Functionality is Key: Recent Progress in the Surface Modification of Nanodiamond

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Dedicated to Prof. Wolfgang Kiefer on the occasion of his 70 birthday

Nanoscale diamond has recently received considerable attention due to the various possible applications such as luminescence imaging, drug delivery, quantum engineering, surface coatings, seeding etc. For most of these fields a suitable surface termination and functionalization of the diamond materials are required. In this feature article we discuss recent achievements in the field of surface modification of nanoscale diamond including the establishment of a homogeneous initial surface termination, the covalent and non-covalent immobilization of different functional moieties as well as the subsequent grafting of larger (bio)molecules onto previously functionalized nanodiamond.

1. Introduction

Amidst the other members of the nanocarbon family, nanoscale diamond has only recently taken a place on the center stage. Nevertheless, research activity soared in the last few years fueled by discoveries such as the stable luminescence from lattice defects[1–3] and the finding that its favorable properties such as chemical inertness, biocompatibility, rather easy availability among others make it an ideal material for biomedical and electronic applications.[4–8] Other forms of diamond, namely microcrystalline and bulk material as well as diamond films have already been used for a long time.[9–12] The surface termination especially of diamond films produced by chemical vapor deposition (CVD) always played an important role in the discussion of the films' properties.[13–15] Typically, the surface of as-grown diamond films is terminated with hydrogen which also ensures the absence of sp^2 carbon on the film's surface.[16] Plasma treatment or thermal modification in air allow to produce a hydrophilic diamond surface carrying either different ketone related groups (either with C=O or the related bridging –O–moieties) or carboxylic acids.[17,18] In 1998 Ohtani et al. reported the chlorination and subsequent formation of quaternary pyridinium salts on a CVD diamond surface.[19] Other important achievements include the covalent grafting of alkyl chains with additional terminal groups onto hydrogenated CVD diamond by the photochemical grafting of the respective alkenes,[20,21] the fluorination of diamond films,[22] radical reactions on diamond films[23] as well as the application of other techniques derived from silicon technology.[24,25] Nebel and coworkers demonstrated the selective binding of DNA strands onto remaining hydrogenated areas of a diamond film after structured surface oxidation.[26] Such biofunctionalized films can be employed e.g.,, in sensor architectures.

In addition to covalent surface modification, diamond films with different surface termination have been used to adsorb organic compounds such as small molecules like allyl alcohol,[27] or complex structures such as DNA or enzymes e.g., for the production of sensing devices or the delivery of therapeutic agents.[28–31]

In addition to those well-established chemical methods and diamond applications employing more or less continuous films, the advent of nanoscale diamond materials with isolated particles enabled the development of new directions in the application of diamond. This feature article discusses the available methods for the reliable and well-controlled surface modification of such nanodiamond starting with materials of different origin.

2. Initial Surface Termination of Nanoscale Diamond and its Homogenization

The diversity of available diamond materials has increased since the early days of nanodiamond made by detonation or shockwave synthesis in the 60's of the last century.[32–34] In addition to those powders that are by now available even on an industrial scale the production of nanoparticles starting from HTHP (high pressure-high temperature synthesis) diamond and CVD (chemical vapor deposition) diamond provides nanodiamond materials with surprisingly different properties. Although the lattice structure (except for the density of twins, dislocations or other lattice defects) is more or less identical for all diamond

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nanoparticles, the size and surface of the resulting particles differ depending on the method used for their production.[35–37] Most of the available diamond nanoparticles carry an oxygenated surface. This is due to e.g., the application of water or ice for the cooling in the detonation process, which results in the reaction with highly reactive hydroxyl species. Additionally, the purification of nanoscale diamond is most often executed using oxidizing mineral acids and/or air oxidation.[38–42] Both treatments lead to the formation of carbonyl and carboxyl groups on the diamond surface. Only nanodiamond derived from CVD films would initially carry a hydrogenated surface as the feed gas for the deposition of the diamond films consists of a carbon source and a significant amount of hydrogen gas to ensure the continued sp^3 hybridization of the deposited carbon by saturation with hydrogen atoms.[16,43,44] However, subsequent treatment for the isolation of single particles from continuous films (such as acid or mechanochemical treatment) also lead to materials with a largely oxidized surface.[45]

The main surface groups that are found on diamond nanoparticles include the above mentioned COOH and C=O groups in addition to different alcohol functions (tertiary, secondary, primary) and ether groups.[46–51] However, other structural elements such as areas with sp^2 carbon of different nature (isolated double bonds, extended areas with π-conjugation up to graphene-like or graphitic structures) are also detectable on nanodiamond (**Figure 1**). The surfaces exhibit different zetapotentials ranging from –50 mV to +50 mV depending on their termination with those groups. Accordingly, the agglomeration behavior of nanodiamond of different origin varies significantly. While nanoparticles derived from HTHP or CVD materials show only a moderate tendency towards agglomeration, detonation nanodiamond usually occurs in strongly bound agglomerates if no countermeasures are taken.[52–54] In recent years several techniques have been developed to produce fully dispersed diamond nanoparticles in different solvents using mostly mechanochemical approaches.[55–60]

It is obvious that for a high reproducibility of further reactions the nanoparticles' surface should be as homogeneous as possible. The initial control of the surface termination will eventually decide on the quality of the final functionalized material and its applicability.

2.1. Carboxylated Nanodiamond

As already discussed above one of the possible surface terminations on diamond is the carboxyl group. It represents the most oxidized state of a carbon surface, where carbon atoms carrying the oxygens are attached by just one single bond to the diamond lattice. They saturate the otherwise dangling bonds on the diamond core (which would be located on the apices of the adamantane units). In order to establish a homogeneous layer of COOH groups on the diamond surface it is necessary to achieve maximum oxidation. This is inevitably accompanied by material loss and size reduction of the diamond core and the formation of carbon dioxide and monoxide as oxidation products.[61] Harsh oxidation can be carried out using mixtures of strongly oxidizing mineral acids (**Figure 2**). A successful mix consists of equal amounts of conc. sulfuric, nitric and perchloric acid or HCl, HNO_3, and H_2SO_4 (reagents to be handled with utmost care!).[38–42,62] It is also possible to apply the so-called "piranha water" (a mixture of sulfuric acid and hydrogen peroxide),[63] concentrated hydrogen peroxide alone[41] or a 3:1 mixture of conc. sulfuric and nitric acids.[51,64] In addition to the formation of the desired carboxyl functions one advantage of these reagents consists in the simultaneous removal of non-diamond carbon. The latter can be also achieved using supercritical water, another strong oxidant (the nature of the resulting oxygen containing surface groups after the hydrothermal treatment requires further study, though).[65,66] In general, the reactivity of disordered sp^2 carbon towards oxidation is significantly higher than that of diamond.[40] Hence, the oxidation of diamond not only introduces oxygenated groups on the surface but also improves the phase purity of the carbonaceous

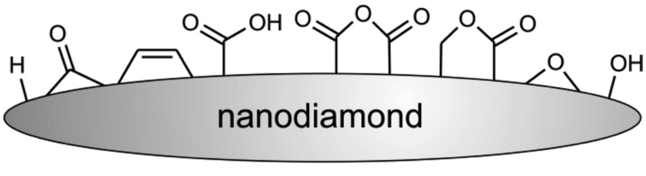

Figure 1. The surface of nanodiamond can be initially terminated with a variety of atoms or groups. The actual surface moieties depend on the production method and the subsequent purification steps.

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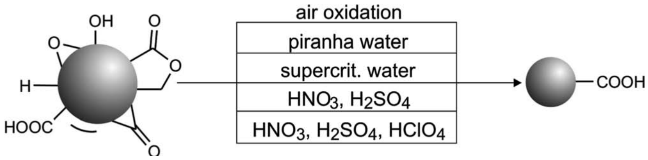

Figure 2. The surface of nanodiamond can be oxidized with various methods. All result in coverage with mainly COOH groups.

material. Other, e.g., metallic impurities are also removed as they are soluble in the acids. To quantify the surface loading with COOH groups several methods are available. One consist in the adsorption of dodecylamine[64] on the carboxylated diamond by zwitterion formation and the subsequent gravimetric determination of the amount of active acid groups. Another method to quantify the amount of acid groups on the diamond particles uses the Boehm titration.[49] However, the results are only reliable if attention is paid to the complete removal of dissolved CO_2 from the analyzed solution immediately before the titration.[67] The technique can be also used to distinguish between oxygenated surface groups of different acidity.

