Review

Nanodiamond and its application to drug delivery

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Abstract

Quasi-spherical diamond crystals having an average diameter of 3.7±0.6 nm are attracting much attention as an ideal material in carbon nanotechnology. In contrast to the other popular nanocarbons including fullerenes, carbon nanotubes and graphenes, our single-nanodiamond can be produced in uniform shape/size on industrial scale. Thus, the most serious problem in nanocarbon industry that persisted in the past 25 years, namely the technical failure to produce highly crystalline nanocarbons in narrow shape/size range does not exist in our diamond from the beginning. Among potential applications of the single-nanodiamond under development, this review concentrates on its highly promising role as a drug carrier, especially for therapeutic-resistant cancer. An interesting possibility of intercalation is proposed as the mechanism of drug transport through blood, which takes into accounts of the spontaneous formation of nanographene layer on the [111] facets, which is then extensively oxidized during oxidative soot removal process to give nanographene oxide partial surface, capable of intercalating drug molecules to prevent them from leaking and causing undesirable side effects during transportation to target malignant cells. A perspective of quantifying the drug delivery process by anticipating orders of magnitude in the number of administered detonation nanodiamond (DND) particles is suggested.

Key words: intercalative drug delivery, detonation nanodiamond partially covered with nanographene oxide, number density effect, carbon nanotechnology, mechanism of nanodiamond-nanographite phase transition, dispersion vs agglomeration

After 25 years of intensive search for new nanocarbon species like fullerene C_{60} and carbon nanotubes, a consensus is gradually being formed among the scientists working in this field that nanodiamond and graphene would be the final choices[1]. We have been concentrating on nanodia-

mond for the last decade[2-4], but recently realized that nanodiamond is actually a hybrid material with patches of nanographene oxide attached on its surface, as first presented before MRS 2012 Spring Meeting, San Francisco, April 12, 2012, Abstract FF7-2. Thus, the final choices are combined into one hybrid material of nanodiamond. In this small review we will start with brief historical survey of nanodiamond and include our latest results on its geometric and electronic structure. When we began research on nanodiamond we simply expected to see a small version of the well-known bulk crystals of diamond, but it turned out to contain surprisingly complex structure consisting of core-shell internal geometry and unexpected migration of electrons to give unprecedented multi-pole particles. The secret of spontaneous formation of such complex structure in extremely short time will be discussed in section—A new generation of drug delivery.

Naturally one would expect a variety of new properties to roll out from such a unique nanodiamond particle[5]. So far our research and development efforts to take advantages of these properties live up to the expectation. One of the most promising results is the use of nanodiamond as the platform of an entirely new drug delivery system (DDS). This DDS methodology has developed well into the stage of animal tests, and the successful results has been published[3, 6-16]. We will introduce here a new proposal, which will explain our past enigmatic observation that no leakage of drug has ever taken place during delivery. A key in this proposal is the high capability of intercalating drug molecules by graphene oxide[17] patches on the surface of nanodiamond.

Finally, unique characteristics, both advantages as well as disadvantages, of nanotechnology that we noticed in the course of the present work will be briefly mentioned in the last section.

What is detonation nanodiamond?

We understand that this journal is primarily directed to medical doctors, but they may not necessarily be familiar with the emerging diamond nanomaterial called detonation nanodiamond (DND)[1,2]. Let us start this section with a brief background of DND. In around 1997, when nanotechnology was gaining popularity, one of us (Eiji Ōsawa) met with Dr. Peter Belobrov, Professor of Physics in Krasnoyarsk National University, Siberia. He showed tunneling electron microscope (TEM) photographs of small round particles in low contrast and having diameters of about 5 nm, and said these were diamonds. At that time, I was just becoming interested in diamond materials as the result of involvement in fullerene research[18], the first nanocarbon ever appeared before

us, and instantly fascinated by the prospect of studying nanodiamond.

Those nanoparticles that Professor Belobrov showed me was the DND. As we learned later, this is one of the four known artificial diamonds that are considered capable of industrial production (Table 1). The strange adjective 'detonation' is given because these crystals were found to grow while detonating a military explosive named Composite B (TNT:RDX≈1:1) in water in a closed iron vessel. Composite B is an oxygen-imbalanced explosive, hence incomplete oxidation leaves un-burnt carbon atoms from thermal decomposition of detonator molecules, which are then exposed to high pressure (about 200,000 atmospheric pressure) and high temperature (1800-2000˚C) zone in the shock wave from detonation for a short while (<1µs). Although detail is still unknown about the events that occurred, but DND particles must have grown during this period of time under the diamond-stable condition prevailing at the center of explosion. These are what I was briefed by Professor Belobrov.

