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Biological Activity of Detonation Nanodiamond and Prospects in Its Medical and Biological Applications

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Abstract—The present review summarizes and analyzes recent advances in the field of medical and biological applications of detonation nanodiamond and, on this basis, considers most promising ways of creation of anticancer and antimicrobial drugs, diagnostic agents, and nanocompositions for orthopedic surgery. In addition, progress in the surface chemistry of detonation nanodiamond is discussed and problems related to purposeful surface modification with a view to obtain detonation nanodiamond with desired properties ensuring their successful application in biology and medicine are considered.

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INTRODUCTION

The chemistry and technology of preparation and applications of carbon nanomaterials constitute a vigorously developing field of chemistry in the XXIth century [1–3]. We can now speak about a peculiar international nanotechnology boom [4–8] which has been pioneered by the United States National Nanotechnology Initiative [9–11]. It has led to the creation of radically new branches of human activity, nanotechnologies [6, 10–18] and nanobiotechnologies [12, 14, 19], which deal with such entities as cells and cell organelles [16] and enable purposeful structural variations of key biopolymers [15, 19, 20] to endow them with desired properties. Nowadays, studies in the field of nanotechnologies are performed at a molecular level via preparation of specific complexes with biomolecules, which makes it possible to solve problems of cell and molecular surgery, i.e., remove damaged cells and correct molecular defects. To solve these problems, radically new materials are necessary, and carbon nanomaterials play a leading role among them. The number of publications on the synthesis of carbon nanostructures and their potential practical uses tremendously increases [21–27]. Carbon nanomaterials include graphene [28], various fullerenes [29–31] and nanotubes [32–34], onion-like carbon [35–39], carbyne (linear acetylenic carbon) [40, 41], hexagonal diamond (lonsdaleite) [42], and detonation nanodiamond (or ultradispersed diamond) [24, 43–46]. The latter is a peculiar material prepared by detonation decomposition of mixed explosives under anoxic conditions [43–48].

Detonation nanodiamond (DND), a novel material discovered in 1980s, was initially designed for technological purposes [45, 49–53] due to relatively high specific surface (300–400 m^2/g) [46] and small particle size [54]. It should be noted that the DND particle size varies over a fairly broad range, from 4 to 100 nm; however, the major part has a size of 5–20 nm [46, 54, 55]. The DND grain size distribution is determined by a number of factors, but primarily by the conditions of synthesis [46, 56–59]. Undoubtedly, interest in DND is also supported by large reserves of starting materials, relatively low cost as compared to other nanocarbons that could became available on an industrial scale (fullerenes and nanotubes), as well as by the possibility for production at a level of more than 10 tons per year, which considerably exceeds market needs. Such production volume for fullerenes and nanotubes is unlikely to be attainable since there are serious difficulties in the implementation of laboratory developments on a large-scale level.

The practice of detonation synthesis, theory of DND grain formation, and problems related to

aggregation of of ultradispersed diamond particles, purification technology, and isolation of DND after detonation synthesis (detonation carbon) were the subjects of numerous publications. However, these issues fall beyond the scope of the present article. Interested readers are referred to monograph [46].

DETONATION NANODIAMOND AS EFFICIENT ADSORBENT FOR MEDICAL AND BIOLOGICAL PURPOSES

Until recently, DND was a traditional subject for studies in the fields of solid state physics and chemistry [60, 61], materials science [52, 62–64], electronics [65], and electrochemistry [49, 50, 52, 53, 66, 67]. In addition, physicochemical properties of DND, primarily highly chemically active surface of nanoparticles [68–82], determine powerful sorption capacity of DND with respect to various organic compounds [82–84], metal ions [85, 86], and biological macromolecules [87–89]. Due to pronounced affinity for bioligands, nanodiamond has found application in various fields of biology [46].

The efficiency of sorption was revealed with respect to both anions [90] and simple neutral molecules such as HF, F_2, HCl, and $CClF_3$ [93]. It was shown the DND not only adsorbs well the above compounds in model systems but also efficiently extract them from real industrial discharges, which ensured practical application of DND in environment protection [91].

Further studies revealed the ability of DND to adsorb positively charged species such as alkali and alkaline earth metal cations [90]; fairly high selectivity of DND for cations ensured efficient separation of a mixture containing 3–4 alkali and alkaline earth metal salts [90], which would be a difficult problem if other adsorbents were used. Detonation nanodiamond was also reported to adsorb oxoacid anions, in particular arsenite, arsenate, selenite, selenate, dichromate, molybdate, and tungstate ions [90], i.e. prospects in environmental applications related to separation of complex mixtures of various substances have been outlined even in pioneering studies on the use of DND.

Thus it was demonstrated that DND is a universal adsorbent, which stimulated rapid development of studies in this line, primarily of those concerning sorption of complex organic molecules, biomonomers and biopolymers [92]. In particular, DND was shown to efficiently adsorb carbohydrates [93], amino acids [94], humic compounds [95, 96], nucleic acids [97], and simple and complex proteins [93, 98]. The application of DND as an adsorbent has been developed most extensively [93, 98–105], and specific prospects were opened just in the use of DND for medical and biological purposes [98, 99, 106, 108]. Relevant studies rapidly acquired applied character, and DND tuned out to be very effective for the isolation of various biomolecules from complex biological systems [93, 95, 99, 106]. Detonation nanodiamonds have found application for fractionation of similar molecules, purification of proteins, and isolation of DNA [96, 99, 106].

Stimulation of studies on sorption of biomolecules and development of efficient methods for the separation of complex mixtures of biologically active substances are determined mainly by the set of unique properties of DND, the most important of which are highly developed surface, high sorption capacity, pronounced surface polymorphism, hydrophilicity, small particle size, retention of native properties of biomolecules after sorption, and the possibility for purposeful surface modification with a view to endow the material with desired properties [46]. Nanodiamond was reported as a new stationary phase for chromatography [95, 99, 106, 108–111], especially for HPLC [94, 112], which is indispensable for separation of complex mixtures of biomolecules [113]. Chromatographic methods are often used in combination with other modern identification and detection methods, e.g., mass spectrometry [99, 106, 107]; thus DND provides a promising material for modern analytical techniques [99, 100]. Taking into account that DND surface contains a large number of protogenic functional groups, this material is very interesting for ion-exchange chromatography [85, 114].

Technologies have been developed for the preparation of modified nanodiamonds with high colloidal stability in dispersed media and adapted to medical and biological studies, which have no analogs in the world [83, 115–119]. It was proved that nanodiamond can be used as polyfunctional adsorbent for efficient large-scale isolation and purification of proteins from primary biological materials and natural sources [88]. Detonation nanodiamond turned out to be an ideal agent for fine additional purification of commercial protein preparations [120, 121]. The use of DND in column chromatography of biopolymers is equally promising [122]. A sorbent for the isolation and purification of proteins by atmospheric pressure column chromatography has been developed for the

first time on the basis of nanodiamond and an inert polysaccharide matrix [123]. Modified nanodiamond was shown to adsorb linear but not ring forms of DNA molecules [97, 124, 125], which suggests the possibility of using nanodiamond for the design of new technologies in molecular biology and genetic engineering. It was reported that some enzymes adsorbed on ND surface retain their catalytic activity [88, 126]; therefore, indicator and diagnostic test systems may be created on the basis of nanoparticle–marker protein complexes [127–129]. Multiuse complexes for medical diagnostics can be obtained from ND particles bearing several enzymes on the surface [121].

However, there are some difficulties related to the use of DND as efficient sorbent for the isolation and purification of biological substances and diagnostic or indicator systems. First of all, the sorption capacity strongly depends on the particle size, so that effective procedures for fine fractionation of DND suspensions and enhancement of the colloidal stability of DND suspensions are necessary. Interactions of DND with proteins are studied most extensively, and just these studies revealed a strong dependence of the DND sorption capacity on the particle size [130]. Here, the model protein was relatively small hemoprotein enzyme cytochrome *c* which is involved in tissue respiration processes and is readily extractable from biomaterials [131]. The molecular weight of cytochrome *c* isolated from bovine heart is 12000 [131, 132]. Cytochrome *c* is well adsorbed by DND clusters, presumably via electrostatic interactions with positively charged amino acid residues in the protein fragment; cytochrome *c* exhibits pronounced basic properties [131], and its isoelectric point falls into the pH range from 10.4 to 10.6 [133]. Numerous studies have shown that DND particle surface possesses a large number of acid groups [136], and an aqueous suspension of DND has an acidic pH value [46]. It is difficult to remove adsorbed cytochrome *c* from DND particles by repeated washings.

We have refined the relations found previously [129] and revealed a clear dependence between the sorption capacity of DND and particle size in the range from 20 to 100 nm.

DND particle size *R*, nm	20± 10	50±20	100± 30
Sorption capacity *q*, μg of cytochrome *c* per mg of DND	0.35	0.25	0.14

Table 1. Molecular weight and isoelectric points of some proteins [131–133] readily adsorbable by DND

Protein or peptide	Molecular weight	Isoelectric point, pI
Vasopressin	1084	10.9
Hemoglobin	68500	6.8–7.0
Ovalbumin	53000	4.6
Bovine serum albumin	65000	4.7
Obelin	21000	4.7
Horseradish peroxidase	40000	3.2–4.7
Growth hormone	21000	10.9
Human immunoglobulin	150000	6.2-6.5
Cytochrome *c*	12000	10.4–10.6
Lysozym	14000	10.7

Increase in the particle size is accompanied by considerable reduction of the sorption capacity with respect to cytochrome *c*; therefore, an important problem is to enrich DND in small-size fraction.

Further analysis of the results showed that the sorption capacity (q) of DND is linearly related to the particle size (R).

$$q = (0.39\pm0.05) - (0.0026\pm0.0004)R;$$

$$n = 7,\ r = 0.97.$$

It should be noted that the sorption capacity of DND toward proteins is also largely determined by the protein nature. The sorption capacity of DND particles with a size of 100 nm with respect to lysozyme (an enzyme that damages bacterial cell walls) is 80 μg/mg; i.e., the q values for cytochrome *c* and lysozyme differ by a factor of almost 600, the DND particle size being the same. Obviously, the nature of protein and its properties are factors determining the sorption capacity of DND [135]. It was interesting to compare the sizes of globules of these proteins to find out how the size of the protein molecule is important for the binding process. The molecular weights of cytochrome *c* and lysozyme are fairly similar, 12000 and 14600, respectively [131, 136]. Both proteins are globular and readily soluble in water, and the sizes of their globules are also similar. Therefore, the size is not a factor determining the sorption capacity. As noted above,

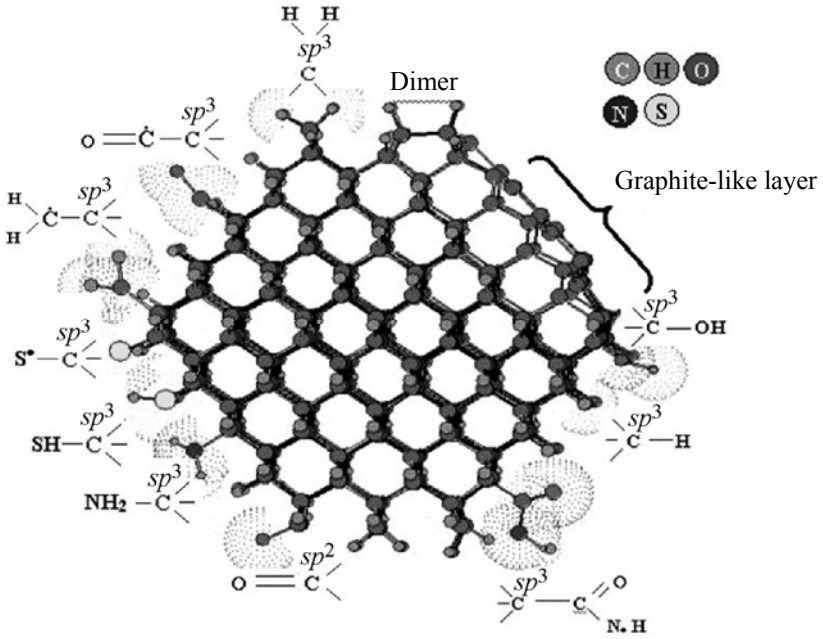


Fig. 1. A model of a DND particle, reflecting the surface structure.

binding of cytochrome *c* to DND surface is likely to be mediated by electrostatic interactions. Therefore, acid–base properties of the protein could be crucial. However, as seen from the data in Table 1, the acid–base properties of lysozyme and cytochrome *c* are very similar. Thus, the sorption capacity is determined by other fine structural features of adsorbed proteins.