Air oxidation is yet another way to introduce oxygen containing surface groups on nanodiamond. Gogotsi and coworkers have reported on the control of the sp^3/sp^2 ratio by means of careful oxidation in air at elevated temperatures.[42] They found that the chosen temperature is decisive for the selective oxidation of non-diamond carbon. A minimum temperature of typically ~400 °C is required for the onset of the oxidation. Above 450 °C then all kinds of nanoscale carbon undergo oxidation; hence the diamond is lost together with the sp^2 material. In the favorable temperature range around 425 °C the sp^2 carbon is selectively etched and a high amount of oxygenated surface groups is established on the remaining nanodiamond. This technique has been used by Smith et al. to remove sp^2 carbon from nanoscale diamond of different diameter and to improve the luminescence properties of inherent N-V centers (nitrogen-vacancy centers) in these diamonds.[68] Other authors applied significantly higher temperatures (and accepted higher material loss) for the complete removal of sp^2 carbon and the oxidation of the diamond surface.[39] The majority of the existing surface groups after air treatment are most likely COOH groups in addition to ketones and aldehydes, ethers and alcohols. A final assessment has still to be done though. Furthermore, the application of air oxidation has also been used to deliberately reduce the size of nanoscale diamond particles. In 2004 Gordeev and Korchagina reported on the different reactivity (and the related size diminution) of nanodiamond of different origin towards the oxidation with air.[69] Gaebel et al. reported on the application of air oxidation for the size reduction of luminescent nanodiamond. They found the smallest nanodiamond (ND) particles still exhibiting a stable luminescence from N-V centers to have a size of 8 nm.[70] Actually, it seems that a limit for the oxidative size reduction exists. Particles smaller than ~4 nm transform into sp^2 carbon easily when heated in air. This is due to the small difference in stability of sp^2 and sp^3 carbon in this size range. Additionally, the reaction heat of the surface oxidation (which is an exothermic process) provides energy locally, therefore furthering the transformation. As small nanodiamonds are also more prone to oxidation than larger diamond objects,[71] they will be removed during air oxidation together with sp^2 carbon. Such treatment results then in the increase of the average size of the remaining diamond nanoparticles and can be used to control the size of the nanocrystallites while improving the material's purity at the same time.[72] All of these oxidized samples (whether air oxidized or treated with oxidizing acids) show a hydrophilic character, typically zetapotentials of –30 to –50 mV and can be dispersed in polar media.

2.2. Hydroxylated Nanodiamond

Not only carboxyl and keto groups are useful for the further functionalization of nanodiamond. Also hydroxyl functions enable a broad variety of subsequent reactions. Therefore, the homogeneous covering of the nanodiamond's surface with a high amount of OH groups is among the most investigated surface homogenization techniques. Several approaches have been reported so far (**Figure 3**). In 2006 Krueger et al. applied

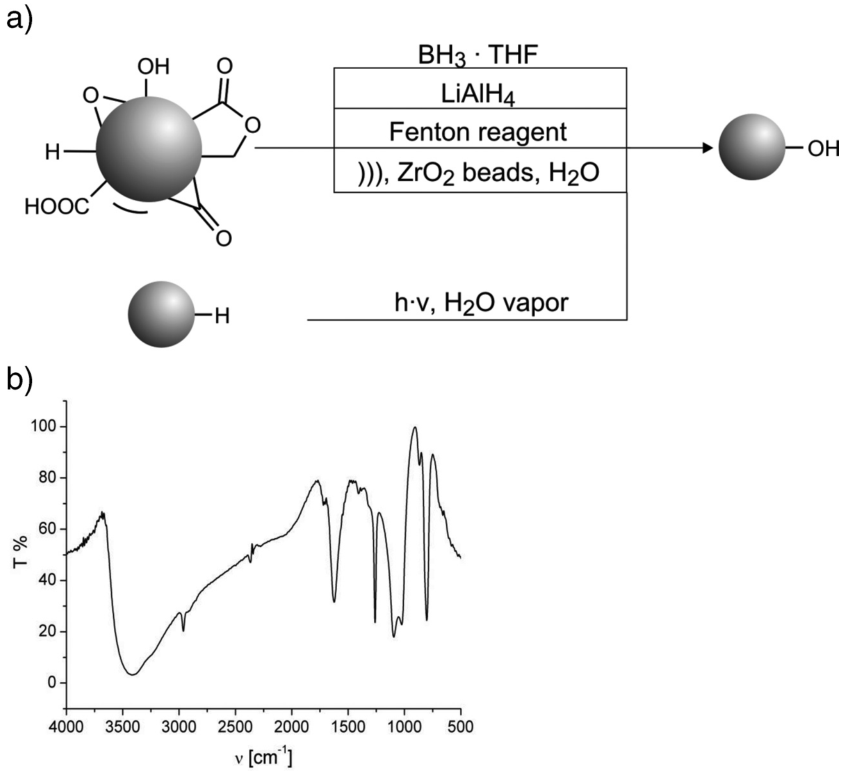

Figure 3. Formation of hydroxyl groups on nanodiamond can be either carried out by reduction reactions of oxygen terminated ND or by the oxidation of hydrogenated ND (a); one simple method is to generate OH radicals mechanochemically. The FTIR spectrum of a detonation diamond sample milled in water shows characteristic signals of OH groups and ether moieties (b).

the reduction of existing oxygenated surface groups carrying C=O moieties (such as ketones, acids) with borane.[73,74] The resulting hydroxylated diamond carried up to 0.5 mmol g^{-1} of OH groups. These OH groups could then be used for silylation or acylation reactions (see below). However, depending on the nature of the initial surface groups on the ND the borane reduction is not always the optimal way to remove all kinds of carbonyl functions. Namely esters or lactones cannot be easily reduced by boranes (and can still be identified after the borane reduction, e.g., in FTIR spectra). On the other hand, the employment of borane brings some added value. The reaction of sp^2 carbon (i.e.,, disordered and graphitic material) with borane followed by an acidic workup can reduce unsaturated fragments such as double bonds to saturated structures with sp^3 hybridized carbon carrying hydrogen atoms (this is also a very simple way to introduce C–H bonds without using gaseous hydrogen). In order to fully reduce all kinds of acid derivatives highly reactive complex hydrides can be used. The best suited is $LiAlH_4$, which is reducing all kinds of C=O related functional groups to alcohol moieties (it cannot remove sp^2 carbon by hydrogenation, though). Lithium aluminium hydride has been used e.g., by Ida et al.,[75] Zheng et al.[76] and Ciftan Hens et al.[77] for the reduction of C=O containing surface groups on different kinds of diamond. Care should be taken, though, that all side products (i.e.,, aluminium oxide hydroxides) are removed. Simple acidic workup using hydrochloric acid is usually not sufficient and complexing agents such as citrate should be applied in the purification process.

Another highly efficient way for the direct establishment of OH groups on the ND surface consists in the reaction of pristine nanodiamond with the so-called Fenton reagent. This mixture of hydrogen peroxide and $FeSO_4$ in strongly acidic solution is well-known to be a versatile oxidant. Garcia and coworkers reported on the successful oxidation of detonation nanodiamond with this reagent.[78,79] The effect of this treatment is twofold: The surface of the diamond is freed from non-diamond carbon by oxidative removal (formation of CO_2) and the OH radicals generated in situ react with the diamond surface forming a hydroxylated diamond ND-OH. Such highly hydroxylated nanodiamond can be used for a variety of covalent and non-covalent interactions with larger functional moieties (see below).

One of the simplest ways to introduce a considerable amount of OH groups on fully dispersed primary particles of nanodiamond consists in the mechanochemical treatment of the initial agglomerates in water. When submitting detonation diamond slurries to attrition milling[52] or beads assisted sonic disintegration (BASD),[55] the particles become significantly more hydrophilic, the zetapotential rises to ~+40 mV (at neutral pH) and stable colloidal solutions of the OH terminated particles in water are obtained (a significant increase of the OH-related bands in the FTIR spectrum is observed, see Figure 3b). These solutions can contain high concentrations of ND (more than 10 wt% ND are usually not possible as gelation due to strong noncovalent interactions by hydrogen bonding occurs at this concentration). It has to be mentioned that all methods mentioned above do not lead to the complete absence of C=O structures when pristine ND material is treated. If this is desired the removal of oxygen containing surface groups is recommended prior to hydroxylation by a method involving OH radicals (Fenton, BASD or attrition milling in water, photochemical hydroxylation).

Girard et al. reported on the photochemical hydroxylation of hydrogenated nanodiamond.[80] The latter was exposed to water vapor in a quartz ampoule and irradiated with UV light. In situ generated OH radicals attack the diamond surface leading to ND-OH. In general, hydroxylated nanodiamond is a very useful derivative of nanoscale ND. It is hydrophilic, easily dispersed in aqueous solution or other polar solvents, typically exhibits zetapotentials of ~+40 mV and can be used to immobilize functional moieties covalently or by adsorption (see below).

2.3. Hydrogenated Nanodiamond

The hydrogenation of the diamond surface starting from oxidized material turned out to be rather difficult. Most reactions using reducing agents do not actually lead to the complete removal of the functional groups but rather to the formation of different types of hydroxyl functions (see Section 2.2). Early reports suggest that the main reactions during the treatment of detonation ND in hydrogen (either at high temperatures or in plasma) are decarbonylation and decarboxylation.[81] Only the direct reaction with elemental hydrogen enables the formation of C–H bonds on the diamond surface. One possible way of doing so is the application of hydrogen gas at elevated temperatures. This method was e.g., applied by Spitsyn et al.[82] However, the authors state that in addition to the formation of C–H bonds, an increase of the amount of OH-groups is observed at the applied temperatures (850 °C). Tsubota and coworkers used the method to hydrogenate sub-micron diamond at ~900 °C. The resulting materials show hydrophobic properties and clear evidence of C–H bond formation e.g., in the IR spectrum.[83] However, this technique is not easily applicable to nanoscale diamond with particle sizes smaller than ~100 nm. The required temperatures exceed the acceptable values especially for very small particles. Typically, ~900 °C are used to achieve a sufficient reactivity. Small diamond particles form significant amounts of graphitic carbon at these temperatures, which cannot be fully avoided by the hydrogen flow. Therefore, techniques requiring less problematic temperatures have to be used. One option is to simply reduce the temperature of the hydrogenation reaction. Several groups have reported on such treatments and observed at least a partial coverage with C–H bonds as documented by the hydrophobic character of the resulting products.[84,85] In organic chemistry the hydrogenation is typically carried out using a metal catalyst, i.e.,, palladium, platinum or sometimes nickel based catalysts.[86,87] So far, no report on the catalytic hydrogenation of nanodiamond has appeared, most likely due to the difficult removal of the catalysts. Namely those catalysts that are prepared on activated charcoal are the most difficult to remove. Others require the employment of oxidizing mineral acids for their removal, which would immediately re-oxidize the diamond surface.