I duly began searching literature for more information on DND, but was soon dismayed by the fact that DND is not mentioned at all in any of the recent books on diamond! DND was popular only in the ex-Soviet countries: International Conference on DND is being held since 2002 every two years in St. Petersburg, and about 1000 papers are supposed to have been published on DND by the year 2006, most of them written in Russian. Why DND was completely neglected in the western science monographs on diamond? I studied the case carefully, and found explanations. The result of my survey was published[19], hence I mention here only briefly but hopefully enough to understand the unfortunate background of DND:

1. DND was discovered four times in Soviet Russia long time ago! It was confirmed that V. Danilenko and two others were the first discoverers, and that their wonderful work was done in 1963[20]. However, no authentic documents are available about these great discoveries.

2. The discovery of DND was long kept secret under Soviet military regime, but gradually became known to western side since about Perestroika (1989).

3. As the usefulness of DND is becoming apparent and attracting attention of various sectors of science in recent years, especially in its luminescent behaviors, a large number of papers are appearing in international journals[4,5], but the origin, characteristics and critical information like

Table 1: Four major manufacturing methods of artificial diamonds

Method	Raw materials	Discovery (year)	Break-through (year)	Form of product	Average size	Country of production	Lit.
HPHT[a]	graphite+Fe	GE (1955)	-	Single-crystalline particles	50µm	China	h
Shock	explosive+Cu +graphite	DeCarli-Jamieson (1961)	-	Polycrystalline particles	50µm	China	h
Detonation[b]	TNT+RDX/water	Danilenko-Volkov-Elin (1963)	NCRI (2002)[d]	Single- crystal-line nanopar-ticles	4nm	Japan[g]	i
CVD	CH_4+H_2[c]	Eversole (1950)	NIMS (1982)[e]	Polycrystalline films	f	Japan, US	h

[a]Hydrostatic high-pressure high-temperature. [b]See text. [c]A number of variations exist, see lit. c. [d]Dispersed primary particles isolated. [e]Reproducible conditions found. [f]Thickness can be as large as mm. [g]Agglomerates are produced in CIS and China. [h]Collins AT. Diamonds in modern technology: synthesis and Applications. In: The Nature of diamonds, Harlow GE (Ed.), Cambridge University Press, Cambridge, pp. 255-272, 1998. [i]Osawa E, Single-nano buckydiamond particles: synthesis strategies, characterization methodologies and emerging applications. In: Nanodiamonds-applications in biology and nanoscale medicine, Ho D (Ed.), pp. 1-33, 2010.
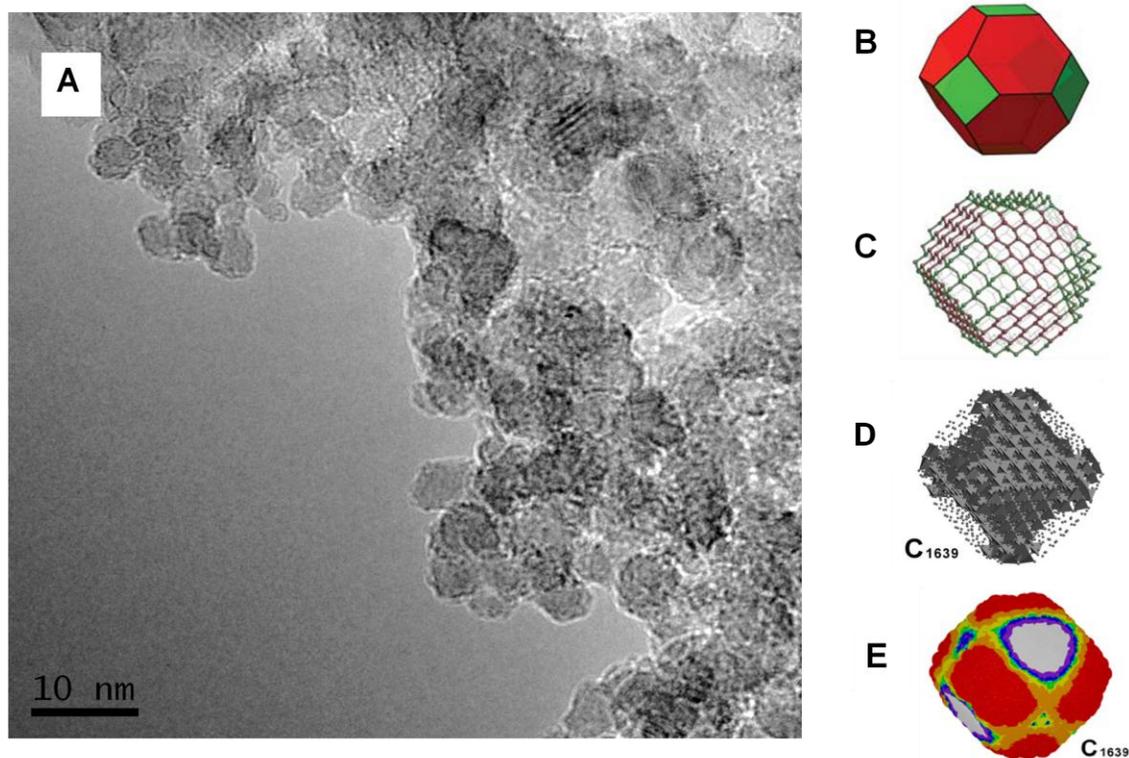
Fig 1. A: An exceptionally good image of detonation nanodiamond taken on an aberration corrected low voltage TEM at Monash University. The four graphical pictures on the right side are taken from refs. 22, 23 to illustrate computed surface characteristics. **B:** Truncated octahedron model, showing [111] (red) and [100], [110] (green) facets, and seen from the same direction as in the three other pictures. **C:** An example of input structure for geometry optimization by SCC-DFTB program, and corresponds to 'living nanodiamond' (LND) immediately after the stopping of crystal growth. **D:** C_{1639} diamond after optimization. The carbon atoms on the [111] surfaces and a few layers vertically below (compare with **B**) have been transformed into sp^{2+x} ($0 \leq x < 1$) hybridization from the initial sp^3 as the result of spontaneous diamond-graphite phase transition. Their nuclei positions are given by dots so as not to hinder the shape of the core diamond, the nuclear positions of which are expressed by filled tetrahedral models. It can be seen that the core diamond is exposed to the surface at [100] and [110] surfaces. **E:** Surface electrostatic fields on the geometry-optimized model. Grey-purple-blue-green colors denote negative charges with decreasing field strengths in this order. Red-orange-yellow colors denote positive charges. See text for more explanations.