The series of proteins shown to be actively bound by DND rapidly expands [85, 87–89, 129, 137–139]. The ability to bind to DND particles was revealed for many proteins performing diverse functions in organisms. Not only cytochrome *c* but also obelin, luciferase, peroxidase, cholesterol oxidase, cholesterol esterase, growth hormone, immunoglobulins (including IgG), bovine serum albumin, rabbit antibodies against intact mouse IgG (RAM), angiotensin I, gramicidin S, bradykinin, myoglobin, ovalbumin, soybean trypsin inhibitor, growth hormone receptor, as well as short peptides were shown to be efficiently sorbed by DND particles [85, 87–89, 98, 99, 106, 107, 128, 129, 137–139]. Thus, DND surface efficiently binds proteins performing catalytic, regulatory, receptor, transport, protective, reserve, medication, nutritional, and other functions. Good sorption capacity is observed toward proteins and peptides with very different acid–base properties and molecular weights (Table 1). High sorption capacity of DND is retained over a broad pH range [140]. As follows from the data in Table 1, the molecular weight of readily adsorbable proteins varies over five orders of magnitude, and their acidity changes in the pH range from 3 to 10 (by the isoelectric point). There-fore, we cannot assert that electrostatic interactions play the determining role in the adsorption of proteins and peptides by DND particles.

High sorption efficiency of DND toward various proteins over broad ranges of acidity and molecular weight predetermined development of studies on practical applications of DND in the chemistry of proteins and clinical diagnostics. It was shown that DND quantitatively adsorbs proteins from the urine of patients with pancreatic diabetes. The adsorbed material can be quantitatively recovered by elution [99, 106].

We utilized high sorption capacity of DND toward proteins in the development and optimization of a non-instrumental immunochemical system for diagnostic of various forms of syphilis, including syphilis in children [141–147]. The use of DND as a basis of such systems could ensure diagnostics of any infectious disease provided that the corresponding specific antigens are efficiently adsorbed the surface of DND particles. The diagnostic system is a complex of an active support, i.e., DND particle, with a specific antigen held on its surface. The diagnosticum operates by the “yes or no” principle and is based on the agglutination occurring if a biomaterial being analyzed contains specific marker proteins (antibodies). Agglo-

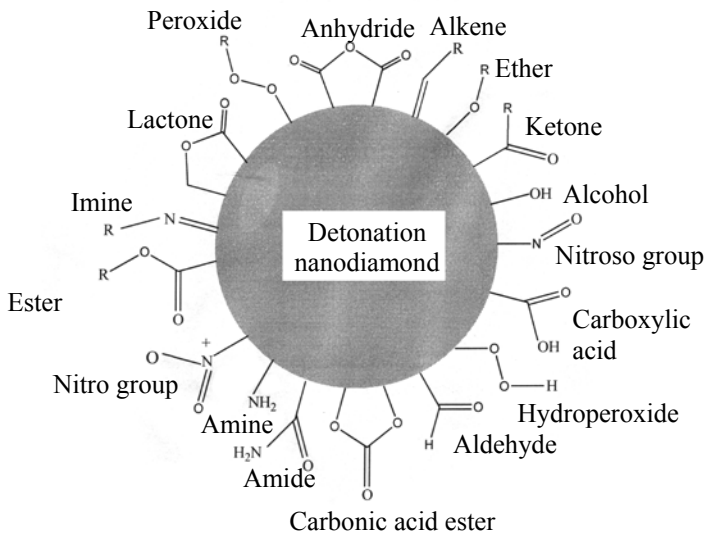


Fig. 2. Surface functional groups on a DND particle identified by physicochemical analysis methods.

merates formed as a result of agglutination can be detected visually. No agglutination occurs if a material contains no specific antibodies. Important advantages of such diagnostic system are its simplicity, low cost, reliability, and the possibility for express analysis; its operating parameters remain unchanged after storage for more then two weeks at room temperature.

With a view to understand the mechanism of binding of chemical compounds with various structures and properties to DND surface it is necessary to consider first the structure of DND particle.

SOME STRUCTURAL SPECIFICITIES OF DND PARTICLES RELEVANT TO THEIR MEDICAL AND BIOLOGICAL APPLICATIONS

Despite a large number of publications on the structure of DND particles [77, 148–150], the problem has not yet been solved finally. It was noted that the elemental composition of DND is complex and difficultly determinable; however, the formula $C_{100}H_{23.7}N_{2.4}O_{22.9}$ was given in [151]. Many authors have shown that the composition of DND strongly depends on the conditions of synthesis and subsequent treatment, primarily on the isolation and purification methods. Therefore, we believe that, unlike such carbon allotropes as nanotubes and fullerenes whose elemental composition is strictly definite. DND should be considered to be a chemical material. In view of the aforesaid, of exceptional importance is the problem of standardization of samples used in various physicochemical and biological studies. Nevertheless, despite the above difficulties, surface chemistry of DND actively progresses, and computer models of DND particles have been designed to explain their physicochemical properties.

Up to now, it has been proved that a DND particle has a complex structure; it consists of a diamond core surrounded by a shell with irregular carbon structure, where carbon atoms occur in different hybridization states, (mainly sp^2); also, there is a layer of surface functional groups which can be identified by a complex of spectral and analytical methods (IR and Raman spectroscopy, solid-phase ^{13}C NMR, electronic spectroscopy, elemental analysis, etc.) [46, 96]. Samples of DND were found to contain carbonyl, carboxy, amide, nitro, hydroxy, and other functional groups [24, 46, 96] whose character strongly depends on the manufacturer and purification method [24, 46, 152].

The first model representing the structure of a DND particle is that proposed in [153]; it was clearly shown that the diamond core is covered by an area with broken diamond structure and that the particle surface bears a large number of various functional groups (Fig. 1) [154]. Further studies on the DND particle structure [46, 155] revealed the presence of graphite nanoplates, onion-like carbon, and probably metal particles embedded in the surface layer. In addition, physicochemical methods revealed lactone, anhydride, and

imine groups on the surface of DND particles [46]. Figure 2 shows the up-to-date structure of a DND particle, which was proposed on the basis of the latest data [96]. It should be emphasized that this scheme reflects only the most probable spectrum of functional fragments. Far from all functional groups shown in Fig. 2 are necessarily present in each DND sample. In keeping with the propose structure, DND particles possess protogenic fragments, so that a DND particle with surface functional groups may be regarded as an amphoteric species capable of being ionized or protonated depending on the acidity of the medium. Various ionogenic polar fragments and groups endow DND particles with high hydrophilicity [156], which provides an important advantage of DND over other nanocarbon materials from the viewpoint of medical and biological applications. The presence of a variety of functional groups on the surface of DND particles should ensure efficient binding of chemical compounds with different structures and acid–base properties. Presumably, just that unique structure is responsible for efficient adsorption of cations, anions, nucleic acids, proteins, and other complex molecules by DND particles.

Proteins are held on the DND surface with different strengths. For example, adsorbed cytochrome *c* is difficult to remove from DND, whereas 40% of adsorbed bovine serum albumin can be desorbed by fivefold washing [129]. The most essential difference between the above proteins is their acid–base properties. Cytochrome *c* is a basic protein, and acidic nature of functional groups on the DND surface is likely to contribute much to the protein binding strength, though the mechanism of protein binding to DND surface is fairly complex (as follows from analysis of published data).

Taking into account the complex structure of adsorbed molecules, broad spectrum of their acid–base properties, the presence of various coordination centers in protein molecules, and the presence of various functional groups on the surface of DND clusters, analysis of the mechanisms of protein binding to DND attracts strong interest. Obviously, the process of protein adsorption involves several mechanisms, including ionic, coordination, hydrophobic interactions, and probable covalent bonding. Studies on the mechanisms of protein binding to DND surface and on the effects of protein properties on the sorption efficiency should help one to find ways for enhancing retention of proteins and peptides by DND particles, which is necessary for further practical uses of such complexes.

On the other hand, despite obvious advantages, DND is not free from some drawbacks essential for its application in biotechnologies, which are related to low colloidal stability of nanoparticles [24]. As a result, it is impossible to obtain stable DND hydrosols without ultrasonic treatment, and it is difficult to maintain a strictly definite DND concentration in hydrosols [46]. Physicochemical properties of DND could not be affected via modification of the diamond core. Therefore, the properties of DND can be altered only by modification of the particle surface.

Detailed studies on the mechanisms of protein binding to DND surface and advances in the modification of DND surface are likely to ensure fine tuning of the sorption capacity and particle structure to fit a certain protein type. These studies seem to be promising since chemically modified DND also displayed a strong ability to bind various biomolecules. Strong binding ability toward various biomolecules was found for DND samples with a high concentration of amino groups on the cluster surface [101].

Covalent bonding of proteins to surface functional groups on DND particles cannot be ruled out. The formation of strong complexes by DND and proteins via covalent bonding involves chemical modification of the DND surface, whereas increase in the dispersity is of secondary importance, though essential. Thus, to achieve a considerable progress in the research of protein–DND interactions, it is necessary to develop systematic studies on the chemistry of DND surface and methods for its purposeful modification under mild conditions, i.e., to develop methods of synthesis of complex DND-based structures containing bio-organic radicals. To some extent, this process may be regarded as analogous to peptide synthesis on a solid matrix.

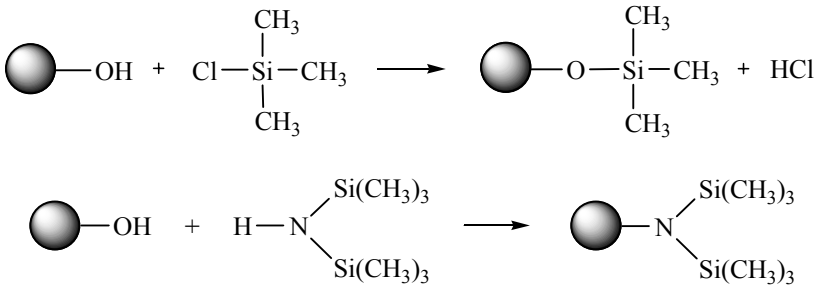
The design of strategy of such work requires further systematic studies on the structure of DND cluster surface. Up to now, a lot of data on this topic have been accumulated in the literature [63, 69, 70, 74, 157–164].