One option to avoid these problems and to increase the reactivity of the hydrogen gas is the hydrogenation in a plasma reactor. In there, the hydrogen molecules are broken apart and highly reactive species in a reductive atmosphere ensure the desired attack on the diamond surface. For diamond films the treatment in hydrogen plasma is a well-established technique.[16–18] When applying it to nanopowders measures against an inhomogeneous reaction of the immense surface (partially hidden and with limited access in thick powder layers) have to be taken. Loh and coworkers repeated the hydrogenation of air-oxidized detonation diamond in a microwave plasma reactor at 800 °C twice for 60 min.[88] Another procedure involves the application of a hot filament for the production of atomic hydrogen which reacts with graphitized nanodiamond to form hydrogenated nanocrystallites.[89] Recently, Girard et al. conceived a special reactor to overcome the inhomogeneity of the reaction, putting the whole sample in a rotating quartz tube and thereby achieving a homogeneous hydrogenation of the diamond powder in a microwave plasma reactor (**Figure 4**).[80,90,91]

2.4. Nanodiamond with sp^2 Carbon at its Surface

In addition to the establishment of a homogeneous layer of directly bound functional groups or atoms, the removal of all existing surface groups represents another option for the homogenization of the nanodiamond surface. For diamond films the so-called reconstruction of the surface is thermally achieved by removing all existing surface heteroatoms or groups. It results in different, highly ordered arrangements of π-bonds on the diamond surface depending on the lattice orientation of the surface.[92,93] The same transformation should be feasible for diamond particles.[94,95] And indeed the partial or even complete conversion of nanodiamond particles into “bucky diamonds” (nanodiamond with a multilayer graphitic shell) or carbon onions (multishell fullerene-like objects) has been reported in the past. The transformation can either be induced by thermal treatment[96–98] or by irradiation with high energy electrons, e.g., in a TEM.[99–101] For a preparative use the thermal treatment conditions have to be chosen carefully in order to form a very thin sp2 carbon layer (preferentially one graphene layer or less). Temperature, duration and the prevailing vacuum are the major factors of success. The actual reactivity of the diamond nanoparticles depends on their size (the smaller, the more reactive), their shape (~spherical is usually more reactive than material with pronounced facets) and the initial amount of sp^2 carbon on the nanoparticles’ surface. Hwang and coworkers for instance reported on the thermal treatment of previously air-oxidized submicron (<0.25 μm) diamond at 1200 °C for 1–3 hours and the subsequent radical reaction of the generated sp^2 carbon.[102] They observed the generation of well-ordered graphitic material which reacted like the sidewalls of a carbon nanotube. For smaller diamond, i.e., detonation ND, the annealing temperatures need to be much lower in order to avoid thorough graphitization and the formation of bucky diamond or carbon onions. We found that a thermal annealing at 750 °C for 2 h and under a vacuum of 10^{-3} mbar is sufficient for the complete removal of the oxygenated surface groups and the formation of reactive sp^2 carbon (**Figure 5**).[103] Higher temperatures always lead to the formation of multilayer sp^2 carbon. If too pronounced the graphitic material governs the properties of the nanoparticle which in the outcome does not behave like a diamond anymore.

Surprisingly, in our hands a better vacuum does not give better results in the annealing step. On the contrary, higher amounts of surface groups remain on the ND surface as indicated by persisting signals e.g of carbonyl functions in the FTIR spectra. It seems that a residual amount of oxygen is necessary for the removal of less reactive surface groups. The reaction could probably be considered as an initial etching step before the actual annealing and formation of sp^2 carbon sets in. Arnault and coworkers observed that detonation ND that has been spin coated onto silicon nitride covered silicon substrates could withstand higher temperatures before the desorption of surface groups or the surface annealing starts. This is either due to the stabilizing effect of the silicon nitride layer or the fact that their experiment took place in very high vacuum (where the proposed initial etching step is not possible as no oxygen traces are present).[104] In addition to the thermal annealing of the ND surface it is also possible to induce the formation of sp^2 carbon by mechanical means. Prolonged milling time (attrition mill or BASD) in the deagglomeration of detonation diamond leads to the formation of sp^2 carbon, most likely as a result of recombination reactions between dangling bonds generated by the mechanical treatment.[56]

Some pristine nanodiamond materials contain varying amounts of non-diamond carbon resulting from graphitization processes during their fabrication, e.g., in the detonation synthesis.[105–107] However, the amount and structure cannot be fully controlled as the harsh production conditions and the various purification steps result in a rather irreproducible composition of the material. Therefore, such disordered non-diamond carbon should be removed even if an sp^2-terminated diamond surface is desired. Several methods have been proven to remove sp^2 carbon from nanodiamond soots. The treatment with supercritical water can be used to selectively etch away non-diamond carbon.[65] It is also possible to use ozone,[108,109] mixtures of

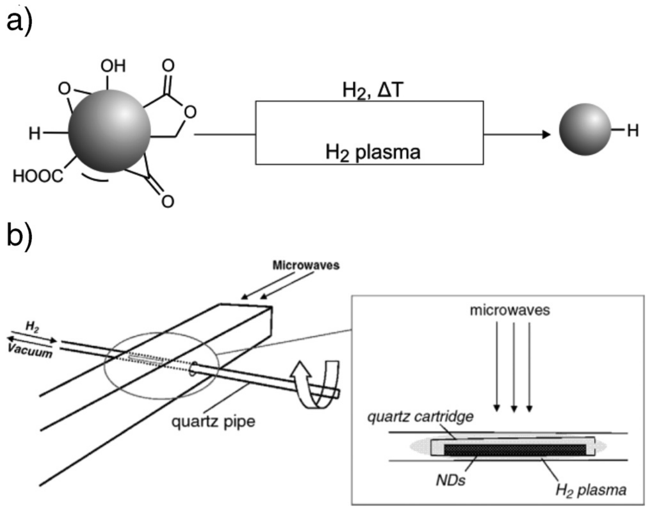

Figure 4. a)The hydrogenation of ND either at elevated temperatures or in a hydrogen plasma leads to the formation of C–H bonds on the surface and hydrophobic properties; b) Scheme of the rotating plasma reactor for the homogeneous hydrogenation of ND. Reproduced with permission.[90] Copyright 2011, Elsevier.