original supplier, particle-size distribution and Raman spectra are often missing.

4. DND has become commercially available since the early 1990s as visible grey powder and has been listed in chemical catalogues under various trade names like 'diamond nanopowder'. However, it is basically wrong to dry single-nanoparticles into aggregates, especially so in the case of DND known to form extremely tight agglutinates. For this reason, even the latest published results are mostly based on aggregates.

5. In 2002, we found that DND agglomerates can be disintegrated by wet attrition milling using 30 μm zirconia beads as the crusher[21]. The product of milling is dark-colored colloid of primary particles (PP) of DND having a diameter of 3.7±0.6 nm dispersed in the attrition media used in the milling, in most cases water. This diameter was obtained only recently by using optimized set of milling conditions. Previously we used somewhat large particles with 4.8±0.7 nm in diameter, and some of the results mentioned in this paper were obtained with these larger particles.

At this point we thought that isolation of primary particles will quickly lead to complete characterization of DND. However, we soon learnt that nanoparticles are much more difficult than chemical molecules to characterize. To begin with, TEM did not prove as useful as we had expected from its size for high resolution observation. Figure 1A reproduces one of the best TEM images we have ever seen. Unfortunately contrasts in images were generally not high enough to obtain detailed information on the shape of crystals. Extremely high tendency of primary colloidal particles to form tight aggregates in the high vacuum of TEM further deprived us of opportunity to see well-exposed surfaces of isolated particles. This was only the beginning of difficulty.

When we accidentally succeeded in isolating PPs by attrition milling, we had no idea about what happened in the mill. The reason was that the tightness of agglomerate was beyond imagination from our knowledge of intermolecular interactions. In addition the colloid thus obtained was intense black in color and so stable that no precipitates occurred after months or even years of storage. These two remarkable features in the PP-DND colloid were difficult to accept. Nevertheless, the dried powder obtained by evaporating water from colloidal dispersion displayed characteristic X-ray diffraction pattern identical with that of bulk diamond. We lost a few years looking for explanations in vain.

Then suddenly answers were given in 2007-2008 by Amanda Barnard who performed systematic SCC-DFTB calculations on smaller polyhedral nanodiamond models[22,23]. She made various models (e.g., Fig. 1B), and subjected them to geometry optimization, and immediately found that spontaneous diamond-graphite transition occurred on the [111] facets. The extent of transition changed depending on the size and shape of models used, but whenever large models were used, core portions always retained some untransformed diamond. A typical optimized structure obtained with the most often used shape of truncated octahedron (Fig. 1A) is reproduced in figure 1D as dots, which shows considerably thick sp^{2+x} ($0 \leq x < 1$) carbon atoms. Taking into accounts of all other results, the ratio of sp^{2+x} to sp^3 carbon is about one-third irrespective of shape and size.

Actually, such a core-shell type structure has been often observed under TEM[21]. We also confirmed by the observation of our PP-DND on an aberration-corrected low-voltage TEM that real graphitic structure appears only on the surface one or two layers[24]. Hence these results can be interpreted to mean that diamond-graphite phase transition, at nanoscale, starts spontaneously but soon stops after one or two layers and produce large strain near the transition points. Spontaneous phase transition on the surface is actually anticipated for DND, based on the similar behavior of metal nanoparticles; but in the case of nanometals, transitions are usually complete.

