Kazan Federal University
Zavoiskii Physical-Technical Institute
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ACTUAL PROBLEMS OF MAGNETIC RESONANCE AND ITS APPLICATION

XV International Youth Scientific School

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Lecture Notes
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Atherosclerotic Plaque and nanostructures

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The nature of the calcification of vessel walls is one of the most urgent problems of cardiovascular pathology. Calcification accompanies the formation of an atherosclerotic plaque, complicates the course of the atherosclerotic process, and results in myocardial infarction, stroke, and acute ischemia of tissue. Calcification is an indicator of the instability of the atherosclerotic plaque.

The mortality rate in Russian Federation from the diseases of the blood circulatory system is about 800 on 100 000 (2000). Arteriosclerotic vascular disease (Atherosclerosis, ASVD) is a condition in which an artery wall thickens as a result of the accumulation of fatty materials. The calcified atherosclerotic **plaque** is an organomineral aggregate in which formation **hydroxyapatite** is significantly involved (fig.1). The spectral and relaxation characteristics of the organomineral radicals correlate with the calcification degree of the atherosclerotic plaque and can be used for diagnostics (fig.2).

A high sensitivity of EPR spectroscopy in the *W* range for small samples provides the

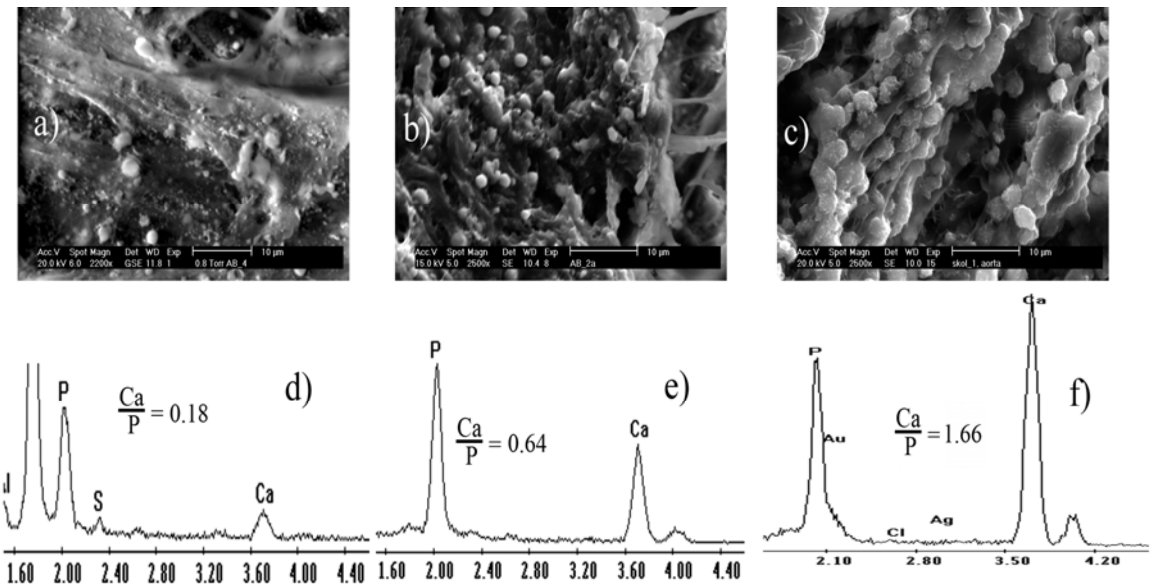

Fig.1. (a–c) Reliefs of the section of the inner aorta wall of patients with atherosclerosis and (d–f) the x-ray spectra of the globular fragments of the cut obtained using the microprobe analysis for low, intermediate, and high calcification degrees Ca/P = (a, d) 0.18, (b, e) 0.64, and (c, f) 1.66, respectively.