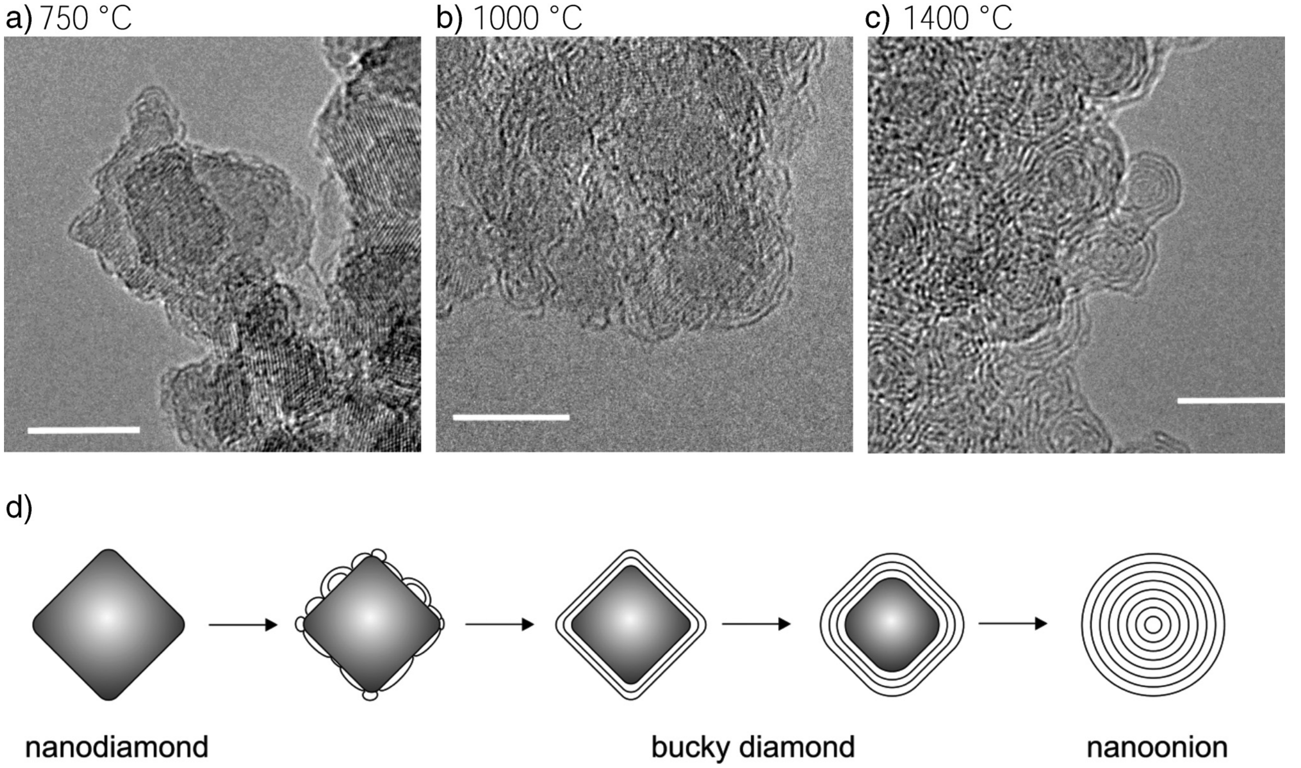

Figure 5. a) HRTEM images of detonation nanodiamond annealed at a) 750, b) 1000 and c) 1400 °C for 2 h at 10^{-3} mbar (all scale bars 5 nm); d) schematic representation of the structural changes induced by thermal annealing at different temperatures (increasing temperature from left to right). For the conservation of the diamond's properties annealing should take place at temperatures below 800 °C. Above this limit significant graphitization is observed for 5 nm particles. Larger particles withstand higher temperatures; nevertheless extended areas of sp^2 carbon are formed on their surfaces, too.

oxidizing acids such as HF/HNO_3 or HNO_3/H_2O_2[40] (see also chapter 2.1) or boric anhydride[110] for the selective oxidation. When gas phase oxidation is used for the etching process, careful control of the temperature and oxygen content of the gas flow is crucial to avoid significant diamond loss.[42] Actually, most purification protocols for the production of nanodiamond with reproducible quality include an oxidation step in order to remove non-diamond carbon. For the introduction of controlled amounts of sp^2 carbon such purified and homogenized nanodiamond is the preferred starting material.

2.5. Amination of the Nanodiamond Surface

The direct amination of the nanodiamond surface is of high interest as it would enable the straightforward binding of a large variety of functional molecules such as bioactive compounds or polymer building blocks by amide formation, reductive amination, nucleophilic attack or direct condensation reactions. However, the direct amination of the nanodiamond surface turned out to be rather difficult. Until now, the direct grafting of amino groups onto the surface of true nanodiamond was not fully successful. The only report on the formation of NH_2 groups on the diamond surface by reacting chlorinated diamond with gaseous ammonia at elevated temperature was carried out using submicron particles (~0.5 μm).[111] However, approaches including the photochemical[112] or plasma treatment[113] with ammonia have been efficient for nanocrystalline diamond films and should eventually lead to aminated nanoscale diamond particles. For the time being, other paths have to be taken in order to establish the highly versatile amino groups on nanodiamond.

Therefore, strategies that establish the amino functions somewhat more far away from the diamond surface have been employed. They include the use of aminated silanes,[73,74] the grafting of aminated aromatic moieties[88] (see also chapter 4.4 for covalent attachment of aromatic rings), and the formation of aminomethyl groups. The latter has been reported by Shenderova and colleagues. They employed a multistep method starting with hydroxylated nanodiamond.[77] After the tosylation and subsequent substitution of the leaving group by nitrile moieties the latter have been reduced to aminomethyl groups using lithium aluminium hydride. As could be seen by the subsequent immobilization of biotin onto the resulting material the reaction sequence was successful. Nevertheless, it actually remains unclear how the substitution of the tosylate could take place as the usually observed S_N2 reaction cannot occur due to the structural situation (the diamond itself is blocking the required nucleophilic attack of the cyanide from the backside). Another reaction mechanism like the formation of an intermediate carbenium ion or the occurrence of a stepwise elimination-addition process should be discussed.

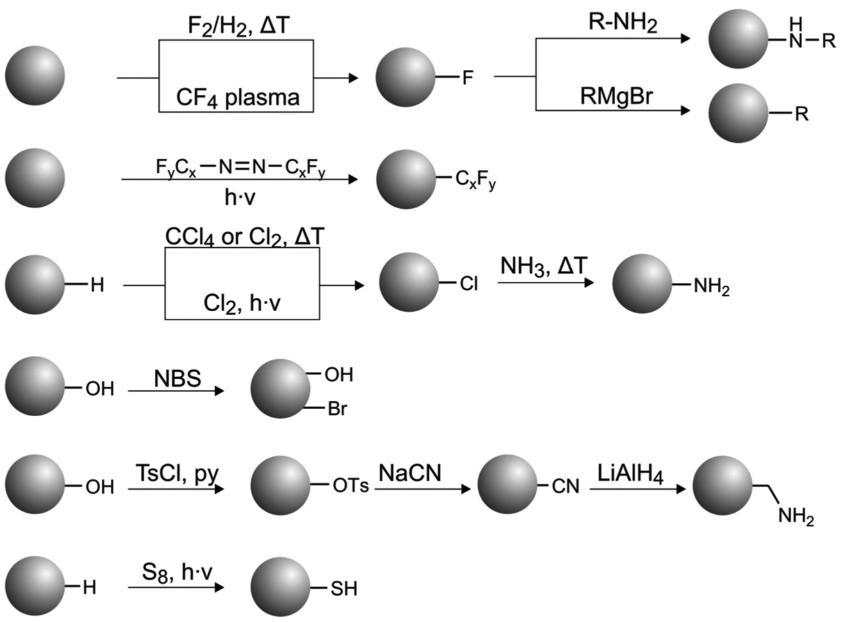

Figure 6. Further methods to functionalize the nanodiamond surface include the halogenation, the amination and the formation of thiol and nitrile groups. Subsequent reactions open further possibilities for homogeneous surface termination (Icons for ND that do not show specific termination symbolize the possibility to start with different materials).

2.6. Other Functional Groups at the Nanodiamond Surface

Besides the already mentioned surface terminations of nanodiamond there exist other functional groups that can be grafted directly onto binding sites on the diamond lattice (**Figure 6**). The most prominent of those "less common" groups is probably fluorine. It can be introduced in a gas phase reaction of F_2/H_2 mixtures at elevated temperatures. Khabashesku and coworkers have successfully applied this technique to achieve high surface loadings with fluorine atoms, which can be easily substituted in subsequent reactions (see below).[114] Ray et al. applied atmospheric pressure plasma with CF_4 for the grafting of fluorine atoms at the surface of different types of ND.[22] Besides the fluorination of the diamond surface the introduction of higher halogens was intensively studied. The most successful method for the introduction of chlorine atoms on the diamond surface is the photochemical reaction of gaseous chlorine with hydrogenated nanodiamond.[111] Other methods include the thermal chlorination with Cl_2 or CCl_4.[82] The partial bromination of nanodiamond was achieved using a wet-chemical reaction of hydroxylated nanodiamond with *N*-bromosuccinimide (NBS) in CCl_4.[79]

However, it turned out that the bond strength of the higher halogens with the carbon atoms is not very high. The resulting chlorinated (or partially brominated) ND derivatives cannot be stored under ambient conditions as they react immediately with air humidity (or with oxygen itself) to form at least partially hydroxylated surfaces as in halohydrines. This is most likely due to the fact that a large number of halogen atoms are bound to tertiary carbon atoms. As they represent good leaving groups and tertiary cations are reasonably stabilized, the cleavage of the bond between the carbon atom and the halogen is likely. In the presence of a sufficiently nucleophilic reagent (such as water) the substitution reaction can proceed easily. This process does not take place in the case of fluorine as the latter is considered to be a rather bad leaving group and only very strong nucleophiles such as metal organic compounds or amines can replace the fluorine atoms.

Other groups of interest include all moieties containing sulfur, namely those where the sulfur has a negative oxidation number. These groups are very useful for the formation or even self assembly of conjugates of ND with noble metals, mainly gold. Such interaction is a prerequisite for the production of plasmonic structures where ND (with luminescent lattice defects) interacts with nanostructures such as cavities or antennas.[115] Nakamura and coworkers have presented a reaction scheme where diamond reacts directly with molecular sulfur.[116] They generated reactive sulfur species from S_8 photochemically. So far, the nature of the groups has not been fully elucidated, nevertheless their interaction with gold surfaces indicates the formation of thiols or related moieties. Besides this direct thiolation of the ND surface several approaches have been presented to establish SH groups at the tip of a short linker. Aromatic linkers can be used, either for the establishment of sulfonic acids or (after suitable reduction) of thiols.[103]

3. Noncovalent Surface Modification

A very flexible and comparatively easy way to establish the required functional groups on the surface of nanoparticles of any kind is the coating with non-covalently attached molecules. Of course this concept is also applicable to diamond nanoparticles. Depending on the termination of the nanodiamond surface the materials exhibit different adsorption properties. The typical nanodiamond after acid treatment exhibits a hydrophilic surface with quite large amounts of different oxygen-containing functional groups (see above). Such surface structures enable the formation of numerous hydrogen bonds with suitable polar compounds. One single interaction of this type might not be as strong as a covalent bond,[117] but typically, several or even large numbers of these bonds are formed by one attached molecule provided that it possesses a respective number of suitable active groups. The contributions of all these non-covalent interactions sum up to considerable overall bond strength. Especially for the immobilization of larger biomolecules this property comes in handy, as the molecules can be used in their unaltered, natural state. Ho and colleagues have in this way immobilized bovine insulin on detonation nanodiamond (**Figure 7**).[118] Further examples include the immobilization of cytochrome c,[119] lysozyme[120–122] and apoobelin.[123] All these molecules retain their functionality, although in most cases with somewhat less efficiency.