Reason for the suspended propagation of phase transition towards inner core in nanodiamond was not apparent. Doubts deepened when we recalled the fact that the transition temperatures have decreased from about 4000K in bulk diamond to less than 1200K in single-nano diamond, hence the transition must be of quite low activation energy and fast in nanodiamond. As all the significant results of Barnard's calculations originate from the suspended phase transition, we were much intrigued in its cause. Explanations in terms of fast freezing of diamond state are unlikely, because large heat capacity of the wet reaction mixture and vessel should keep the diamond growth region hot enough to maintain the region at high temperatures.

We start from the well-accepted DeCarli-Jamieson theory[25] of the conversion of the surface of [111] facet to nanographene layer by the least nuclei movements, as shown in the conversion of **C'** to **F** (the first reaction in Fig. 2). An important prerequisite for the transition to proceed is that the freshly formed nanographene layer must move apart from diamond by a vertical distance of about 1.5Å to

the optimum van der Waals interaction, before starting the next step, **F** to **F'**. However, as all the edges of the first nanographene layer are bonded to the neighboring facets in DND, this layer remains close to the new diamond surface having radical centers. This disposition as shown in **F** offers an ideal configuration for migration of free electrons from electropositive nanodiamond to electronegative nanographene by Hoffmann's orbital-interaction-through-space (OITS) mechanism, to generate negative electrostatic potential field over the nanographene layer and positive electrostatic potential field over the new [111] facets (**D'**). The positive field will be spread by hyperconjugation through parallel σ-bonds in the diamond crystal lattice, as seen by Barnard and Sternberg[22]. Reverse electron migration is difficult due to the large difference in electronegativities between the facing layers, thus further propagation of nanodiamond-nanographene transition is suspended. As the surface nanographene layer in **F** has small freedom of movement in the vertical direction known as rippling, it could happen that one more step of phase transition takes place to form the second nanographene layer (**F'**), but this will definitely be the last step. The OITS mechanism of suspending D-G transition in nanodiamond agrees with TEM observations: we sometimes see two graphitic layers, but usually only the single graphene layer and never the three-layered nanographitic shell.

Interestingly enough, the well-known illustration of bucky diamond drawn by Galli and coworkers[27]

clearly depicts the strained bonds connecting the surface graphene patches and diamond core (Fig. 3).
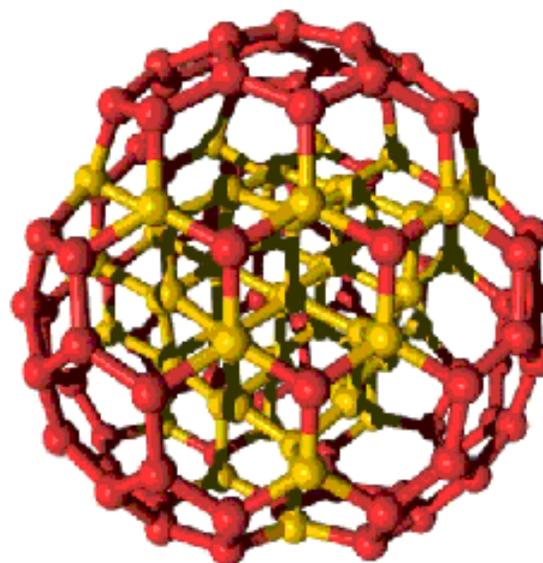

Fig. 3. Reproduction of the original drawing of bucky diamond by Raty et al. (reference 27), which faithfully illustrates the highly strained bonds between graphitic patches and the neighboring facets. See text for discussion.