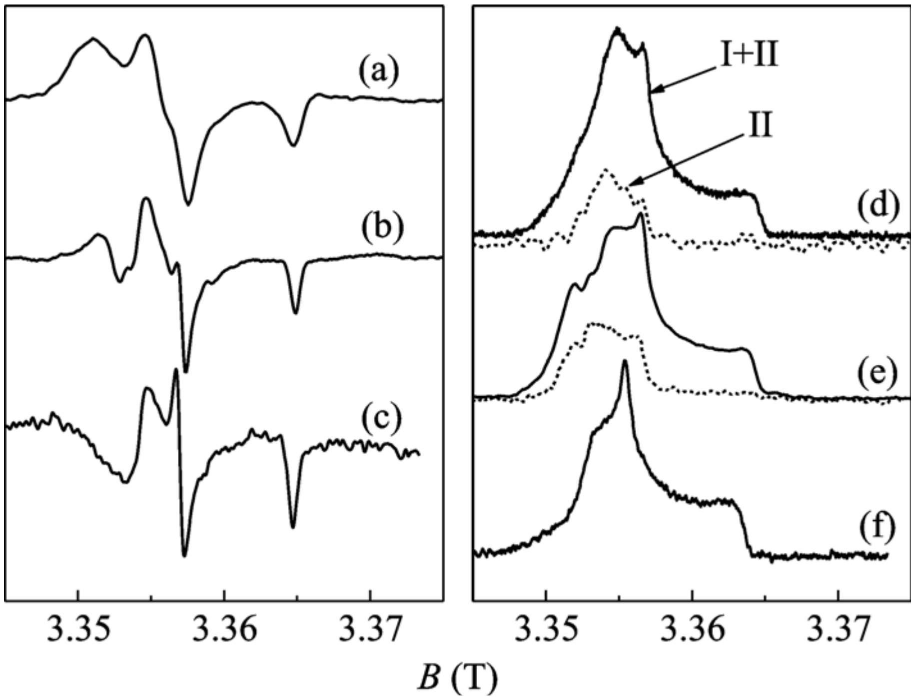

Fig.2. (a–c) Stationary EPR spectra and (d–f) spin echo spectra in the *W* range for the samples of (a, d) the atherosclerotic plaque with the maximum calcification degree, (b, e) enamel, and (c, f) mammoth tusk. The dashed line shows the EPR spectral component of center II.

premises for creating new, including low-invasive diagnostic methods for atherosclerosis and other diseases [1, 2].

The fabricated nano biomaterials with biomimetic structures and functions are expected to bear high bioactivities and unexpected biological effects, and ultimately can well serve as biomedicinal devices for human disease treatment. Many commercial substitute materials now have been developed, including natural and synthetic polymers, human bones, synthetic ceramics and composites especially hydroxyapatite [3].

Hydroxyapatite (HAp) is one of basic materials used in bone implant surgery. Due to such features as high biocompatibility, osteoconductivity, very good adaptation under *in vivo* conditions and chemical composition mirroring that of bone mineral and teeth enamel it is widely applied to fill bone defects in orthopedics, maxillofacial surgery as well as in stomatology. HAp nanoparticles have the potential to improve current disease diagnosis due to their ability to circulate in the blood and distribute in the body to image tissues and cells or to deliver a payload for bio-imaging and therapeutical applications. Sorption activity to a number of ions including those of some heavy metals and radio nucleotides makes the HAp based substances important not only in the biomedical area but also for waste management and in catalysts production [3, 4].

Conventional continuous-wave (cw) X-band EPR (frequency of about 9 GHz) is widely used for the detection, structure localization, qualitative and quantitative analyses of radiation defects (which are usually ascribed to the different carbonate, phosphorous, hydroxyl and oxygen radicals) created by X-ray, UV or gamma irradiation, for the detection of the intrinsic paramagnetic impurities, investigation of interaction with some paramagnetic ions such as Gd^{3+} or Mn^{2+} sorbed on hydroxyapatite or embedded into the lattice, etc [5 – 8]. In this work we demonstrate that the abilities of the modern conventional and pulsed EPR techniques, higher sensitivity and spectral resolution of the high-field EPR spectrometers could significantly extend the boundaries of EPR for the investigations of the HAP based tissues in very small amounts including nanoparticles.