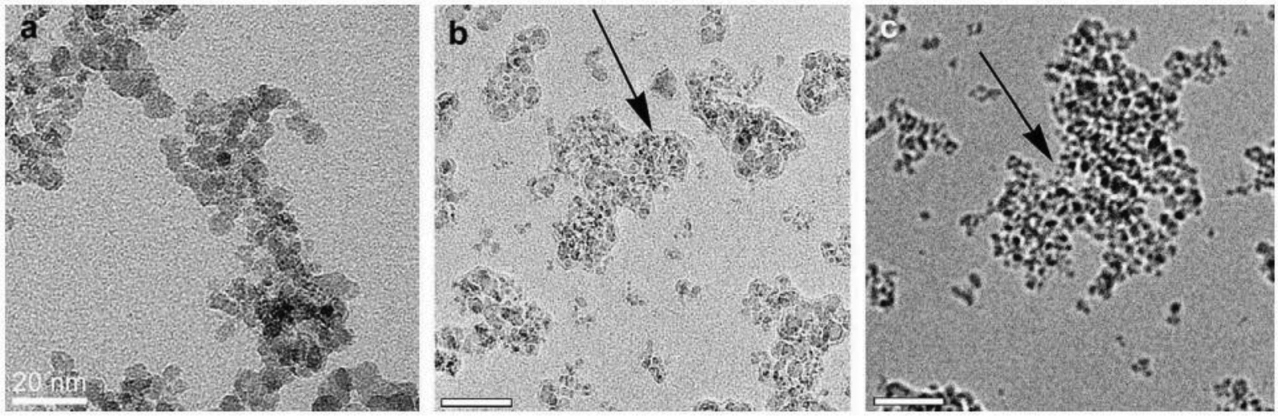

Figure 7. HRTEM images of a) untreated ND; b) ND-insulin conjugates (the arrow indicates the layer of organic matter around the NDs; c) as expected the treatment of the ND-insulin conjugates with aq. NaOH leads to the removal of the biomolecule and the redispersion of the ND (scale bars in b,c: 50 nm). Insulin non-covalently binds to the ND surface in water by means of electrostatic and other interactions. The shift to an alkaline environment alters the insulin surface charge characteristics, thereby causing release from the ND surface. Reproduced with permission.[118] Copyright 2011, Elsevier.

Also drug molecules and other bioactive compounds can be immobilized by non-covalent interactions on the surface of ND particles. Such conjugates can be used to deliver drugs or to solubilize too lipophilic compounds by grafting onto the nanodiamond. Ho and coworkers have reported on doxorubicin immobilized on ND for a controlled release of the drug.[124,125] Other antitumour compounds that have been non-covalently bound to nanodiamond include 10-hydroxycamptothecin (HCPT)[126] and paclitaxel.[127]

The non-covalent immobilization of large molecules can be also used to coat the nanodiamond with a homogenous shell of a defined polymer. These conjugates can either be intended for the direct application as a composite or to present a certain functional group on the outer surface of the coated ND particle. Chang and coworkers have used *L*-polylysine to produce an ND conjugate with a high number of primary amino groups. These can then be functionalized e.g., by amide formation. In a similar way, they have produced ND-polyarginine conjugates.[128,129] Other composites are formed by the non-covalent conjugation of ND and PANI (polyaniline),[130,131] ND and polyethyleneimine[132] or ND and poly(lactic acid) (PLLA)[133] The biodegradable ND-PLLA composite can be used as a component for biodegradable implants. Recently, the research on non-covalently conjugated composites of ND with polymers has gained considerable momentum as the resulting properties of the composites are very beneficial.[49,59,134–136] In general, the non-covalent incorporation of nanodiamond into polymer matrices results in improved mechanical strength of the material as can be seen in **Figure 8** for a composite of polyvinyl alcohol (PVA) and ND.[135] Therefore, applications not only in implants but also as sturdy and light-weight (construction) materials can be envisaged. Another strong point of diamond is its thermal conductivity which is not accompanied by electrical conductivity (as it is the case for all metallic heat dissipators). Composites containing a nanodiamond concentration above a certain threshold exhibit better thermal conductivity compared to the unfilled polymer.

4. Covalent Surface Modification

For many applications the stable grafting of functional moieties is of high importance. Besides the non-covalent immobilization (which can be quite stable due to multiple interactions!) the formation of covalent bonds between the nanoparticle's surface and the immobilized unit is very useful. The bonding scheme can be adjusted to the structure and functionality of the immobilized molecule. When e.g., enzymes or other bioactive compounds are immobilized non-covalently, the high number of binding sites on the diamond surface might actually hamper

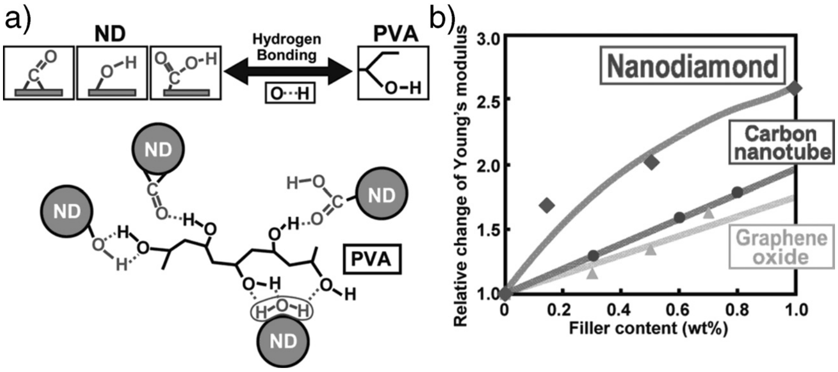

Figure 8. a) Schematic structure of the non-covalent PVA-ND composite. The principal interaction consists of hydrogen bonding between the OH groups of the polyvinyl alcohol (PVA) with oxygen containing surface groups on the ND; b) The incorporation of ND into PVA leads to a significantly stronger increase of the Young's modulus compared to identical amounts of other carbon nanomaterials. Reproduced with permission from.[135] Copyright 2011, American Chemical Society.

their proper function. The strong interaction over large fractions of the molecule's surface can modify its three-dimensional structure or cause an unfavorable orientation of the compound on the surface of the nanodiamond. In these cases it is desirable to enable a specific and preferentially site-selective binding of the functional molecule onto the surface of the nanoparticle, far away from the actual active site of the bioactive compound. If necessary, a stiff linker molecule can ensure the absence of non-specific interactions between the ND surface and the immobilized moiety. These objectives are conveniently met using covalent immobilization. In most cases indeed a spacer or linker unit will be used between the bonding site on the ND surface and the reactive site of the functional molecule.

Starting from different structures on the nanodiamond surface a variety of bonds can be formed by conventional organic chemistry. Although being considered inorganic as a bulk material, nanoscale diamond actually behaves like a huge organic molecule (it is in fact a hydrocarbon with high carbon content and "a few" functional groups at its periphery). It can be considered to be a giant polymantane (family of hydrocarbons consisting of multiple adamantine units). However, the reactivity of nanodiamond is not directly predictable from the chemistry of adamantane or its higher analogues, although these molecules represent the closest relatives concerning the structural properties.[137] Steric hindrance, electronic differences and the nature of the existing surface structures somewhat influence the behavior of ND towards organic reagents. Nevertheless, nanodiamond samples terminated with the groups and structures mentioned in chapter 2 can be considered as at least moderately reactive compounds. In the following paragraphs transformations starting with different surface groups directly grafted onto the ND surface will be discussed. Some of these reactions can be carried out starting with different initial groups (like the arylation using aromatic diazonium salts). They will therefore appear in different contexts to emphasize the flexibility of the surface chemistry on nanodiamond.

4.1 Substitution of Halogens by Nucleophilic Reagents

Halogenated diamond can be considered a suitable starting material for the grafting of more complex moieties. Especially fluorinated diamond nanoparticles serve as substrate for nucleophilic substitutions. The mode of grafting ranges from ethers over amines to C–C single bonds.[114] It is not fully understood, why fluorine can act here as an efficient leaving group. Typically, fluorine atoms are not considered to easily leave the molecule even in protic solvents resulting in the formation of the respective cationic species (as required for the nucleophilic attack in an S_N1 reaction). On the other hand, a classical S_N2 reaction with the nucleophile attacking the reaction center (i.e., the carbon atom) from the backside is hardly imaginable as the diamond particle is in the way! Therefore, other mechanisms must play a role. One possibility consists in a two-step process where the nucleophile acts initially as a base (which would also explain why only highly basic nucleophiles such as amines and metal organic compounds are typically used) leading to the elimination of fluoride and a proton in an E1cb-like mechanism.[138] In the second step the resulting double bond could be attacked by the nucleophile now acting as such. Although nucleophilic additions to double bonds are usually not favored for normal π-bonds, the strained geometry and the electron-poor nature of the surface double bonds on diamond (see also diamond films or C_{60})[139] allows the occurrence of this kind of reaction. In order to proof this hypothesis, it would be effective to apply non-nucleophilic bases to study the proposed initial elimination step (demonstrated by the loss of the fluorine atoms) or nucleophiles with negligible basicity to show either the impossibility of their grafting (and thereby proving the hypothesis) or their reaction with the diamond surface in a different process.