MODIFICATION OF DND PARTICLE SURFACE FOR MEDICAL AND BIOLOGICAL PURPOSES

The presence of various functional groups on the surface of DND particles enables several ways of

purposeful surface modification which affects a considerable part of atoms constituting a DND particle since about 15% of atoms in a 4-nm particle are those located on its surface and are therefore accessible for modification [46]. Modification can be performed both in a solvent and in the gas phase. Three ways of surface modification seem to be promising: oxidation, reduction, and direct replacement of functional groups on the surface of DND clusters, which follow different mechanisms [74, 96, 165–168].

A fairly well studied modification method is replacement of surface functional groups. Among a variety of surface functional groups, a considerable area is occupied by hydroxy groups that are convenient structural fragments for modification via replacement [74, 80, 159]. In particular, surface hydroxy groups on DND particles can be replaced by trimethylsiloxy and bis(trimethylsilyl)amino by reactions of DND with chloro(trimethyl)silane and hexamethyldisilazane, respectively [169]. The silylation product is a chemically modified DND cluster with covalently bound trimethylsilyl group.



The process includes a number of steps, the first of which is transformation of surface hydroxy groups into a fragment that can readily be replaced by nucleophiles. Replacement of the surface hydroxy groups by trimethylsiloxy or trimethylsilylamino makes DND particles more hydrophobic, which essentially changes physicochemical properties of DND suspension. Such modification ensures purposeful control over the properties of DND particles and opens wide prospects in the design of systems for delivery of biologically active substances, whose controllable surface properties facilitate penetration through cell membranes.

A large number of DND derivatives of the general formula ND–O–Si(OMe)$_2$(CH$_2$)$_3$–NHR (where ND is a DND particle, and R = H, COX, Gly, Ser, Ph, or Gly-Phe-Cly-Phe) were synthesized according to the above procedure [170]. Such biologically important fragments as amino acids (glycine, serine, and phenylalanine) and Gly–Phe–Gly–Phe oligopeptide were covalently bonded to DND particles through silicon linkers [170]. Covalent bonding of a peptide fragment through a linker does not restrict its high mobility, which should facilitate its further participation in various chemical transformations; these transformations may be regarded as transformations of oligopeptides immobilized on a solid support (DND clusters). Modification of DND particles with peptide fragments provides a way to peptide synthesis on a solid nanomatrix; taking into account high dispersity of DND, the rate of polypeptide chain growth on ND particles may be fairly high.

Further studies have shown that the surface hydroxy groups can be successfully replaced by halogens [74, 159]; the latter can be substituted by cyano and phenyl groups and more complex fragments such as amino acid residues [74, 159, 163, 171–173]. However, these processes require fairly severe conditions. For example, substitution of hydroxy groups by chlorine is successful only at 425°C [74, 149]; such conditions are inadmissible for appending protein or polypeptide fragments.

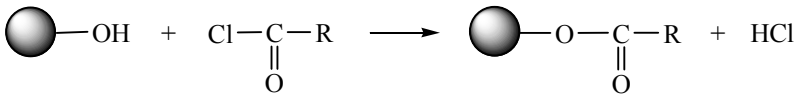
Another way of DND surface modification consists of replacement of hydroxy groups by hydrogen (i.e., reduction) [174]. The reduction also requires very drastic conditions (a stream of hydrogen at 850°C) and leads to sharply increased hydrophobicity of DND clusters. Hydrophobization of the surface of DND particles may be achieved via replacement of covalently bonded halogen atoms in halogenated DND clusters by hydrocarbon radicals via reactions with organolithium and organomagnesium compounds. Hydrophobization of DND clusters and enhancement of their affinity for nonpolar media is important from the viewpoint of creation of antifriction additives, antibacterial agents for oils, and antimicrobial

additives for organic coatings. Such modification is quite feasible since the replacement of surface functional groups can now be carried out in nonaqueous medium [80].

$$ND–Hlg + LiAlk \rightarrow Alk–ND + LiHlg$$

$$ND–Hlg + AlkMgBr \rightarrow Alk–ND + MgBrHlg$$

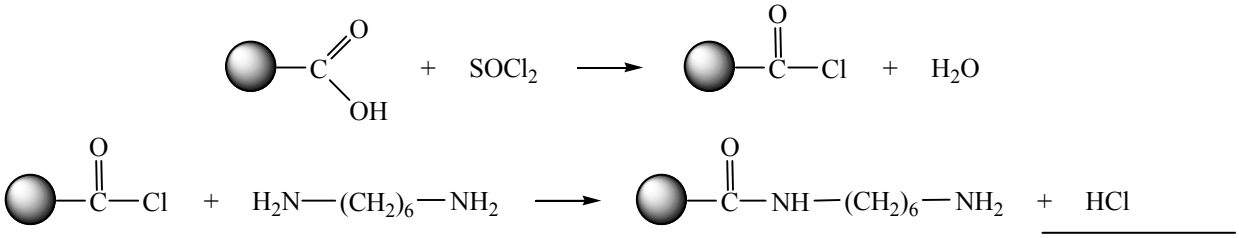
Hydrophobization of DND particles is also possible in polar medium, via replacement of hydrogen in the surface hydroxy groups by acyl radical with the use of carboxylic acid chlorides [175].



The products are well dispersed in organic solvents. The hydrophilicity of modified particles is lower by a factor of 20 than that of unmodified material. Of particular interest is modificatin of DND surface with long-chain acyl residues containing 10 to 20 carbon atoms. Such acyl radicals are the most important structural units of transport molecules capable of penetrating cell membrane barriers. Modification of DND with biologically active radicals may considerably increase their ability to penetrate cells.

Chemical modification of DND in nonaqueous medium is a logical extension of studies aimed at obtaining stable DND suspensions in multicomponent mixtures with an organic solvent as the major component. Stable DND sols were prepared in aqueous ethanol containing up to 80% of the latter, as well as in dimethylformamide and dimethyl sulfoxide [184]. The possibility for obtaining stable suspensions of DND in DMSO is an important achievement [84, 176], for this solvent is widely used in medical practice due to its ability to readily penetrate tissues [84, 176].

In future, functionalization of DND with unsaturated hydrocarbon fragments would be interesting. The products may be consistently incorporated by covalent bonding into polymeric films for medical and biological purposes. Another way of covalent bonding of DND to polymeric matrix with a view to improve physicomechanical characteristics and endow materials with other useful properties (e.g., bactericidal) could be based on modification with polyamines. The feasibility of this approach follows from the data of [177] where DND particles were modified with ethylenediamine. Here, the starting material was DND particles enriched in surface carboxy groups.



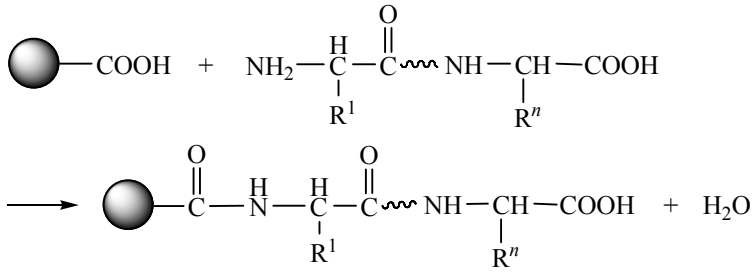
Covalent incorporation of DND particles into a polymeric matrix is especially important for medical polymers since it prevents loss of biologically active material (i.e., DND itself) and biologically active fragments covalently bound to the DND surface) into biological medium, so that the biological effect is localized in an ultrathin polymer film.

However, modification of DND surface with hydrocarbon fragments and polyamines is a matter of future studies, for practical application of such materials requires a fairly large volume of production of modified DND, which in turn implies large-scale manufacture of nanodiamond standardized by not only particle size but also character of surface functional groups. The latter problem is especially difficult since surface functionalization is determined mainly by the conditions of the post-synthesis treatment rather than by the conditions of detonation synthesis. Product standardization is obligatory in large-scale manufacture of modified DND, for the conditions of their synthesis should be thoroughly detailed and should be kept unchanged regardless of the starting material lot.

As we already noted, the synthesis of DND derivatives containing a biologically active fragment seems to be promising [170]. Addition of, e.g., a peptide fragment through a silicon-containing linker, is

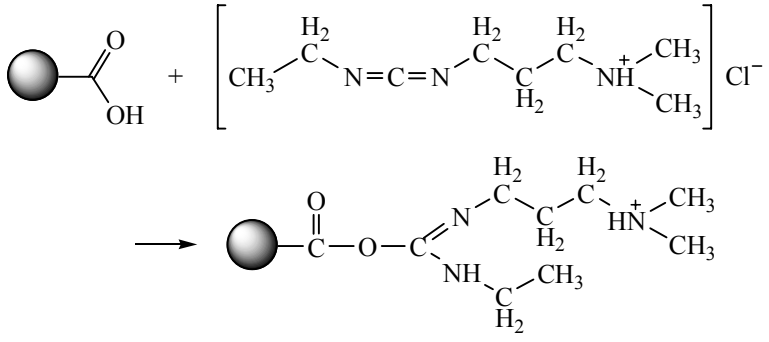
not the only possible way of such modification. A fairly efficient method for the addition of peptide fragments is based on preliminary oxidation of DND particles with ozone, which considerably increases the number of surface carbonyl groups on DND cluster [178]. Enrichment of DND surface in carboxy groups may be achieved by treatment with perchloric [179] or nitric acid at elevated temperature and increased pressure through intermediate formation of nitric acid esters on the cluster surface [46]. Treatment with oxidants strongly appreciably increases the number of surface carboxy groups; however, elevated temperature promotes intense decarboxylation [180]; this eventually leads to hydrophobization of the surface rather than to increase in its hydrophilicity. Oxidative modification may involve the outer layer of carbon atoms in DND clusters, thus affecting their sp^3-hybridization [181]. Damage of the diamond structure is possible only in samples after having been subjected to oxidative purification, in which the surface contains almost no non-diamond carbon [46].

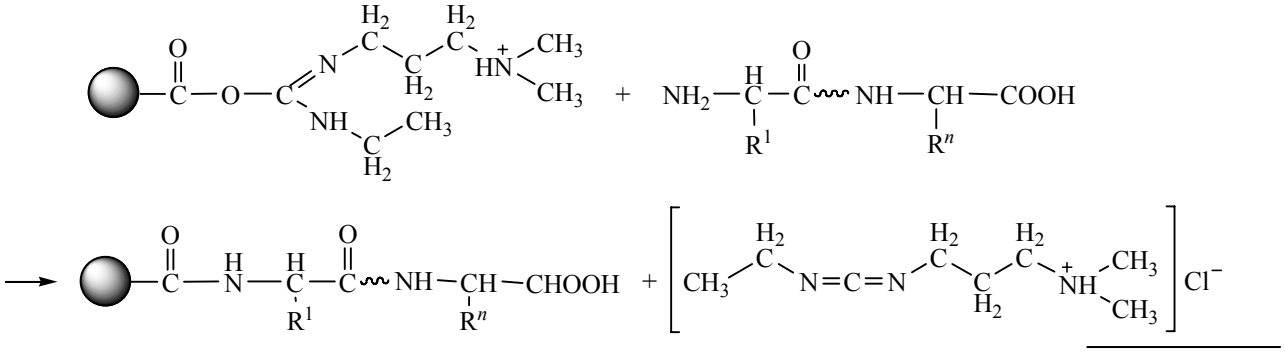
If carbonyl fragments are present on the surface of DND particles, their mild functionalization with amino acids, peptides, and proteins is possible. Functionalization with preliminary oxidation is advantageous due to the fact that peptide fragments add to DND particles via covalent amide bonding with surface functional groups. This approach ensures addition of various polypeptide fragments in the natural mode, at the N-terminus.