Although Galli's bucky diamond model was too small to evaluate manifestation of the strain effect, the larger models of Barnard shows that surprisingly large proportion of outer carbons in the diamond core are sp^{2+x} hybridized, hence reflecting enormous strain generated on the nanosurface.
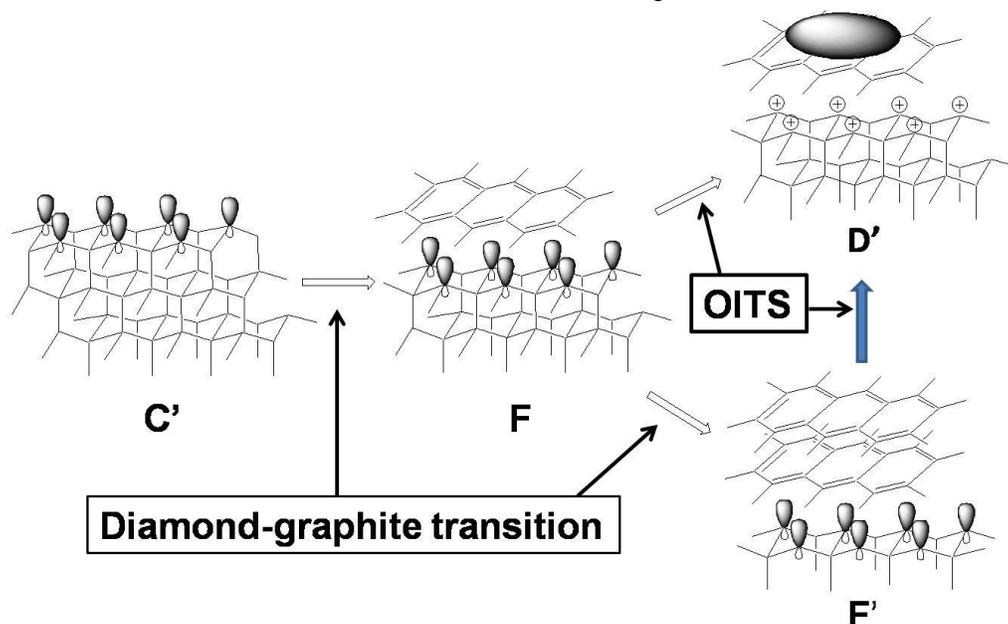
Fig. 2. Snapshot illustrations of nanodiamond-nanographene phase transition process. Refer structures **C'** and **D'** to the corresponding notations in figure 1. **F** is supposed to prefer going to **D'** by the orbital interaction through space (OITS), rather than going to **F', F"…** to produce nanographite. See text for more explanation.
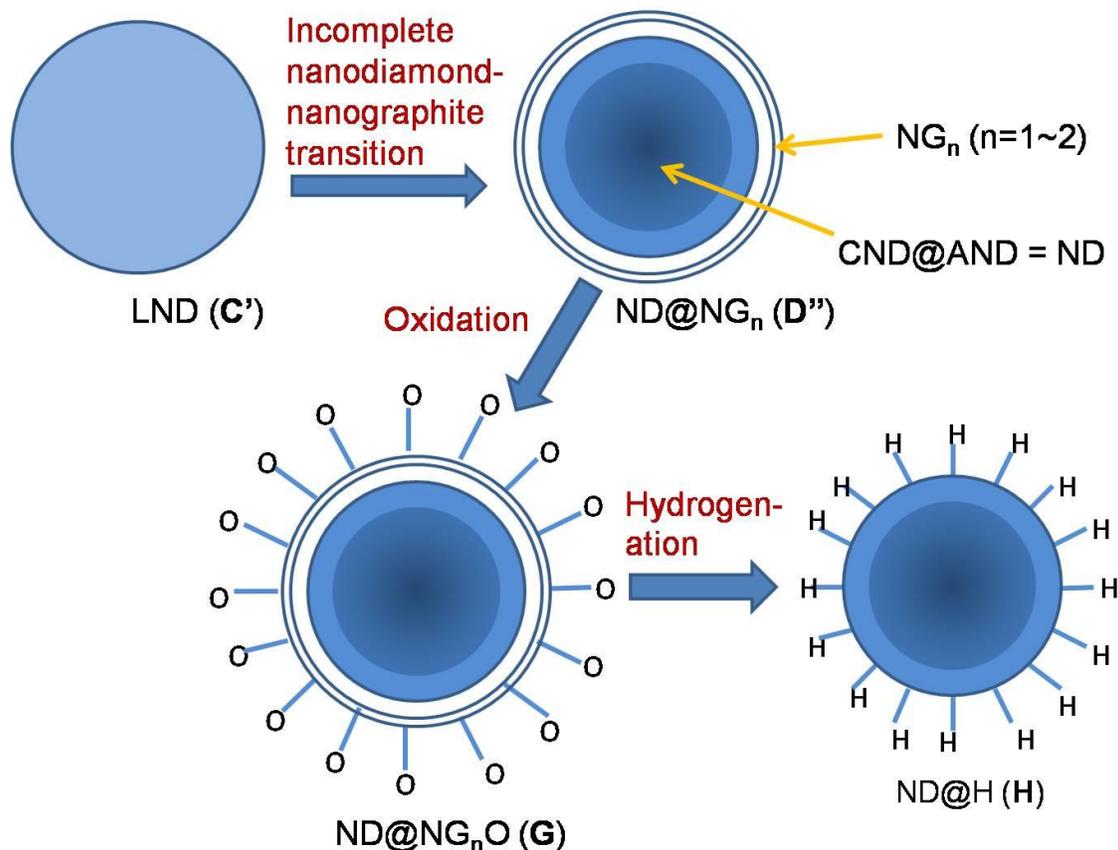
Fig. 4. Cross-sectional illustrations of the structural characteristics in various forms of detonation nanodiamond. LND: living or growing nanodiamond, ND: core nanodiamond, but it consists of amorphous diamond (sp^{2+x}-hybrdized, 0<x<1, AND) layers surrounding crystal-line nanodiamond (CND). NG: nanographite. Here, the term @ does not necessarily mean strictly concentric onion-like disposition of two spherical shells, but is used in a much looser context. Thus ND@NG means non-spherical nanodiamond partially covered with nanographite patches. **D”** depicts a double-layered NG shell. Oxidative removal of soot is supposed to turn NG into nanographite oxide (NGO) as well. ND@NGO (**G**) is considered to represent primary particles of detonation nanodiamond (PP-DND). Perhydrogenation of **G** to hydrogen-terminated nanodiamond ND@H (**H**) will be a good way to prepare a standard sample of nanodiamond.