Since the fluorination processes of the starting material requires harsh reaction conditions, there are often more convenient ways to achieve similarly functionalized nanodiamonds based on diamond particles with other initial surface termination. Nevertheless, the replacement of fluorine atoms by amines and metal-organic reagents (Figure 6) represents a useful method, especially for the direct alkylation or the formation of amines directly bound to the diamond lattice.

Amino groups can also be formed starting with chlorinated nanodiamond.[111] The reaction with gaseous ammonia very probably leads to the replacement of chlorine atoms by amino groups.

4.2 The Formation of Amides and Esters on Carboxylated ND

One of the most reliable grafting methods for the immobilization of large proteins is the coupling of amino groups from their side chains onto carboxylated species by the formation of an amide. But also other molecules with free amino groups can be coupled to nanoparticles using efficient peptide coupling techniques as long as the nanoparticle carries carboxylic acid moieties. The direct reaction of amines with COOH groups is enabled by auxiliary reagents such as EEDQ (*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) or the well-known carbodiimides.[140] On the other hand, the respective acid chlorides also undergo amide formation when reacted with amines. This is how Gogotsi *et al.* produced a hydrophobic nanodiamond material. They started with oxidized nanodiamond samples, which carry a high number of carboxylic acid groups. After activation with thionyl chloride they react easily with dodecylamine to form amide bonds.[133,141] The introduction of long hydrocarbon chains gives rise to improved dispersibility in hydrophobic solvents. Interestingly, the functionalized diamond material shows a distinct blue fluorescence upon excitation at 410 nm. The reason for the luminescence is yet to be explored. Lee's research group used the amide linkage to introduce an imidazolinium bromide onto the diamond surface (**Figure 9**). The diamond adduct was found to be highly soluble in ionic liquids and may allow the development of new diamond based composite materials.[142]

Amides can also be generated, if the diamond surface carries amino groups to which carboxylic acids are applied in the presence of a coupling agent. Boukherroub and coworkers used 4-azidobenzoic acid and DCC to graft azide containing groups on nanoscale diamond carrying aminomethyl groups.[143] The amide bond exhibits a reasonable stability against hydrolysis even under moderately basic conditions. However, both

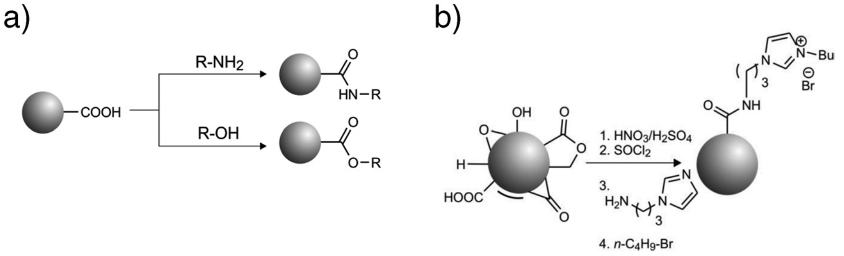

Figure 9. a) Schematic reaction of carboxylated ND with amines and alcohols. Typically, the reaction is either carried out after the formation of the acid chloride or coupling reagents known from peptide chemistry are used; b) By a stepwise carboxylation and chlorination ND-COOH was formed and subsequently reacted with an imidazole-substituted amine. After the ligation the ionic structure was generated by alkylation of the imidazole nitrogen.[142]

ND-CO-NHR and ND-NH-CO-R adducts may be difficult to handle in biological systems as protease enzymes are capable of cleaving the generated amide bonds.[144] On the other hand, this cleaving process might enable a controlled release of immobilized moieties for bioapplications such as drug delivery.

In addition to amide formation, the carboxylic group can be used to form ester linkages when suitable alcohols are applied as reaction partners. These reactions can be performed either directly using acid catalysis or via the significantly more reactive acid chloride. However, the chemical stability of esters compared to amides is reduced, hence such conjugates would be prone to cleavage in aqueous environments (see also Section 4.3).

4.3 Functionalization of Hydroxylated ND

In the case of hydroxylated nanodiamond the initial surface functionalization can be used to carry out a great variety of chemical reactions (**Figure 10**). One example is the generation of ethers, which Cheng and co-workers achieved by reaction of ND-OH with alkyl chlorides in the presence of NaH.[76,127] It shows that NaH is able to deprotonate the surface OH groups on the diamond which then act as nucleophiles that attack the alkyl halide to form an ether.

The hydroxyl groups on nanodiamond can also be used to open the epoxide structure of glycidol and initiate a polymerization. Since the applied diamond starting material contains not only hydroxyl groups but also carboxylic acid functionalities, Komatsu et al. concluded that the branched polymer may be attached to the diamond surface by ester groups as well. Nonetheless, the obtained polyglycerol-diamond conjugate (Figure 10b) shows a very good solubility in various solvents (e.g., up to 20 mg ml^{-1} in water). Moreover, the modified diamonds can be sorted by size-exclusion chromatography (SEC) and characterized by solution NMR spectroscopy.[145]

Furthermore, ND-OH is able to react with carboxylic acid chlorides forming the corresponding esters. Again, the grafting of long alkyl chains increases the solubility in aprotic solvents.[146] However, it has to be mentioned that such ND-esters of alkyl carboxylic acids are not stable against protic solvents such as water and short-chained alcohols. When dispersed in water, methanol or ethanol the acyl groups are cleaved from the surface and the material is recovered as hydroxylated ND. In higher alcohols, such as isopropanol or *tert*-butanol this effect is much less pronounced. Other solvents, namely rather nonpolar ones such as THF (tetrahydrofurane) or dichloromethane, can be used to stably disperse the "esterified ND" without decomposition due to its increased hydrophobicity induced by the long alkyl chains.

The OH functions of ND-OH can be also used for the reaction with oxophilic reagents such as trialkoxysilanes. Using (3-aminopropyl)trimethoxysilane, the terminal amino group of the latter can be subsequently reacted with the carboxylic terminus of peptide chains.[73]

However, the diamond-O-Si bonds are quite sensitive to hydrolysis (especially at lower pH values), which limits the application for protein immobilization in bioapplications. A good alternative is the grafting of peptides on benzoquinone activated diamond nanoparticles.[147]

Another issue related to silanized ND (but not restricted to it) is the occurrence of multiple graftings and intermolecular condensations. These lead to increased agglomerate size and a rather large organic shell surrounding the ND core. Typically, not all of the three alkoxy groups in a conventional trialkoxysilane are able to react with the surface of a single ND particle

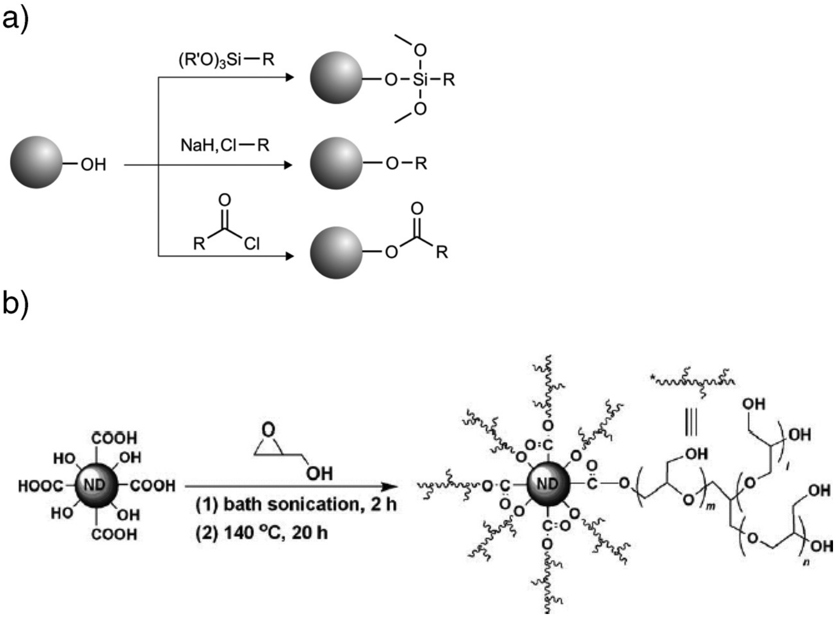

Figure 10. a) Schematic representation of a selection of further grafting reaction onto ND-OH; b) the ring-opening polymerization of glycidol in the presence of oxygenated ND leads to the formation of highly hydrophilic and soluble ND-polyglycerol conjugates which can be sorted by size exclusion chromatography. Reproduced with permission.[145]

(e.g., due to steric constraints and the lack of a sufficient surface concentration of OH groups).