In light of the long history of therapeutic application of HAp, it hypothesized that this compound may be of interest in the management of heavy metal-induced disease [4]. But little is known about the physicochemical background of the interaction of the impurities (including lead ions) even with the calcified bulk tissues and very few structural studies have been reported. Hydroxyapatite is a hexagonal material with 44 atoms per unit cell. Because of this large unit cell size, it is only recently that HAP has been studied using quantum mechanical methods.

Two nonequivalent calcium positions Ca(1) and Ca(2) are distinguishable in the HAP structure. The Ca(1) ions lie along a line parallel to the crystal c-axis and connected to each other by three shared oxygen ions resulting in a "Ca(1) channel". The Ca(2) ions form perpendicular to the c-axis triangles with two hydroxyl groups. This scheme forms an "OH channel". The 9-fold 4f Ca(1) and 7-fold 6h Ca(2) sites are both available for cationic substitution. The "hand-made" rule that the ions with the larger ionic radii and higher than Ca^{2+} electronegativity readily occupy Ca(2) positions seems to be not true at least in the investigated HAp nanomaterials (fig.3, [9]).

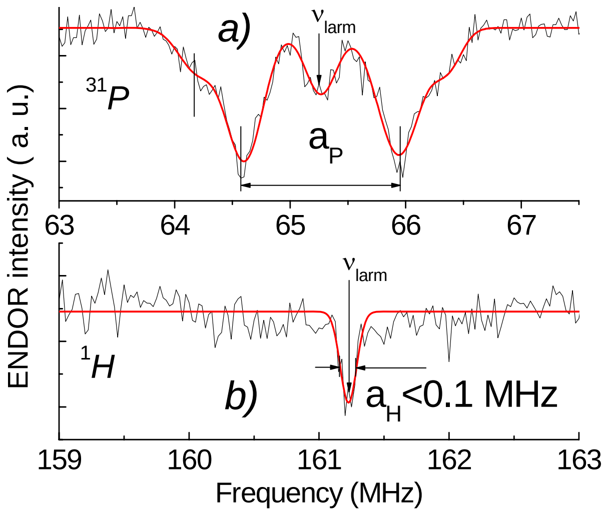

Fig.3. W-band ENDOR investigations of X-ray irradiated nanoparticles (20 nm and larger) of synthetic hydroxyapatite $Ca_9Pb(PO_4)_6(OH)_2$ show that the lead ions probably replace Ca(1) position in the hydroxyapatite structure while in calculations and bulk experiments Ca(2) site is preferable [8].

Among the diversity of the methods of the synthesis of the hydroxyapatites' powders and nanoparticles the wet (precipitation) chemical procedure involving the aqueous solutions of calcium nitrate, diammonium hydrogen phosphate and ammonium hydroxide is the most commonly in use. The main advantages of the process are that its by-product consists primarily of water and the probability of contamination during processing is very low, fast production rate and low processing costs. Its disadvantages are that it requires washing of the precipitate to remove nitrates and ammonium hydroxide and that the resulting product can be greatly affected by even a slight difference in the reaction conditions. For example, by means of EPR ad ENDOR techniques it is shown that during the wet chemical precipitation synthesis process nitrate anions from the reagents (by-products) could incorporate into the OH channels of the hydroxyapatite structure [10].

Conclusion

New possibilities of applying multifrequency (high-frequency) electron paramagnetic resonance approaches in medicine are demonstrated on an example of the investigation of a calcified atherosclerotic plaque. W-band pulsed EPR and ENDOR investigations of X-ray irradiated nanoparticles of synthetic hydroxyapatite $Ca_9Pb(PO_4)_6(OH)_2$ are performed. Incorporation of nitrates into the OH channels of HAp nanostructures is detected.

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