in the whole sample, being in $4f^7$-state, namely $N^*_{Gd(4f7)}$, is: $N^*_{Gd(4f7)} = N_{Gd(4f7)}\cdot M_{DNA} = 7.448\cdot10^{18}$. Hence, each DNA molecule contains approximately $N^*_{Gd(4f7)}/ N_{DNA} = 2490$ Gd^{3+} ions in $4f^7$-state. As the number of helical turns in the DNA molecule is equal to $8\cdot10^5 /6{,}6\cdot10^3 = 120$ from here it follows, that on each turn of DNA helix 2490 / 120 = 20.7 (~21) Gd^{3+} ions are located.

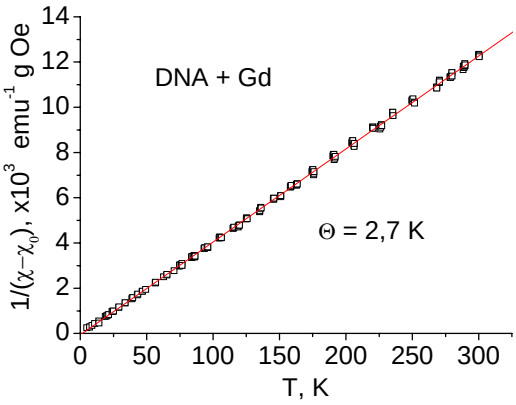

Fig. 2 Temperature dependence of the $1/(\chi-\chi_0)$ value for sample Gd DNA at the field 526 Oe. Mass of the sample is 4 mg.

The χ_0 value also was calculated from the high-temperature range of magnetic susceptibility curve. Calculated value $\chi_0 = 8*10^{-6}$ is positive, that can be explained by prevalence of Van-Vleck contribution

in magnetic susceptibility in comparison with diamagnetic contribution.

Using this value of χ_0 one can evaluate temperature dependence of $1/(\chi-\chi_0)$ value. Linear approximation of this value gives paramagnetic Curie temperature value Θ = 2.7 K (Fig. 2). Taking into account this circumstance we can suppose that at low temperatures the formation of ordered system of atoms Gd^{3+}, seated on phosphate groups, is possible. The analysis of χ(T) value at increasing temperature shows that the value of Curie-Weiss C constant depends on the temperature. The paramagnetic Curie temperature changes sign on the interval 100-300K, also [Table 1]. These facts can be explained by assumption of spin structure rearrangement while the temperature changes. The prehistory of cooling down to liquid nitrogen temperatures don't affect to result of magnetic experiment. Nevertheless cooling to helium temperatures gives us the difference in sign of χ_0, if we cool in the zero magnetic fields (ZFC) or nonzero (FC) field. This detected tendency to "spin-glass" or frustration rearrangement in Gd DNA samples at low temperatures was not detected in DNA Cu samples[4] with rigid nanobridges between DNA molecules. This fact illustrates that molecules in DNA with Gd have some degrees of freedom. Liquid crystal dispersion (LCD) DNA with Gd is not relatively rigid. It is obvious, that Gd^{3+} ions seated on the phosphate P^{2+} group are suffered by intra helix and extra helix Coulomb and magnetic interactions.

The step distances between the pairs are 3,4 Å. Hence, obtained from geometry of a molecule of DNA the distance between next atoms Gd on phosphates groups will be ~7 Å. Direct exchange interactions between Gd ions cannot exist. The extrachain magnetic exchange interaction also insignificant, because the whole turn of the helix is equal 34 Å, so nearest Gd ion on other helix (second chain) is located on rather long distances (~17 Å). Hence, magnetic ordered state of single-dimension chains of Gd ions located on the helix spatially ordered phosphate complexes at low temperatures is not obvious. Weak magnetic interaction is likely caused by dipole-dipole interaction or by indirect exchange interaction through oxygen atoms. Low value of paramagnetic Curie temperature (~ 1 K) supports this assumption. The difference between ZFC and FC magnetic moment measurements in DNA with Gd at low temperatures is likely deal with the weakness of ordered cholesteric phase due to uncompensated ion charge Gd^{3+} ions interaction seated on P^{2-}complexes.

Comparison of magnetic properties of samples of DNA with Gd and with La shows, that DNA with Gd possesses greater magnetic moment. As a result we can provide the calculation of number of ions Gd connected with molecules of DNA. After that the mass concentration Gd is 32 %. Now it is available molecular constructions with a few percent of mass concentration of gadolinium content[5]. Increased Gd concentration in DNA can be useful for neutron capture therapy with more efficiency.

Acknowledgements

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