However, the potential of direct functionalization is restricted primarily by serious steric hindrances appearing due to very close position of the carbonyl fragment to the cluster surface; it may also be located in a specific pocket formed by other functional groups. In addition, carboxy groups on the DND surface are usually covered by a tight hydration shell and/or are involved in hydrogen bonding with water molecules.

The difficulties related to steric shielding in the addition of large molecules (such as peptides and proteins) may be overcome via consecutive surface reactions including the following steps: (1) oxidation of DND to increase the number of surface carboxy groups; (2) preparation of intermediate functional derivatives; and (3) replacement of transient functional groups by target peptide fragments. The key problem in such transient modifications is proper choice of a leaving group which should effectively react with a DND cluster and then be readily replaced by peptide fragment. Functionalization of DND with peptide fragments using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride was reported [182, 183]; this reagent is known to readily react with various organic compounds containing a carboxy group. Addition of carbodiimide to the surface carboxy groups gives a covalently bound derivative.

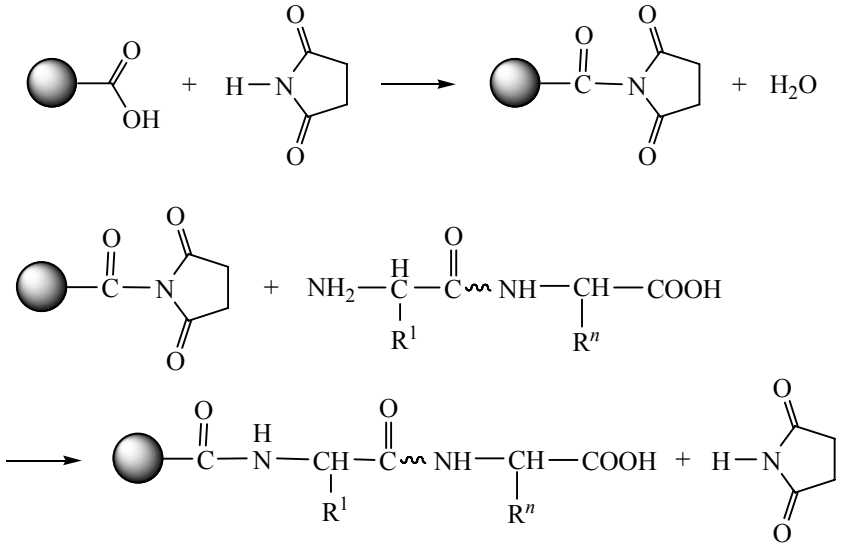




The transient fragment is then replaced by peptide fragment which adds to the DND cluster by the terminal amino group.

As an example of such protein fragment, fairly large and complex growth hormone was studied [182]. The above transient modification scheme is general, and it does not change essentially as applied to any other protein ligand.

Transient DND surface modification with the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is by far not a solitary surface modification method utilizing readily leaving groups. Transient fragments in the above functionalization method were selected taking into account that the substrate (DND after oxidative treatment) was enriched in surface carbonyl and carboxy groups. Succinimide fragment is a traditional functional group ensuring good results in the synthesis of carboxylic acid derivatives [184]. It was used in the synthesis of functionalized DND derivatives. Preliminary functionalization of DND particles with succinimide gave succinimide derivative, and the succinimide fragment was then replaced by peptide or protein.



A considerable disadvantage of this procedure is that the addition of a peptide fragment is possible only through its N-terminus. In this case, the final product will always exhibit acidic properties especially pronounced in the addition of short peptides, for the number of covalently bound fragments may be fairly large. Furthermore, the addition of a polypeptide exclusively at the terminal amino group cannot yet be achieved. Analogous reaction is possible with side-chain amino groups of basic amino acids, primarily of lysine and arginine, i.e., the modifiction process yields a complex product having surface peptide fragments with irregular conformations. This should be taken into account in the addition of fairly large peptide molecules characterized by a definite native three-dimensional structure responsible for their biological activity.

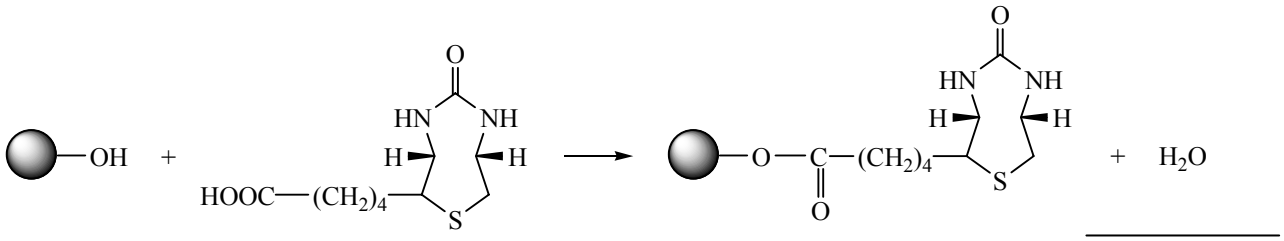
The problem of conservation of protein conformation upon immobilization on DND clusters is very important. There are published data on covalent immobilization of fairly large protein molecules on DND clusters [170, 174, 185–189]. The protein in these associates retains its native properties [182], primarily its enzymatic activity, over a long time, sometimes up to 15 days at room temperature. The long-term conservation of the activity of protein enzymes immobilized on DND clusters indicates that the architecture of protein globule is retained, and the duration of activity suggests even some stabilization due to complex formation. The conservation of native properties of proteins upon immobilization was reliably proved by studying the activity of DND loaded by enzymatic systems responsible for bacterial cell lysis. A suspension of DND with covalently bonded lysozyme (by the amino group) induced lysis of of *E. coli* cells upon contact over a period of 4 h [182]. Protein-loaded DND clusters are promising from the viewpoint of development of immunoenzymatic assays and biochemical analytical systems. However, the available proofs are clearly insufficient to contend that protein immobilization occurs just via covalent bonding. A DND particle with a size of 4–10 nm could bear several thousand protein molecules. Obviously, the mechanisms of protein binding may be different, and most protein molecules are likely to be adsorbed by the nanocarbon material. Protein molecules can be held via electrostatic or weak dispersion interactions, and only a small amount of protein may be linked to surface nanodiamond groups by covalent bonds. The difficult removal of a protein from the DND particle surface does not prove covalent bonding; for example, some proteins, in particular cytochrome *c*, cannot be removed even by repeated washings [133], though no direct proofs for covalent bonding of the protein to DND particles were given; the starting material was not subjected to oxidative modification, and the number of surface carboxy group therein was minimal. Therefore, while preparing complex functional DND derivatives it is also necessary to ensure "controlled" functionalization, i.e. generation of a definite number of carboxy or hydroxy groups per unit area of DND particle surface. A solution of this problem is possible, for chemical treatment of the same DND material could lead to increase in the number of both hydroxy and carboxy groups on the surface. Treatment of carboxylated DND particles [170, 187, 190, 191] with strong reducing agents, such as diborane or lithium tetrahydridoaluminate, reduces the number of COOH groups or even completely removes them from the DND surface, whereas the concentration of hydroxy groups considerably increases [46]. The subsequent treatment of reduced DND with a strong oxidant enriches the surface with carboxy groups [46]. Thus, the starting material may be appropriately prepared by chemical treatment to further functionalization with a view to endow it with desired biologically important properties.

As already noted, retention of native properties of polypeptides and proteins is the most important problem related to their immobilization on the surface of DND clusters. Their native properties may also be affected as a result of sorption [192] which involves both hydrogen bonding and dispersion interactions responsible for steric architecture of proteins and hence for their functionality in biosystems [131]. The oxidation, substitution, and reduction processes with participation of surface functional groups in DND often require fairly severe conditions causing complete denaturation of proteins. Therefore, it is essential that covalent coupling of protein fragments to DND clusters be carried out under mild conditions. For this purpose, surface functional groups may be preliminarily activated by various physical methods, e.g., UV or microwave irradiation, ultrasonic treatment, and gamma irradiation. However, the change in the surface energy of DND particles achieved as a result of such activation rapidly vanishes, whereas preliminary addition of a protein modifier into the system is impossible since the above physical treatment induces denaturation of proteins. Therefore, physical activation may be applied only at the stage of introduction of transient fragments, which could lead to increase of their number and hence of the number of coupled peptide fragments. Nevertheless, even when the addition of biomolecules to DND particles is carried out under mild conditions, it is necessary to verify whether the native properties of the attached bioligand were retained. For this purpose, enzymes are the most convenient models: variation of the enzymatic activity indicates the degree of damage to the native protein structure. Many enzymes, in particular luciferase, catalase, and cholesterol oxidase, retain their catalytic activity at the native level after immobilization on DND particles [128, 193], which suggests very insignificant structural reorganization of these proteins, primarily in the vicinity of the active center; rigid relation between the structure and activity in enzymology is well known [194].

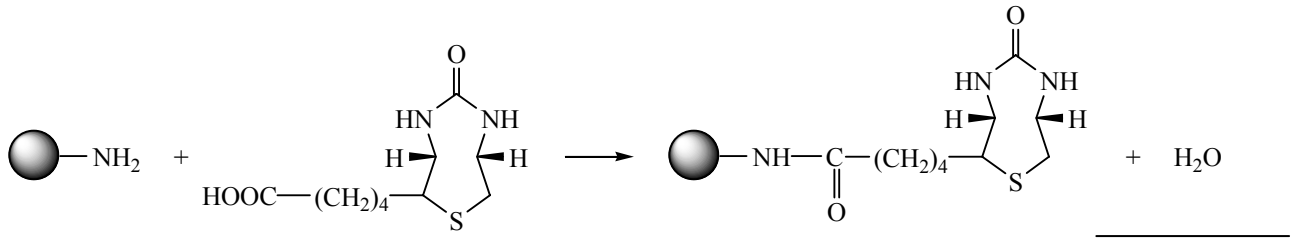
Another promising way of studying structural variations of proteins upon immobilization on a carbon support (DND particles) implies the use of specific receptor proteins. It is well known that receptor function is the most important function of membrane proteins [97, 131, 195]. Ligand–receptor interactions are characterized by high selectivity. Ligand–receptor complementarity is determined by specificities of high-level structure of the interacting proteins. If a protein receptor and a protein ligand immobilized on the surface of DND cluster effectively interact with each other to produce the corresponding complex, it may be asserted that no essential change in the conformation of the protein ligand has occurred. Studies performed in a number of laboratories [182] have shown that binding of many proteins to DND surface has not impaired their native activity. A classical example is retention of the ability of immunoglobulin (IgG) to bind to the corresponding receptor [196]. It was shown that IgG is effectively coupled with DND particles to give the complex IgG–DND. Mouse IgG receptor (RAM) was used as test protein. Immunoglobulin and RAM form the complex IgG–RAM. Coupling of RAM with DND particles gives the complex DND–RAM. It was interesting to elucidate whether the proteins immobilized on DND particles are capable of interacting with each other. It was found that the immobilized proteins did not lose their ability to form a complex like DND–IgG–RAM–DND. Taking into account that one DND particle can bear several thousand protein molecules, it was also interesting to find out how the presence on the DND surface of other proteins inert toward IgG receptor will affect the binding ability. Bovine serum albumin (BSA) was selected as an inert protein, and the complex BSA–DND–IgG was thus obtained. The presence of BSA in the complex did not affect to an appreciable extent binding of immobilized immunoglobulin to the receptor protein immobilized on DND particles as well. In this case, the complex BSA–DND–IgG–RAM–DND formed. Retention of native properties was observed for a broad series of proteins [182, 185].