A workaround would be the application of mono- or dialkoxysilanes which are less prone to such crosslinking side reactions. Furthermore, the simultaneous destruction of existing and/or emerging agglomerates using the BASD setup (see above) prevents the formation of large, inhomogeneous aggregates of silanized ND particles. Due to the continuous generation of fresh diamond surface the method can be even used to produce functionalized primary ND particles and to enable the solubilization in nonpolar solvents (provided the applied surface moiety imparts the necessary hydrophobicity to the ND).[56] The sonochemical reaction also furthers the closure of the silane shell by condensation reactions of neighboring silanes and hence avoids the formation of larger multilayer shells and aggregates (**Figure 11**).

Additionally, it is possible to convert the surface OH groups into other functionalities like NH_2, Cl and Br. The establishment of these heteroatoms on the diamond surface is achieved by wet chemical synthetic routes and allows for other reaction paths to build up the primary functionalization (see above).[78,79]

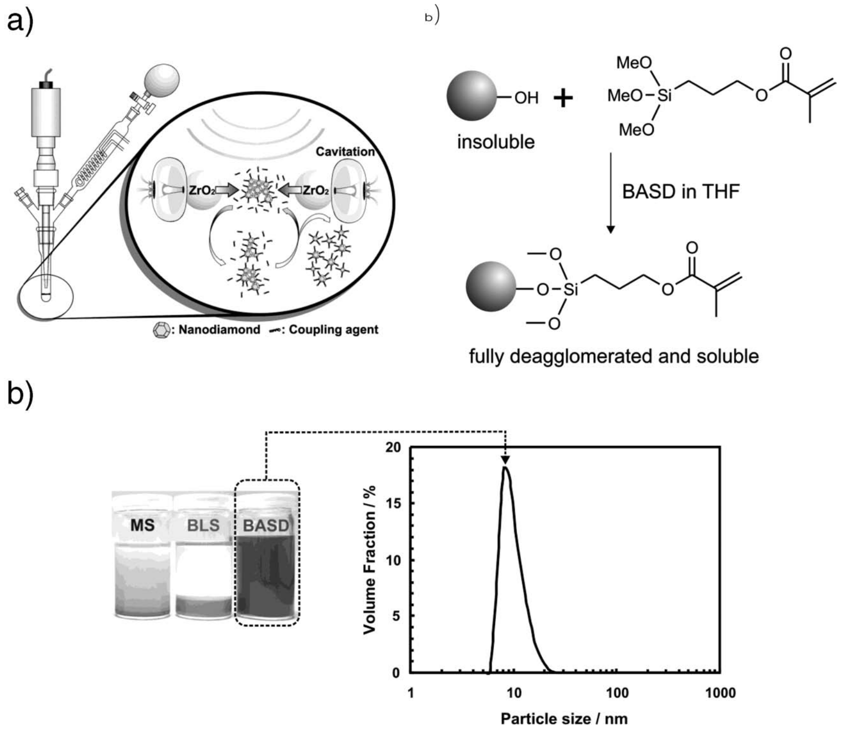

Figure 11. The silanization of hydroxylated nanodiamond leads to strong crosslinking and agglomeration of the nanoparticles if no countermeasures are taken: a) An effective way to obtain fully deagglomerated particles with dense surface functionalization is the beads assisted sonic disintegration (BASD); b) By the continuous formation of fresh surface the particles are eventually completely covered with surface moieties and in the case of the reaction with an nonpolar silane become soluble even in nonpolar media such as tetrahydrofuran (THF); c) Compared to magnetic stirring (MS) and bead-less sonication (BLS) the sample reacted with the silane under BASD conditions become soluble in THF with a particle size of <10 nm (determined by dynamic light scattering). b) Reproduced with permission.[56] Copyright 2009, American Chemical Society.

4.4 Grafting onto Hydrogenated and Annealed Nanodiamond

The hydrogenated diamond surface is known to be accessible to a variety of reactions. For diamond films the photochemical and electrochemical functionalization of such surfaces has been studied in detail. A recent review by Zhong and Loh describes the possible transformations in great detail.[148] Some of these reactions can be transferred to diamond nanoparticles as well. Nakamura et al. modified hydrogenated submicron diamond powder by photolysis of elemental sulfur. UV irradiation of elemental sulfur generates polysulfide radicals which abstract hydrogen atoms from the diamond leaving dangling bonds on its surface. Recombination of the dangling bonds with the radicals present in the reaction mixture leads to thiol terminated diamond samples. In subsequent processing steps the thiol decorated diamond was deposited on thin gold films yielding an immobilized diamond monolayer. Moreover, first successful efforts were made to align sulfur-modified diamonds on gold-patterned Si films by self-assembly.[116]

Another possibility to graft molecules radically onto diamond surfaces was reported by Komatsu and coworkers who immobilized ω-amino carboxylic acids. Benzoyl peroxide served as thermal radical starter. The resulting surface modification is proposed to be established by ester functions.[149] The thus incorporated amino groups could be used for further transformations such as the immobilization of a fluorescent dye.

As mentioned above, the immobilization of organic moieties on the diamond surface by heteroatom bonded linkers (i.e., O, N and S) can be problematic for further applications in terms of the required stability against e.g., enzymes. Therefore, the formation of even stronger covalent bonds can be required in respective cases. The carbon–carbon single bond would exhibit the necessary inertness as enzymes typically do not cleave ordinary C–C bonds. Ways to form these bonds are therefore at the center of recent activities in the field of diamond functionalization (**Figure 12**).

The photochemical grafting of ω-alkenes onto hydrogen terminated films of nanocrystalline diamond has been known for a fairly long time. The applied alkenes are attached to the diamond surface by C-C single bonds.[150] Nakamura et al. transferred this technique for the first time onto submicrometer diamond powder. They decorated the hydrogenated diamond with a optically active amide capable of recognizing racemic compounds.[151] Later on, the UV grafting of alkenes onto nanoscale diamond with hydrogenated surface was reported by Girard et al.[80]

Aryl diazonium salts are another class of useful reagents for the grafting onto hydrogenated diamond. In the case of diamond films with electrical conductivity (e.g., by

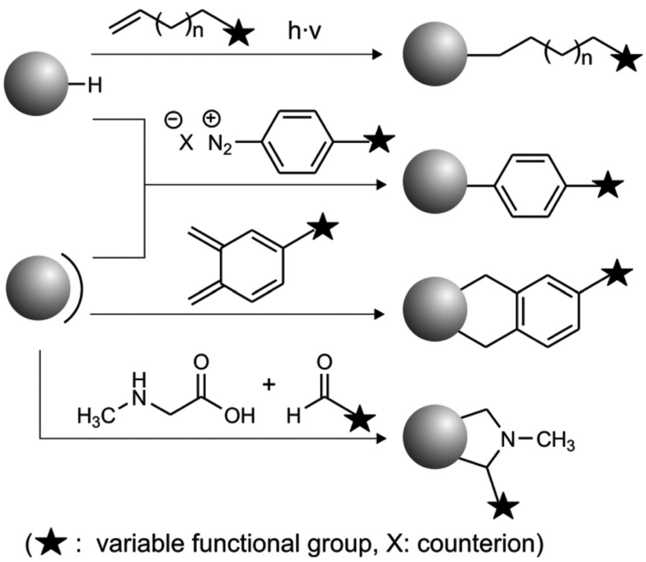

Figure 12. Hydrogenated and thermally annealed nanodiamond materials undergo a variety of reactions that lead to C–C single bonds between the diamond core and the functional moiety. These include (from top to bottom) the photochemical alkylation using ND-H and terminal alkenes, the arylation using the respective diazoniums salts and either annealed or hydrogenated ND, the Diels–Alder reaction of annealed ND with ortho-chinodimethanes and the Prato reaction on the same material.

boron doping) the reaction can be carried out electrochemically. This avoids the use of additional reagents and formation of side products. However, such a strategy is difficult to be transferred to nanodiamond particles as they are not doped nor do they exhibit a sufficient electrical conductivity. Hence a chemical immobilization has to be used instead.

Aryl diazonium compounds can be either generated in situ or directly applied as a salt (e.g., as tetrafluoroborate).[80,90] They are also able to attack the hydrogenated diamond surface in a radical reaction. The exact mechanism of the attack is not yet fully elucidated, cationic species might therefore also play a (minor) role.

Independent of the active species involved in the reaction of the aryl moiety of such diazonium salts with the diamond surface not only C–H terminated diamond can be modified using this reagent. As already reported for carbon nanotubes, sp^2 carbon readily reacts with diazonium salts.[152] Therefore, the C=C double bonds of thermally annealed diamond should easily react with diazonium compounds as well. This was shown to be the case especially for aryl moieties with electron withdrawing groups which increase the reactivity of the supposed reactive species.[103] The actual bonding of the aryl moieties is identical to the one achieved by the grafting of the groups onto hydrogenated diamond as sp^3 hybridized carbon atoms carrying the functional unit are formed in both cases. However, the residual surface terminations in the case of incomplete reactions are different: C–H terminated diamond or residual π-bonds will induce different properties and have to be chosen according to the respective requirements.