It is likely that the strain produced by bucky shells in our optimized PP-DND is at least partly absorbed by angle deformations in the thick sp^{2+x} layers. Such disorders are known in diamonds and sometimes called amorphous diamond[26].

The special internal disorders, together with the suspended D-G transition and the lowered D-G transition temperature, are unique features inherent to nanodiamond. Figure 4 once again summarizes the unique features in terms of cross-section cartoons with a few improvised nomenclatures. ND@NG$_n$ (n=1 or 2) is a local but high-energy minimum. In the next step of oxidative removal of soot, these strained edge bonds will be preferentially broken by the oxidizing agents to give various oxygen-containing functional groups[17]. The oxidation reaction was initially aimed at removal of soot, but it has profoundly affected the nanodiamond particles as well; the nanographene or thin nanographite that were firmly bound to the mother nanodiamond above [111] facets, are freed as nanographene oxide or thin nano-

graphite oxide. Then there arises an interesting question: Will these oxides detach themselves from nanodiamond?

We think that these nanooxides are firmly bound at their original positions on the positive surface of [111] facets of nanodiamond with its negative electrostatic potential field (see **D'** in Fig. 2).The interfacial Coulombic bonding between the nanooxide patch and nanodiamond must be as strong as those in the crude agglomerates of DND. Thus, the most likely candidate structure of the PP-DND is ND@NG$_n$O (**G**) as given in the lower line of figure 4. This picture agrees with high positive ξ-potential of NGO/DND colloid observed (+50~60 mV).

This is the latest interpretation of electronic structure of a PP-DND prepared by milling of typical DND agglomerate purchased from a manufacturer in China[28]. Barnard's calculations were performed on small polyhedral models (cube, cuboctahedron, octahedron and their truncated derivatives) up to about

1600 atoms. The abnormally tight agglomeration among PP-DND particles was interpreted by Barnard to arise from the facet-facet electrostatic attractions between multi-pole polyhedra[23].

Fundamental research in DND is going on. One of the serious problems that we still cannot solve is the difficulty in purification. Recently we found electrophoresis promising[29] and intensive work is going on to separate major impurities in PP-DND by this method. Black color of colloidal solution of PP-DND is still a pending problem. We definitely need to establish a standard nanodiamond having simpler structure than PP-DND particles. For this purpose, we

suggest to adopt perhydrogenated DND, or ND@H (**H**, Fig. 4). This structure is also called as a nanodiamondoid, the hydrocarbon homologue of adamantane, and has been the subject of a few studies[30], but it is still difficult to remove sp^2 impurities.

A temporary survey of physical constants obtained by using the present level of PP-DND is given here for reference purposes (Table 2).

A new generation of drug delivery

As briefly referred in introduction, preliminary screening stages of our DDS on DND platform have well progressed, and the most advanced front

Table 2: Properties of dispersed detonation nanodiamond (NGO/DND)

Property	Value[a]	Note
Particle-size distribution, nm	3.7±0.6 (new) *4.8±0.7 (old)*	DLS DLS, X-ray, TEM
Elemental composition, %	*C 89.84, H 1.01, N 2.20, O 5.76, ash 1.19*	Dried sample highly hygroscopic[21]
Diamond C content, %	*92.9±0.3*	Based on [111] diffraction intensity with ZnO as external standard
Density, g/cm^3	*2.99*	Picnometer
Number density, particles/g	$1.26×10^{19}$ *$0.615×10^{19}$*	Spherical diamond approximation
Surface area, m^2/g	*283.8* (exp) *1665* (calc)	BET on IICI aggregate[24]
Nanopore, nm	*3.25* (exp)	BET on IICI aggregate[24]
Spectra	*IR, Raman, NMR, EPR*	Ref 24, b
TEM	Fig. 1	Ref 24
SEM	*For IICI and CICI agglomerates*	Many publications
ξ-potential, meV	+52	At pH 4.88, rt
Geometry	Quasi-spherical, core-shell	See text
Band gap, eV	*4.5*	c
Luminescence, nm	*575, 637*	Zero-phonon lines for NV0 and NV- complex, d
Cyctotoxicity	*None*	e
Metallc impurity, ppm	Zr2.7	ICP using an in-house calibration graph