Insofar as native properties of proteins remain unaffected upon immobilization on DND particles, the latter may be quite efficient as means for targeted drug delivery, including delivery of complex, e.g., peptide drugs, as well as for molecular diagnostics. The possibility for the addition of a large number of ligands to a single DND particle implies possible creation of complex integrated polyfunctional systems containing both diagnostic and therapeutic moieties in a single species. The potential use of DND as drug carriers is based on their ability to penetrate cell membrane [197], thus bringing into a cell the corresponding ligand coupled with carbon cluster.

Bioligands generally have a complex structure and are polyfunctional, so that they can be fastened to preliminarily chemically modified carbon support in several modes. Typical versions of covalent bonding of a bioligand to carbon support may be considered with biotin as an example. Biotin is a low-molecular-weight vitamin which has been used in immunoflourescence analysis since the middle of the XXth century [198]. Biotin exhibits both acidic and basic properties; therefore, it should be capable of adding to DND clusters over a wide range of pH. Coupling of biotin to DND may follow cluster may follow both ionic and covalent bonding mechanisms. There are two most probable ways of covalent bonding of biotin to the surface of DND clusters. The first of these involves hydroxy groups which are present in sufficient amount in all DND samples, regardless of the manufacturer and purification method.

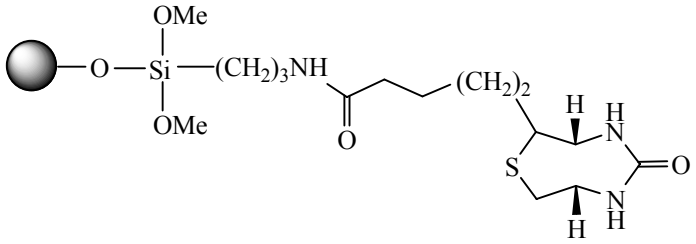


An essential disadvantage of this route is poor yield of the product. The reason is that the large number of surface hydroxy groups favors formation of a tight multilayer hydration shell around DND particles [201], which hinders modification. The hydrophilicity of DND particles can be reduced by transformation of hydroxy groups into amino. This process includes two steps: replacement of surface hydroxy groups by halogen atoms and subsequent replacement of halogen atoms by amino groups by the action of ammonia [74,

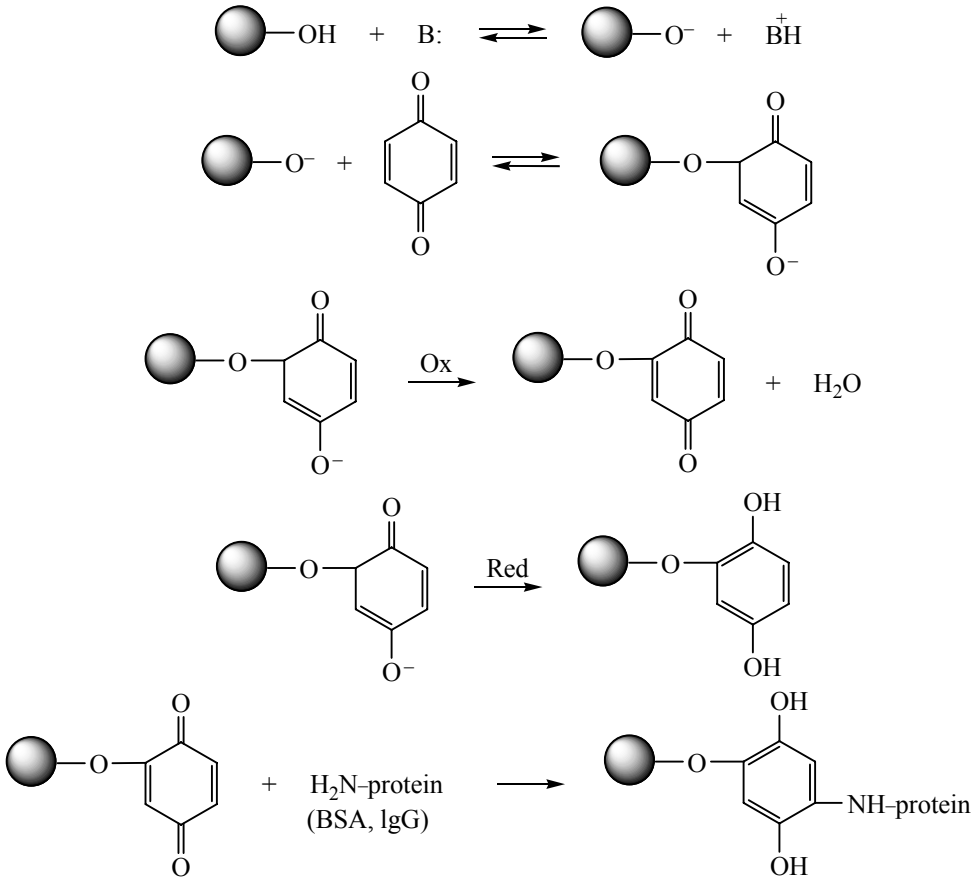


159]. The aminated DND particles are then brought into reaction with biotin.

If DND surface is enriched in hydroxy or amino groups, covalent bonds are formed through the carboxy group of biotin. It is also promising to append biotin molecule to DND cluster through a neutral silicon-containing linker, as shown below.



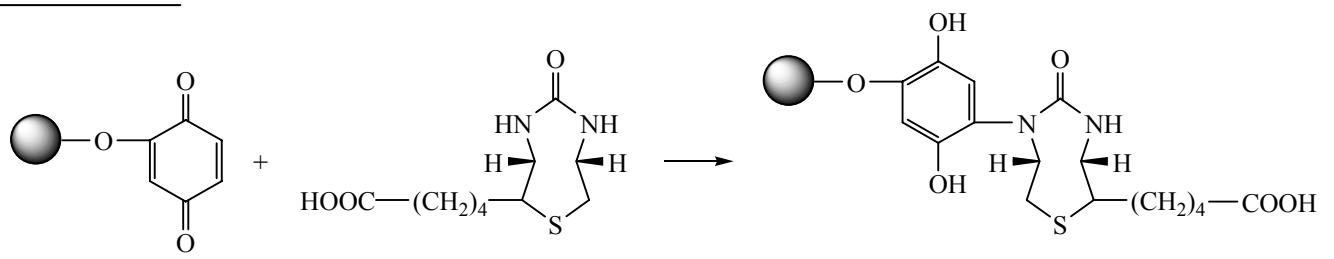
Both unsubstituted and substituted quinones were also reported as linkers [200]. Structures containing a quinone linker are obtained in several steps. One of the most important steps is formation of a nucleophilic species as a result of proton elimination from surface hydroxy groups. Attack by nucleophilic species on a



quinone gives an adduct which can be either oxidized to quinoid derivative or reduced to substituted hydroquinone. Oxygen dissolved in reaction medium can act as oxidant. The oxidized adduct is a convenient intermediate product for subsequent covalent bonding with a protein.

Addition of a ligand, including a high molecular weight protein, gives rise to hydroxy groups in the linker fragment, and these groups are solvated to a considerably lesser extent than the surface hydroxy groups; therefore, such functionalization allows control over hydrophilic–hydrophobic properties of the product. The presence of additional hydroxy groups in the linker may also enhance antioxidant activity of modified DND.

The use of benzoquinone as linker fragment opens new ways of loading DND clusters with biotin. Covalent bonding of biotin through the carboxy group is not always desirable. In this case, peptide ligands are usually added by free NH_2 groups. If benzoquinone is used as linker, biotin can be coupled through the endocyclic nitrogen atom.



This mode of addition generates quite different reactivity of the DND-biotin conjugate; various peptide fragments could be attached to this conjugate with conservation of the biotin moiety as specific immunofluorescent label provided that proteins capable of performing one or another function are immobilized on the cluster surface.

The formation of a DND complex with a firmly attached ligand ensures delivery of the latter into a cell. It was reliably proved that DND particles with a size of 4 to 100 nm penetrate cell membrane [182]. However, in biological and medical practice, penetration of such complex into a target cell should be controlled in each particular case, for just targeted delivery of biologically active ligand provides therapeutic effect. In this connection, the problem of detecting the DND–ligand complex inside target cells becomes important. The simplest and most reliable method consists of cluster visualization.

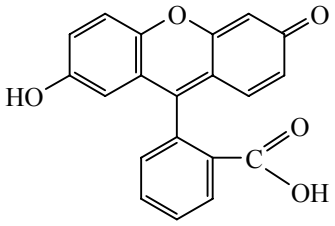
Visualization of DND clusters may be achieved on the basis of their fluorescent properties arising from surface defects primarily due to inclusion of nitrogen atoms [201–203] during the synthesis. The range of DND emission is usually within λ 500–800 nm upon excitation at λ 488–532 nm [185, 201, 207]. The most common emission ranges depending on the excitation wavelengths are given below:

Excitation wavelength, nm	488	532	633
Emission wavelength, nm	500–530	580–700	640–720

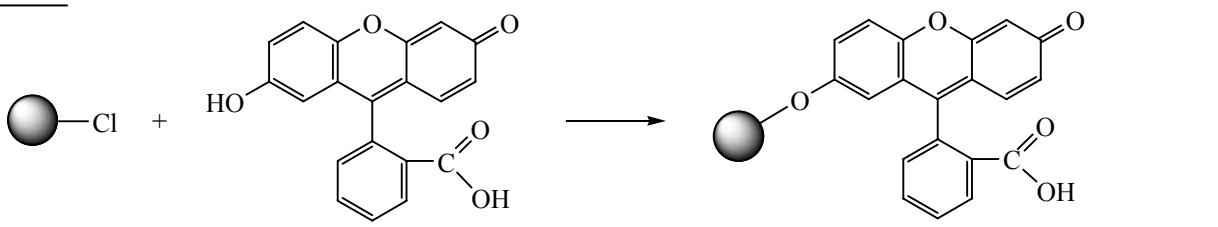
The intrinsic fluorescence intensity of DND is fairly high. Fluorescence spectroscopy allows detection of DND in various media at a concentration of 1 μg/ml [185]. However, this method cannot be used for quantitative measurements since the emission intensity increases in parallel with the number of defects [204, 205]. Detonation nanodiamond has not been standardized as a material, and the emission intensity of different samples varies in going from one manufacturer to another and from one lot to another. In addition, the fluorescence intensity depends on the particle size [182]; fluorescence of different particle size fractions originates from different types of defects. The emission of DND particles with a size of 5 to 50 nm is determined mainly by surface defects, whereas particles larger than 100 nm show fluorescence due to internal defects [46]. Insofar as DND-based therapy and diagnostics require compositions with extremely low DND concentration, it is desirable to enhance the emission by special methods. One of these includes initial high-energy (3 MeV) proton beam irradiation of DND, followed by annealing for h at 800°C. This procedure increases the emission intensity of DND particles with an average size of 100 nm by two orders

of magnitude [54]. Obviously, this method cannot be applied to DND conjugates with bioligands because extremely severe conditions could induce inactivation of biologically active fragments.

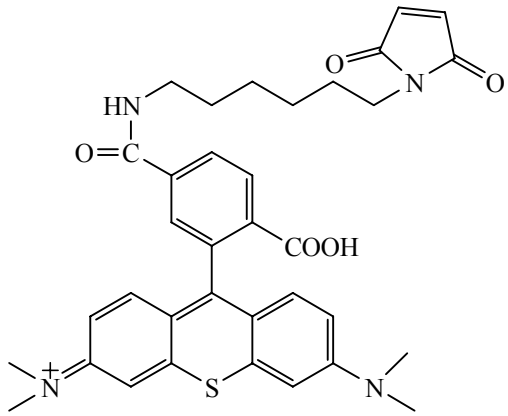
Another ways of raising the emission intensity are variation of the particle using special processing techniques, chemical modification of DND surface, and preparation of composites. Chemical modification of the surface with chromophoric fragments enables variation of the emission wavelength over a wide range and increase of the emission intensity. Moreover, covalent bonding of fluorescent moieties to DND particles ensures emission of the complex after delivery to target location where it should be detected; this makes it possible to design fluorescent materials for medical purposes on the basis of modified DND. In particular, a DND complex with a fluorescein dye, dihydroxyfluoranuranin A, was prepared [182, 185].



It is believed that dihydroxyfluoranuranin A covalently adds to DND particles through the hydroxy group of the dye molecule [206]. It is advisable to attach the dye fragment to chlorinated DND particles which can be obtained (see above) via replacement of the surface hydroxy groups.

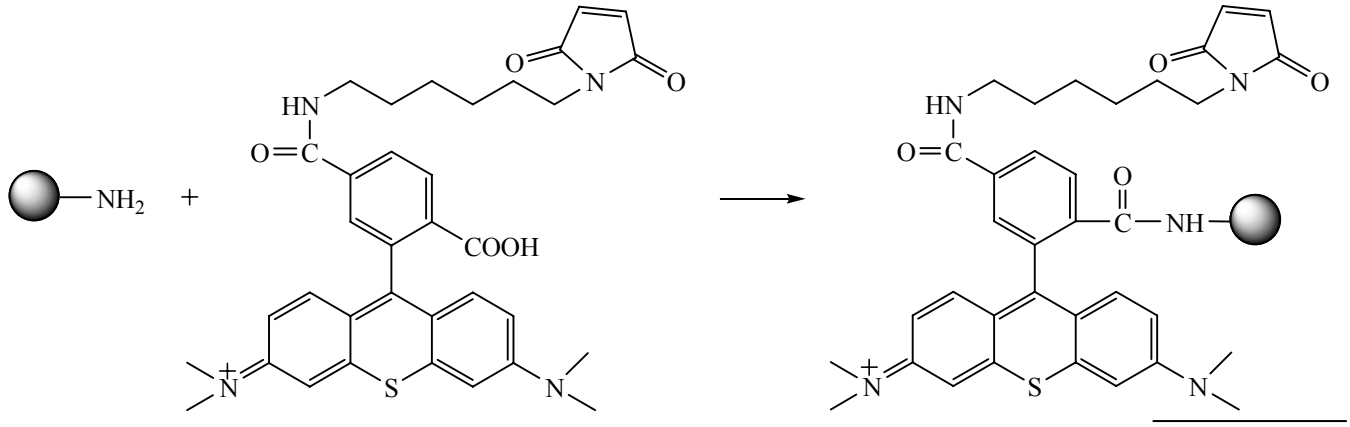


The resulting DND cluster exhibits strong yellow–green fluorescence and readily penetrates cell membranes; it can be detected by strong fluorescence in its localization region [185]. A set of fluorescent probes coupled to DND particles can be considerably extended. For example, a rhodamine dye showing strong orange–red fluorescence was used as fluorescent label attached to DND particles.



Here, covalent bonding is likely to involve the carboxy group of the fluorescent dye and surface hydroxy groups of DND [207]. We believe that replacement of halogen, which can be carried out in nonaqueous medium, is more promising, so that the series of fluorescent ligands may be extended. Taking into account serious hindrances to the addition, created by the hydration shell surrounding DND particles, it seems to be more convenient to append fluorescent label to aminated DND particles which are hydrated to a considerably lesser extent. Just this way is likely to be preferred for immobilization of the rhodamine derivative on DND particles, and the process can be conducted in aqueous medium.

Due to diversity of surface functional groups on DND particles the set of dyes that can be coupled thereto via covalent bonding is almost unlimited. Moreover, several fluorescent labels may be attached to a single cluster, which is especially important from the viewpoint of detection of DNA damage. Of particular interest is combination of a fluorescent label and a biologically active fragment with some therapeutic function in a single cluster. Further development of studies on DND functionalization is anticipated to enhance the selectivity of penetration of DND particles into different cells. Systems containing a fluorescent label provide precise control of the drug–target interaction. Extensive studies are now performed with a view to obtain fluorescent probes on the basis of DND [96, 208–211]. Fluorescent labels ensure reliable



indication of the penetration of DND into cells, detection of drug-modified particles inside cells, control of therapeutic effect with simultaneous direct control of DND location in the target place, and quantitative assessment of the concentration of DND and ligands coupled thereto in cells. Penetration of 5–100-nm DND particles bearing a fluorescent label through cell membranes and their ability to accumulate in cytosol were proved by fluorescent spectroscopy [211, 212].

The cheerful prospects and achieved progress in practice stimulate further development of theoretical studies on the surface chemistry of DND, primarily development of analytical approaches and methods for reliable determination of covalent bonding of ligands to DND. The above given data allow us to consider detonation nanodiamond mainly as sorbent, support, and carrier for delivery of therapeutic and diagnostic agents to the target place, which is provided by the unique chemical properties of the surface of DND clusters.

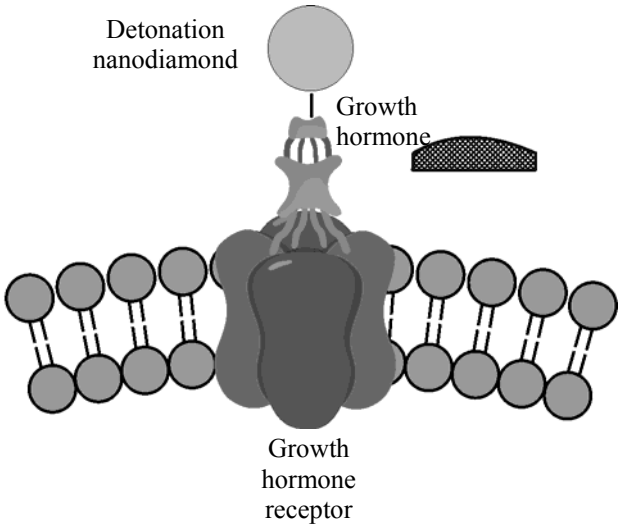


Fig. 3. Interaction of growth hormone-charged DND particles with the corresponding receptors.

DETONATION NANODIAMOND-BASED NANOTECHNOLOGY TOOLS FOR BIOLOGICAL AND MEDICAL PURPOSES

Development of research on DND surface functionalization and indisputable proofs for retention of native properties of biomolecules immobilized on DND particles enabled creation of efficient nanotools for cell therapy and cell surgery. One of the first systems of this type was based on growth hormone (which is a polypeptide) covalently bonded to DND particles through its N-terminus and surface carboxy group. The resulting conjugate is capable of interacting with the growth hormone receptor [182], the latter being an integral membrane protein [213]. A scheme of the ligand–receptor interaction is shown in Fig. 3.

It should be noted different cell types are characterized by considerably different numbers of membrane receptors. The ratio growth hormone/growth hormone receptor (GH/GHR) appreciably changes in some cancer types, e.g., in particular in intestinal cancer [214]. The presence of cancer cells in biological material may be revealed by luminescence methods using the complex GH–DND–GHR, which opens a way to early detection of cancer diagnostics. In addition, healthy and cancer cells are differently sensitive to physical effects, including laser irradiation, and their sensitivity considerably changes in the presence of DND. Binding of DND to cell surface through the GH/GHR complementary pair, followed by laser irradiation, kills 60% of cancer cells and only 10% of healthy cells [182]. The cell surgery system based on the GH–DND–GHR complex may be regarded as a specific nanoknife [215, 216] which selectively cuts off cancer cells.

Selective cell disruption with the aid of DND is based on its unique property, i.e., the ability to change the cluster volume under laser irradiation. The chemical basis of this effect is inclusion of nitrogen atoms into the diamond core of a cluster, which creates defects in the diamond structure with formation of of C–N=O groups in the bulk particle. Laser irradiation at λ ~530 nm induces elimination of gaseous nitrogen which is accompanied by increase in the particle size from 8 to 90 nm [216]; this popcorn-like effect underlies the operation of DND as a nanoknife.

BIOLOGICAL ACTIVITY OF UNMODIFIED NANODIAMOND

The ability to penetrate cell membranes and the presence of a large number of various surface functional groups makes DND not only a potential carrier of biologically active substances but also an independent biologically active material. Diverse biological activity of DND was noted by several authors [217, 218]. Unmodified DND affects the life cycle viruses [24], growth of micromycetes [219–222], and protein production by microorganisms [223]. At present, detonation nanodiamonds are considered as means for drug delivery to affected organs [97], anticancer [224–235] and antioxidant agents [226, 227, 236–238], and non-toxic enterosorbents [239, 240].

Reliable proofs for the penetration of DND into cells, which were obtained with the use of luminescent labels, allow us to discuss biological activity of unmodified DND samples. Taking into account prospects in using DND as means of delivery of drugs and diagnostic agents, first of all we must consider the toxicity of DND and its effect on vital activity of various cells. It was found that DND is almost nontoxic (LD_{50} = 7000 mg/kg in white rats, per os) [241], though the problem of toxicity of nanomaterials is fairly complex [242, 243]. Usually, the toxicity of nanosized species increases as their particle size decreases and the specific surface increases [244–247], i.e., particle size distribution could strongly affect the toxicity parameters. Furthermore, there are virtually no experimental data on chronic toxicity of nanocarbon materials, including DND. No pronounced cytotoxic effect of DND was found. Contact with DND particles with a size of 5 to 100 nm over a period of 4 h induced death of no more than 10% (relative to control) of cells of normal human lung epithelium, lung cancer, and kidney cancer [201, 248, 249]; this means the absence of pronounced direct cytotoxic effect, but influence on metabolic processes cannot be ruled out. Significant variation in the blood composition was observed in *in vivo* experiments where an aqueous DND suspension was administered per os to laboratory animals over a period of two weeks [225]; in particular, the total number of leukocytes increased by 45%, which was rationalized by a non-specific immune response to DND.

Although DND does not induce direct cytotoxic effect, complete inactivity of this material toward living matter cannot be spoken about [250, 251]. Detonation nanodiamond is a unique material integrating a very low toxicity with pronounced biological activity at both molecular and cellular levels. Taking into account the effect of DND on the number of leukocytes [42] and the ability of DND particles to penetrate into cells and accumulate in the cell cytosol [182], a systematic study of the effect of this nanocarbon material on living cells was necessary. An appropriate model is needed for such systematic studies. New medical agents are traditionally tested on an accessible material, and erythrocytes are usually used as such material [252]. In fact, DND affected a number of key biochemical parameters of erythrocytes, primarily those related to peroxidation processes and activity of the major antioxidant enzymes [253]. After a 2-h contact of DND with a suspension of erythrocytes in saline, the concentration of protein peroxidetion products increased twofold, whereas peroxidation of lipids remained almost unaffected [231, 232, 234, 235]. In addition, a moderate methemoglobin-forming effect of DND was found [254]. The observed influence of DND on lipids is very consistent with the weak direct cytotoxic effect since the latter originates mainly from enhancement of peroxide oxidation of membrane phospholipids. Some authors even supposed membrane-stabilizing effect of DND under certain conditions [255]; however, we believe that such statement requires careful verification. Activation of methemoglobin formation may ensue from the oxidation of the heme iron not directly with DND but with secondary products of protein peroxidation, the corresponding peroxide radicals and hydrperoxides that are capable of initiating oxidation of the heme iron under aerobic conditions [256–262]. Very small amount of these intermediates is sufficient to appreciably raise the concentration of methemoglobin, for the oxidation of heme iron is a radical chain process whose development is determined mainly by reactive oxygen species and organic peroxides [131, 263–274, 266, 268].