[a]Italic numbers taken on old samples having larger diameter. See the first line. [b]Panich AM, Shames AI, Vieth HM, Osawa E, Takahashi M, Vul' AY. Nuclear magnetic resonance study of ultrananocrystalline diamonds. Eur J. Phys. B, 2006; 52:397-402. [c]HuangH, Dai L, Wang DH, Tan LS, Osawa E. Large-scale self-assembly of dispersed nanodiamonds. J. Mater. Chem. 2012; 18:1347-1352. [d]SmithBR, Inglis D, Sandness B, Rabeau JR, Zvyagin AV, Gruber D, et al. Five nanometer monocrystalline nanodiamond with luminescent nitrogen-vacancy defect centers. Small 2009; 5(14):1649-1653. [e]Schrand AM, Johnson J, Dai L, Hussain SM, Schlager JJ, Zhu L, et al. Cytotoxicity and genotoxicity of carbon nanomaterials. In: Safety of Nanoparticles: From Manufacturing to Clinical Applications. Webster TJ (Ed.), Springer Science + Business Media, New York, Chapter 8, pp. 159-187, 2009.

recently succeeded in curing breast and lung cancer in mice, which otherwise quickly develop anti-therapeutic resistance[7]. Other targets that have been successfully challenged with our DDS include diabetes[8], gene delivery[9], siRNA delivery[10], therapeutic antibodies[11], water-insoluble therapeutics[12], and liposome[13]. NGO/DND loaded with Gd(III) proved effective in increasing contrast of MRI[14]. Delivery of therapeutics-NGO/DND conjugates is also attempted by embedding in multi-layered polymer films[15,16] and polymer hydrogels. All these works are documented and even a multi-authored book on this topic is published[3]. For this reason we will concentrate below on the very recent re-interpretation on the drug carrier mechanism based on the latest information on the structure of PP-DND.

Graphene oxide hypothesis

As briefly mentioned at the end of the previous section that [111] facets on the surface of dispersed PP-DND are considered to be covered with negatively charged nanographene oxide layer firmly bound in face-to-face fashion with the positively charged nanodiamond surface. It should be added here that the oxidation conditions in the soot-removal step of manufacturing process of DND are strenuous. Most of the manufacturers use hot nitric acid under pressure whereas a few of them use $KMnO_4$ in hot sulfuric acid, in order to completely gasify amorphous carbons (soot). It is hence reasonable to consider that the edge bonds of nanographene layer(s) are broken to free nanographene oxide (NGO) layer(s). Due to strong electrostatic attraction between the negatively charged NGO plane and positively charged [111] facet, NGO pieces will not detach itself from DND. Thus, such nanodiamond should be termed as NGO/DND. As graphene oxide is well-known[17], we should be able to predict the properties of NGO/DND.

Intercalation hypothesis

One of the most remarkable properties known to graphene oxide is its high capacity of intercalation[31-33]. Inevitably, we expect that, when used as the drug carrier, NGO/DND particle should be able to intercalate considerable amounts of solvent water, other solvent molecules, ions and polar molecules. Binding energy of these polar molecules will be much larger, at least twice, when intercalated than when simply absorbed on the top of surface. Consequently, we can assume a two-stage adsorption process when doxorubicin is loaded onto a NGO/DND particle. At first the drug will find itself sitting on the top of [111] facet through strongly ionic anchoring interaction between ammonium group of doxorubicin hydrochloride molecule and carboxylate group on the edge of NGO patch, $>N^+ \cdots O=C<$. Then, doxorubicin will migrate into the interlayer space in the back of NGO for higher binding energy. There will be substitution equilibrium between the drug molecules and preceding occupants of water at the abundant binding sites. We may further assume that the equilibrium can be precisely controlled by choosing the proper concentrations of competing occupants. In the case of doxorubicin, the competitor for binding can be H^+ or metal ions like Na^+ or K^+. Namely we can achieve very slow release of drug, after confirming that all the administered drug-ND conjugate particles have completely entered into the cancer cell, by adjusting pH or salt concentration of blood. The *slow release* of drug molecules from the carrier within the malignant tumor cell is one of the goals in our idea of new DDS. So far this goal is under control during our preliminary animal tests. The other goals are suppression of side effects from the apoptosis-inducing drugs like doxorubicin; and biocompatibility. Both goals have been achieved to satisfactory levels. It is hoped that quantitative equilibrium experiments be extensively studied *in vitro* to differentiate the intercalation and surface absorption-desorption mechanism.

The graphene oxide and intercalation hypotheses presented above are at the moment under strict experimental confirmation by applying TGA, DSC and other analytical techniques. A few other, no less interesting applications are being developed, and described elsewhere[34].