The data given above allow us to conclude that detonation nanodiamond exhibits a direct pro-oxidant effect which differs essentially as applied to proteins and lipids. After treatment of a suspension of erythrocytes with DND over a period of 2 h, the protein peroxidation product content increased twice, whereas only a gain of 10–15% was achieved in the lipid peroxidation. Being an efficient pro-oxidant toward proteins, DND readily reacts with enzymes, so that the activity of the latter should change appreciably. It is known that the key antioxidant enzymes, superoxide dismutase and catalase, are severely damaged by oxygen radicals [275]. It was proved [276] that reactive oxygen species induce structural changes in plasma superoxide dismutase (decomposition into particular subunits) and that the formation of new aggregates with altered steric localization of the active centers changes the enzymatic activity.

Heme-containing proteins are damaged most strongly [277], and catalase is just a heme-containing protein [131]. Therefore, variation of the activity of the major antioxidant enzymes by the action of DND may be regarded as expected. In fact, DND contact with erythrocytes reduces the activity of antioxidant enzymes therein, i.e. the pro-oxidant effect of DND includes a direct effect (increase of the rate of accumulation of protein peroxidation products) and an indirect one (inhibition of antioxidant enzyme activity). It should be noted that the antioxidant enzymes are differently affected by DND. The most sensitive to the damaging effect of DND is catalase; it lost 80% of activity after a contact with DND over a period of 2 h, whereas the activity of superoxide dismutase decreased by only 20% [235, 253]. The pro-oxidant effect of DND may be responsible for enhanced DND-induced apoptosis. It is now beyond doubt that activation of apoptosis always involves profound changes in processes occurring with participation of reactive oxygen radicals [278, 279]. In fact, enhanced apoptosis was observed in the presence of DND, but the concentration of the latter was fairly high, about 100 μg/ml, and the contact time was fairly long, about 72 h [182, 279]. As a result, 20% of cells died. Thus, the pro-oxidant activity of DND was proved by the results of numerous studies on the activation of apoptosis and effects on the antioxidant enzymes, rate of methemoglobin formation, and protein peroxidation processes.

The pro-oxidant effect of DND should give rise to antimicrobial activity of this material. It is well known that enhancement of the generation of reactive oxygen species is one of the main tools for suppressing the ingress of viruses and bacteria into cells [280]. Phagocytosis, i.e., the process of engulfing foreign species, involves enhanced generation of reactive oxygen species by phagocytes [281].

DETONATION NANODIAMOND AS ANTIMICROBIAL AGENT

Keeping in mind the above stated, we tested DND for antimicrobial activity using both bacterial cultures and microscopic fungi as test material. It was found that micromycetes are more sensitive to DND than bacteria [221]. Among a large number of tested cultures, the most pronounced sensitivity to DND was observed for *Cladosporium herbarum*, *Ulocladium chartarum*, *Penicillium spinulosum*, and *Penicillium glaviforme*. Thus, DND is a promising material for the design of protecting systems against microbial damage, but development of technologies for the application of antimicrobial protecting systems is an important problem.

There are several versions of using DND in antimicrobial protecting systems: direct addition of DND to a medium, development of self-curing coatings on the basis of the sol–gel technology, preparation of DND-filled films, membranes, and filters filled, and probably other systems based on carbon materials, including DND [221, 282]. Fairly extensive studies have been performed to obtain DND-based antimicrobial coatings [221, 229, 282–284]. For large surfaces with a complex shape, the most appropriate are self-curing coatings doped with both pure DND and with combinations of DND with other fillers capable of enhancing the antimicrobial effect [285–287]. Such additives may be classical biocides, i.e., tin, silver, and chromium compounds, organic biocides, and also photosensitizers which could boost the biocide effect upon exposure of such coatings to air [229]. The type of coatings is determined primarily by the conditions of their use, which may be very diverse, from building construction and architecture to food and seed storage, veterinary and medicine, light industry, and emergency services. Depending on the needs and conditions, these types include sol compositions simply added to water or foods, gels, ointments, and films, and modular polymeric units where DND particles have already been added to the constructional material or a DND-containing material has been applied to the module surface. In addition,

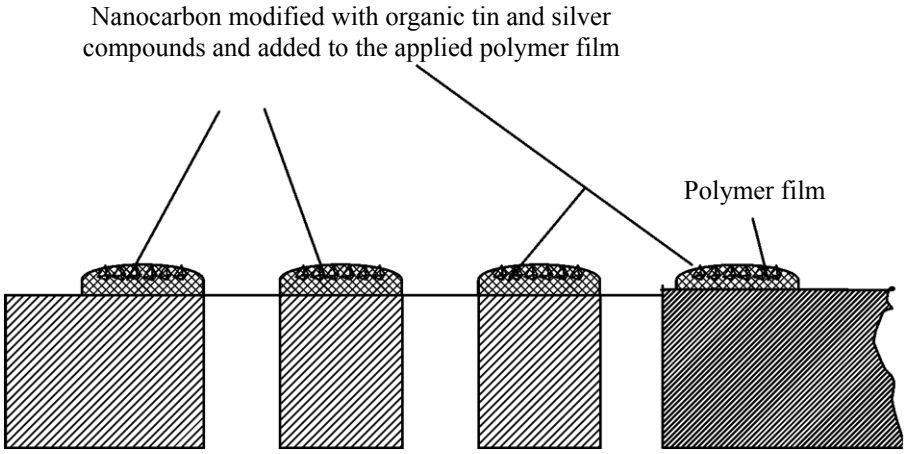


Fig. 4. Sandwich membrane containing an active filler in the ultrathin polymer film.

films, filters, and sandwich-like composites may be used. Highly expected are studies on DND-based self-curing coatings, bactericide films and membranes, and filtering modules containing DND in the active zone. From the viewpoint of medical applications, the design of ultraporous water-and-gas tight materials exhibiting pronounced antimicrobial properties attracts much interest.

We propose an example of such system, which is shown in Fig. 4. Its structure may be represented as a sandwich consisting of a porous support coated with an ultrathin (micron level) polymeric film containing active additives [229], in our case, detonation nanodiamonds. This, at first glance, simple solution requires, however, careful testing and substantiation. First, it is necessary to select a proper support material which should meet a number of requirements.

The support should be strong, it should not be harmful to humans and animals (i.e., it should be made of a nontoxic material), and should be resistant to sterilization and durable. Membranes for large-scale production of antimicrobial protection systems should be standardized by porosity to ensure required rates of filtration of gases and liquids, and, naturally, they should provide antimicrobial protection. The most important problem to be solved while developing polymeric coatings is the retention of antimicrobial activity upon immobilization of the active material in a film; this should assure environmental safety of such materials and minimize side effects in their use. Taking into account very low toxicity [182] and good compatibility with both high- and low-molecular-weight organic and inorganic compounds [288], DND is a very promising material for the above systems. Manufacture of goods possessing antimicrobial properties requires good compatibility with polymers and film-forming ability of DND; in addition, the latter should constitute a basis for multicomponent dopes exhibiting synergistic effect.

Thus the development of antimicrobial protection systems includes selection of a support and a polymer to generate a micron layer on the support surface. The polymer should be compatible with the active antimicrobial filler, and (what is the most important) the antimicrobial dope should retain its bactericidal properties in the filled film and should not be washed off from the sandwich coating; in this case, the polymeric film can be filled even with those biocides whose environmental hazard despite their high efficiency does not allow their direct application to a medium to be protected.

Initially, we selected lestosil (a polyphenylsil-sesquioxane–polydimethylsiloxane block copolymer) as ultrathin film-forming polymer due to its relatively low molecular weight, good compatibility with fillers, fairly fast curing, satisfactory adhesion to support surface, and the possibility for restoring pores after sub-micron coating by the potting method [289]. The manufactured membrane was tested for antimicrobial activity with simultaneous modification of the micron layer with various antimicrobial dopes. As the latter we used DND, tin compounds (dibutyltin dilaurate), colloidal silver, and composite dopes containing DND and colloidal silver or DND and organotin compounds. Silver compounds have long been known as antimicrobial agents, while tin compounds also exhibit

antimicrobial properties. The proposed technologies allowed us to sharply reduce the amount of the active dope, which is very important if such expensive material as colloidal silver is used. As concerns tin compounds, their immobilization is necessary because of their toxicity, so that they should exert antimicrobial effect in film without leaking into the environment. In this case, highly efficient and safe, so-called "green" antimicrobial coatings may be obtained.

The developed porous antimicrobial sandwich-like coatings based on DND-filled track membranes were tested on *Penicillium glaviforme* microscopic fungus using a solid agar medium. The results are collected in Table 2. We found no leakage of the toxic tin compound; therefore, the proposed sandwich-like coating may be regarded as environmentally safe, and DND may be used as an efficient nontoxic dope to antimicrobial coatings for various applications.

For successful market promotion of the developed coatings it is necessary to test them on a wide series of cultures, optimize the concentration of additives in the polymeric matrix, extend the set of additives with a view to find more efficient dopes exhibiting a broad spectrum of antimicrobial activity while being immobilized, and examine the effects of physical factors (such as light ultrasound) that are capable of enhancing the antimicrobial effect. It is also necessary to develop a technology for the fabrication of antimicrobial coatings on a large surface area.

PROSPECTS IN USING DETONATION NANODIAMOND IN THE DESIGN OF ANTICARCINOGENIC AGENTS

As follows from the aforesaid, the potential of unmodified DND as biologically active material is now based on its ability to interpose in processes with participation of reactive oxygen species and on the pro-oxidant effect. Taking into account the pro-oxidant effect of DND and different sensitivities of cells to reactive oxygen species, it was interesting to consider the possibility for creation of DND-based anticarcinogenic agents. It has been proved that carcinogenesis is accompanied by dramatic changes in the radical oxidation of proteins and lipids. Carcinogenesis arises from damage to the DNA structure by the action of primary and secondary radicals generated in cancer patients and is also accompanied by strong impairment of the activity of antioxidant enzymes [290, 291]. Therefore, the use of medicines affecting the radical oxidation processes may be promising in oncological practice. The positive effect of DND on the general well-being of cancer patients was reported fairly long ago [24, 46]. However, it was necessary to obtain experimental proofs for the inhibition of tumor growth and cancer cell death by the action of DND. Tests on human kidney and lung cancer cells showed that the effect of DND was fairly weak (no more than 15% of cancer cells died); however, a distinct relation between the DND particle size and antitumor effect was revealed: the smaller the particle size, the stronger the effect. This indirectly supports the assumption that the biological activity of DND is determined by surface functional groups.