Advantages and disadvantages of nanotechnology

Persistent neglect of dispersing nanodiamond, or nanoparticles in general, before use by majority of workers, seems to arise from the lack of recognition on the *smallness* of nanoparticles, especially in single-nano particles. First of all, it must be made clear that our diamond product, dispersed NGO/DND, is invisible in dispersed state. This means that when one buys visible nanodiamond powder from commercial suppliers, they are aggregates; hence it must be dispersed to invisible primary particles before use. However, it is generally difficult in most of the laboratories to find intense ultrasonic processors and instruments to measure the particle size of nanoparticle colloids. Hence many people work on un-dispersed nanodiamond powder and interpret the results in terms of dispersed particles. Why is this practice still going on? The reason would be that these people do not realize the smallness of nanoparticles. Another reason seems to be that chemistry hardly had this problem.

Molecules are, by 2 to 4-digits, smaller than nanoparticles and usually dissolve in appropriate solvents

giving molecularly dispersed solution. In this way or the other, molecules can be purified to 100%. Due to this fortunate situation, chemistry has developed quickly in the past 200 years. There is still another reason that made chemistry much easier than nano-technology, and this is the central concern of this section, which is the fact that early wise chemists created a nice way to measure molecules by a unit called *mole*, which is essentially weight-based number. Mole number of any chemical is obtained by dividing its weight by its molecular weight. One mole of any molecule contains the same number of mole-cules, namely 6.02×10^{23}, called Avogadro number. In this way, chemistry has nicely avoided using very large number for daily use.

Single-nano particles correspond to low polymers in terms of size and number of constituent atoms. For example, our 3.7nm NGO/DND particle consists of 3882 carbon atoms to give a molecular weight of 46,583, if we assume a hypothetical spherical di-amond particle with the same density as bulk di-amond. Then, simple computation gives a useful quantity: the number of particles contained in a unit weight of NGO/DND, or number density, which is equal to 1.29×10^{19} particles. Such large number of particles in 1g demonstrates how small one particle of NGO/DND is. Let me give a more direct example: 1µl (fraction of one drop) of 0.1% colloidal dispersion of NGO/DND contains about 10^{12} or one trillion or million times million particles!

The number effect, as we tentatively call it, means that the astronomical number of single-nano par-ticles exist in a very small weight. In the DDS on NGO/DND platform, or generally speaking any op-eration with single-nano particles, each particle be-haves independently in its function, hence the over-all effect is proportional to the number of particles used. In DDS, it is not easy to calculate the neces-sary number of particles to cure a cancer patient, but basically we want to cure the patient with the smal-lest possible number of drug molecules in order to avoid unnecessary side effects. In other cases like using NGO/DND particles for the seeding of homoe-pitaxial CVD diamond film, computation of neces-sary number of seeds is easier and crucial for suc-cessful experiment.

We have seen unexpectedly complex structure of NGO-DND particles. This is not a small piece of bulk diamond, the homogeneous and closest packed carbon atoms, but has highly complex, unimaginable and heterogeneous structure, in both geometric and electronic sense. It is likely that other nanoparticles have similarly complex structures and function like nanofactories.

Nanoparticles are different from molecules in that the former are of complex constitution like PP-DND, whereas the latter are simply made of atoms, many of which being common among different molecules. Hence we cannot replace the number of particles by conventional unit like *mole*, but we must use differ-ent number density for different nanoparticles. This is a common principle in nanotechnology, unknown to many workers.

Nanotechnology has long gone out of the list of in-vestors, because visible developments are too slow. However, all the indications in science and technol-ogy are clearly, visibly and rapidly moving towards nano. Investors do not realize the situation because they rarely read scientific papers. At the same time scientists are realizing the difficulty in nanotechnolo-gy better and better. We suppose nanotechnology will be visible to everyone at least a few decades later. It is hoped that earlier applications of nano-technology will appear soon so that the benefit of nano will be recognized well by public.

Summary

Detonation nanodiamond, the latest nanocarbon to appear in the arena of nanotechnology, began to yield to our research to reveal its structure and properties only recently. It is the smallest known sin-gle crystalline diamond (3.7 nm in diameter) among man-made diamonds that can be produced on in-dustrial scale. Geometrically, it is of a core-shell type with the shell consisting of patches of graphene oxide strongly bound on [111] facets in face-to-face mode by Coulombic force. Free spins that were generated during the first step of spontaneous di-amond-graphite transition on the new surface of di-amond core are all moved over to the graphene oxide layer to produce negative electrostatic field above the surface, whereas corresponding positive electrostatic field are generated in the diamond core.

One of the most promising applications of DND is its use as the platform for a new DDS, wherein the gra-phene oxide patches serve as firm pockets for drugs to be stored or intercalated deep below the patch during transport to malignant cells. Animal tests have been conducted successfully to cure mice in-fected by breast and lung cancer, which in the ab-sence of nanodiamond carriers would develop strong resistance to chemotherapy.

Generally slow developments of nanotechnology is defended here by invoking unprecedented difficulties inherent to this new technology, aggravated by our inability to purify nanoparticles. Number density ef-fect was presented to be one of the basic assets of nanotechnology.

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Conflict of interest: None

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