As already noted, the effect of a medicine may be enhanced using physical activation. In fact, joint action of visible and IR irradiation and DND added to a cell culture increased the fraction of dead cancer cells by about 20% relative to control (DND without irradiation). Oral administration of DND inhibited the appearance and growth of the tumor in white rats with transplanted Pliss' lymphosarcoma and prolonged the animal life. Biochemical analysis of the animal blood showed considerable variation of the intensity of

Table 2. Antimicrobial activity of composite sandwich-like coatings on track membranes against *Penicillium glaviforme* inoculated onto a solid agar medium (in all cases, the porosity parameters were similar)

Characteristic of the antimicrobial layer in sandwich coating	Test results
A layer of lestosil on a track membrane	No antimicrobial effect
A layer of lestosil doped with DND	Moderate antimicrobial effect
A layer of lestosil doped with dibutyltin dilaurate	Weak growth inhibition
A layer of lestosil doped with colloidal silver	Almost no antimicrobial effect
A layer of lestosil doped with DND and dibutyltin dilaurate	Complete growth inhibition
A layer of lestosil doped with DND and colloidal silver	Moderate growth inhibition

peroxidation processes; in particular, reduction of the degree of protein peroxidation was observed in tumor-bearing animals (in which it was increased as compared to healthy animals), and the activity of the key antioxidant enzyme, superoxide dismutase (which was inhibited by tumor growth), was restored. This effect is very consistent with the data of [255] where stabilizing action of DND on integral proteins in erythrocyte ghosts and the ability to change surface energy of proteins in solution were revealed. Thus, DND in animals bearing Pliss' lymphosarcoma behaves as efficient antioxidant inhibiting peroxide degradation of biopolymers. We can conclude that, depending on the conditions, DND can exhibit both oxidative and reductive properties and act as radical initiator, i.e., pro-oxidant, or in some cases (as in the development of carcinogenesis) normalize processes involving reactive oxygen species, i.e., act as efficient antioxidant.

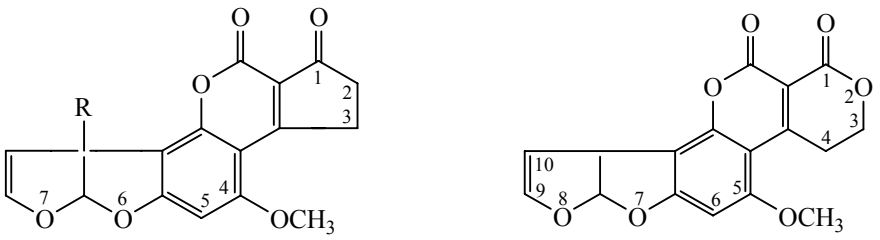
In order to prove that the observed antioxidant effect of DND is not occasional, a number of *in vitro* experiments were performed using classical model systems. In particular, it was found that DND efficiently quenched chemiluminescence initiated by peroxidation of lipids with reactive oxygen species generated by the Fenton reaction. The antioxidant effect of DND is comparable with that intrinsic to classical antioxidants, such as quercetin, flavonol, and cystamine. Thus, DND is a low-nontoxic biocompatible material exhibiting both oxidative and reductive properties in reactions with reactive oxygen species.

The effect of DND on electron transfer and radical oxidation processes is very consistent with paramagnetic properties of DND particles [46, 292–294]. However, the mechanism of action of DND on radical processes involving biomaterials is fairly complex, and some its specificities still remain unclear. It is known that erythrocyte membrane acts as a primary receptor for labile electrons generated by tunnel transfer processes with participation of intermediate products formed in stepwise four-electron reduction of oxygen in the course of tissue respiration. At present, a nanoparticle is considered to be a quantum system capable of delocalizing electrons (accumulation of excess information). The pro-oxidant mechanism of the interaction between DND and a biological entity consists of doping of the latter with electrons of a nanoparticle until saturation. If the possibility for delocalization of electrons is retained, a nanoparticle will exhibit antioxidant effect, i.e., depending on the conditions in the contact zone with a biological target, antioxidant effect may be observed in peroxidation processes. Presumably, contact of a nanoparticle with a biological target disturbs the character of intercellular (intracellular) electron motion, which may affect triggering mechanisms of the most important cellular processes and cause cells to change their state, specifically launch or block peroxide degradation processes.

DETONATION NANODIAMOND AS ACTIVATOR OF POISON DEGRADATION

Active participation of DND particles in radical reactions should lead to strong variation of the reactivity of ligands bonded to the particle surface. In fact, many very stable substances essentially change their reactivity upon immobilization on the surface of DND clusters, which may be of great importance for the design of complex biologically active compositions, detoxification systems, and medicines of new generation. In the latter case, DND may be regarded as a carrier and activator of target-selective pharmaceuticals. Detoxification of aflatoxin in the presence of DND was among the first studies that revealed essential change of the reactivity of a chemical substance as a result of binding to DND. Highly toxic aflatoxin produced by *Aspergillus flavus* microscopic fungus can be represented by several related structures (examples are shown below). Aflatoxin is readily adsorbed on the surface of DND particles, and this mere fact attracts practical interest, for the concentration of aflatoxin in biological medium may be reduced to a considerable extent only a s a result of sorption. Aflatoxin is very stable, but, being in contact with DND, it fairly readily undergoes decomposition with such oxidants as potassium permanganate, hydrogen peroxide, and ozone.

Among the aflatoxin family, aflatoxin B_1 decomposes most efficiently in the presence of DND; it was shown that aflatoxin B_1 is well adsorbed by DND particles. The molecule of aflatoxin B_1 lacks protogenic fragments; therefore, its bonding with surface functional groups is determined by interactions that are different from ionic. Most probably, these are hydrogen bonds and dispersion interactions. It is believed that detoxification of aflatoxin *in vivo* is most likely to involve opening of the lactone ring in its molecule. Decomposition of aflatoxin *in vitro* may be achieved by the action of oxidants (see above); however, complete degradation of the toxic compound



I **II**

I, aflatoxin B_1 (R = H), aflatoxin B_2 (R = H, 8,9-dihydro), aflatoxin M_1 (R = OH); **II**, aflatoksin G_1, aflatoxin G_2 (9,10-dihydro).

cannot be attained in this way. More than 65% of aflatoxin was decomposed by the action of oxidants in the presence of DND, whereas no aflatoxin was detected in a DND suspension after joint treatment with potassium permanganate and hydrogen peroxide (unlike control sample which was subjected to analogous treatment but in the absence of DND). The catalytic activity of DND in the decomposition of aflatoxin is very consistent with the catalytic effects of DND in electrochemical processes and reactions with inorganic compounds [60, 295–298].

Thus, detonation nanodiamond may be used not only as enterosorbent which reduced the active concentration of xenobiotics in biological media but also as activator of decomposition of poisons entering into organism. The search for low-toxic substances favoring biodegradation of poisons always remains an important problem. A combination of low toxicity, high sorption capacity, and the ability to activate decomposition of stable molecules (i.e., catalyze detoxification) make DND a promising material from the viewpoint of its application under emergency conditions. Further research on the catalytic activity of DND in a number of chemical reactions showed wide prospects in the development of studies in this line.

While considering potential applications of DND as catalyst of xenobiotics biodegradation, of particular interest is to elucidate the mechanism of this catalytic effect. The mechanism of the catalytic effect of DND on the decomposition of aflatoxin still remains unclear; probably, it involves activation of aflatoxin molecule via change of its conformation as a result of adsorption. Effective aflatoxin degradation may also be encouraged by the ability of DND to generate reactive oxygen species under certain conditions, which was repeatedly noted by many authors and is likely to be a determining factor responsible for the anticarcinogenic effect of DND. The effect of various nanocarbon materials on processes mediated by reactive oxygen species is extensively discussed in scientific literature, and it has been proved experimentally.

NEW DETONATION NANODIAMOND-BASED MATERIALS FOR ORTHOPEDIC SURGERY

A combination of such properties as high sorption capacity, the ability to bind cations and anions, and effective penetration into various tissues, including bone tissue (if the particle size does not exceed 5 nm) [299] makes detonation nanodiamond extraordinarily promising for orthopedy and surgery [300]. It was

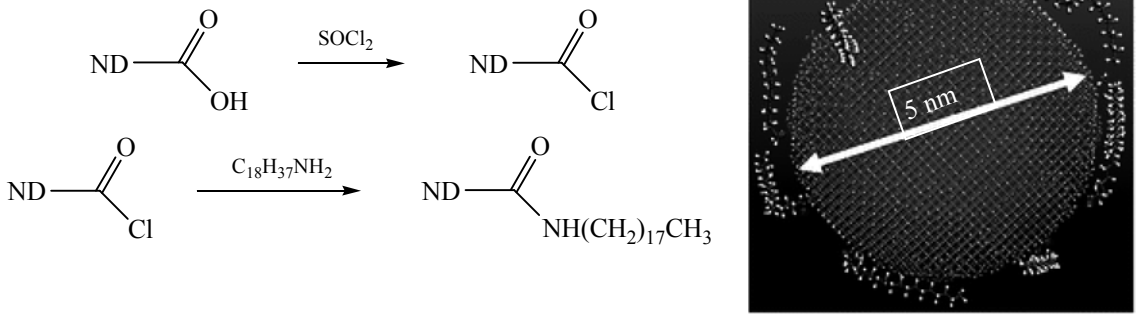


Fig. 5. A scheme of DND surface hydrophobization via covalent bonding of octadecylamine for the fabrication of an orthopedic nano-anchor.

shown that hydroxyapatite effectively deposits on the surface of DND particles to afford a fairly strong material. Calcium cations retained on DND particles react with orthophosphate anion. The resulting composite based on DND particles and calcium orthophosphate rapidly replaces lost bone tissue. Another attractive application of DND in orthopedy and surgery is the manufacture of orthopedic screws and anchors for replacement surgery. This application is based on the ability of DND to from complexes with polymers to considerably improve their mechanical characteristics [301–312]. Complexes of DND with biodegradable polymers may be sufficiently fast to fabricate surgical screws that merely dissolve after completing their mission. Here, the key problem is concordance between the surface properties of nanodiamond and properties of the polymer, which may be finely tuned via functionalization.

Figure 5 shows a scheme of preliminary variation of the hydrophobic/hydrophilic balance with the use of modified DND with a view to fabricate a nanoanchor for implanting into bone tissue [313].

A higher level of using DND in orthopedic surgery implies creation of implantable elements stimulating the bone tissue growth due to the presence in the implanted material of specific proteins, bone growth factors. The latter can be applied onto the implant surface via preparation of DND–protein complexes and addition of these complexes to an ultrathin polymeric film which is applied to the implant surface. Due to the presence of bone growth factors such implants could act not only as a support for further bone growth but also as an agent initiating formation of bone tissue.

However, in our opinion, the major applications of DND in medical practice should be based on its ability to intervene in radical processes and exhibit anti-/pro-oxidant properties. These applications include the following:

(1) Development of anti-senescence cosmetic agents and means for protection from UV radiation;

(2) Design of antibacterial and antiviral preparations, including large-area antimicrobial coatings, for various purposes, from cosmetic and food industries to applications in emergency services and disaster medicine;

(3) Development of antioxidants and anticarcinogenic drugs;

(4) Creation of wound healing agents and means accelerating regeneration of tissues;

(5) Design of immunomodulating agents.

The size of DND particles, their low toxicity, high biocompatibility, good sorption capacity, and the ability to penetrate into tissues extend the scope of potential applications of DND in medicine and biology, so that this nanocarbon material seems to be promising for the design of means for molecular–cellular diagnostics, drug delivery to affected organs, detoxification, separation and analysis of complex mixtures of organic and inorganic compounds and biological fluids, as well as for coating of bone implants, valves, and items for replacement surgery.

Market promotion of DND as promising material requires joint efforts of researchers in different fields of science, probably in the framework of a unified megaproject, laboratory, or specialized research center.

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