Besides the immobilization of aryl moieties by C–C single bonds the annealed nanodiamond is a very suitable starting material for other C–C coupling reactions, where C=C double bonds are a prerequisite. In those cases the surface can be considered to carry either isolated double bonds or even extended (conjugated) π-systems that resemble fullerene-like structures as proposed for sp^2-terminated nanodiamond by computational methods.[153]

Krueger and coworkers performed the Diels-Alder reaction on thermally annealed diamond samples. Such a reaction is well-known for C_{60}. Due to its curvature and electron deficiency the fullerene was never observed to undergo such a reaction as the diene component. Correspondingly, the partially graphitized diamond surface acts as the dienophile and undergoes a [4 + 2] cycloaddition with in situ generated *ortho*-quinodimethanes. This reagent has been chosen since the formation of an aromatic system in the course of the reaction ensures the irreversibility of the grafting.[154] Conventional dienes turned out to yield only low surface loadings due to the favored *retro*-Diels-Alder reaction.

As indicated by the possibility of Diels-Alder reactions the surface of annealed nanodiamond is accessible for pericyclic reactions. Another grafting technique of this type is the 1,3-dipolar cycloaddition of azomethine ylides, called the Prato reaction, to the surface of pre-annealed nanodiamond. Here, aldehydes and amino acids serve as ylide precursors as already reported for the functionalization of carbon nanotubes.[155] The resulting diamond-pyrrolidine conjugates may carry various side chains with other functional groups.[156]

4.5 Subsequent Reactions of Surface-Modified Nanodiamond

The initial homogeneous surface termination ensures the success of the following diamond functionalization. Here, some basic particle properties (e.g., colloidal stability, particle size) may already be affected. Particularly with regard to later applications the diamond surface needs to be farther decorated with adequate, more complex moieties. They can be attached in appropriate subsequent reactions.

In this paragraph only a selection of possible reactions for the modification of surface-modified nanodiamond will be given. Basically, all kinds of organochemical reactions can be carried out on suitably surface-terminated carbon surfaces. Most of the occurring problems are actually not related to the reaction itself but most often to issues related to homogeneity of the transformations, the removal of side products or the stability of initial surface groups against the necessary reaction conditions. All ND materials mentioned so far in the report can be used for the further grafting of functional moieties such as dyes, drugs, labels, catalysts and the like.

One of the most versatile methods for the further grafting of larger moieties is the so-called “click chemistry”. Immobilized azides and alkynes on nanoscale diamond can be transformed to substituted triazoles upon the Cu(I)-catalyzed “click” reaction with the complementary moiety (azide for immobilized alkyne and vice versa).[143,157] As the reaction tolerates a large variety of other functional groups and can be carried out in water the conjugation of very complex (bio)molecules can be efficiently achieved. Using a mixture of alkyne and carboxyl terminated ligands for the surface termination of the ND even an orthogonal

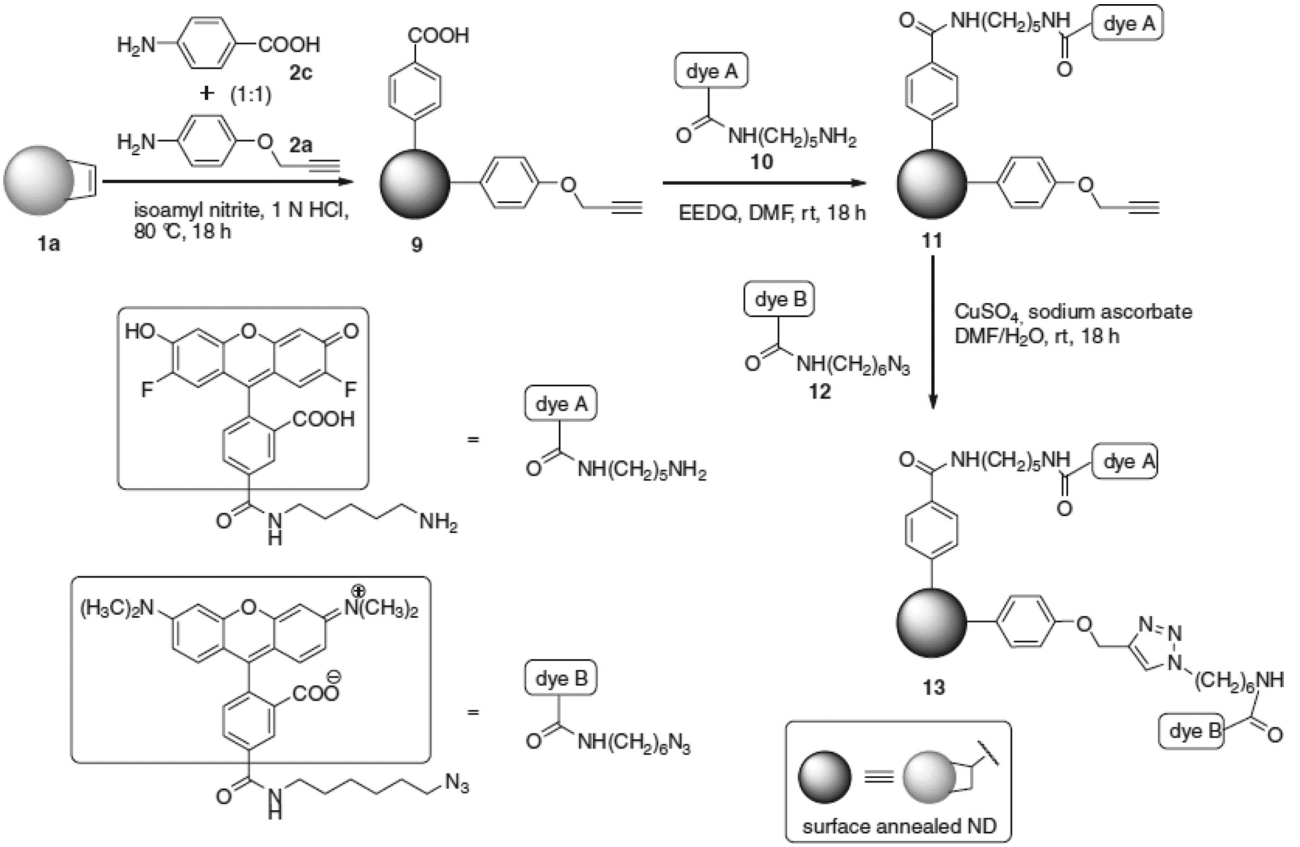

Figure 13. Orthogonal surface functionalization of ND using different diazonium salts. The subsequent formation of triazoles and amide bonds enables the independent grafting of two different moieties such as the fluorescent dyes Oregon Green (by amide bond) and TAMRA (by triazole formation). Reproduced with permission.[157]

functionalization is achieved as these groups can be addressed independently in subsequent reactions (**Figure 13**).[157]

Loh and coworkers took the concept of C–C linkage to the next level. They managed to couple arylboronic acids by a Suzuki reaction with arylbromides that were grafted onto nanodiamond by diazonium chemistry.[88] The same authors used covalently grafted phenyl boronic acids for the capture of glycoproteins. As the covalent immobilization of the biomolecules by reaction with the boronic acid was aspired, undesired nonspecific binding had to be reduced. Thus, the deployment of alkyl chains as molecular spacer led to more selective glycoprotein capture compared to the direct grafting of the boronic acid onto the diamond surface. In both cases arylboronic acids serve as specific binding sites.[158]

Gene delivery has become another interesting bioapplication for diamond nanoparticles. Martín et al. demonstrated that triethylammonium functionalized diamond pairs electrostatically with a plasmid carrying the green fluorescent protein (GFP) gene and enables the crossing of HeLa cell membranes. The GFP expression in the transfected cells was observed by fluorescence microscopy.[78] Dahoumane et al. subjected bromoethylphenyl decorated diamond nanoparticles to atom transfer radical polymerization in order to generate a shell of spacer molecules incorporating a multitude of covalent binding sites for bovine serum albumin.[159] For biomedical applications nanodiamond particles can also be grafted with alkyl spacers terminated with therapeutic moieties. The immobilization of paclitaxel yields diamond conjugates which show anticancer activity in human lung carcinoma cells.[127]

Spacers are typically employed to increase the distance between the diamond surface and the functional moiety. A larger distance might be necessary to allow the flexible orientation of e.g., biomolecules or to avoid nonspecific adsorption (backbinding) of the active compounds. The latter can occur when hydrophilic diamond surface are used for the immobilization of biomolecules carrying a multitude of protic surface groups. Obviously, suitable spacers are not limited to alkyl chains. In order to improve the solubility in polar solvents, polyethylene glycol (PEG) moieties can be integrated into the primary surface functionalization. Such units have been immobilized by amide formation by Komatsu and coworkers onto pre-functionalized ND carrying terminal amino groups. These had been established by the radical grafting of ω-amino acids onto hydrogenated ND. In a further step they attached fluorescein or DY635 as fluorescent labels onto the PEG shell to yield diamond adducts suitable for imaging purposes in biological media (**Figure 14**).[149]

Recently, diamond nanoparticles were also used as supporting material for a proline-based enantioselective catalyst enabling the asymmetric aldol reaction. Depending on the reaction conditions the addition of benzaldehyde derivatives and cyclohexanone yielded ca. 10% product with 60–80% ee.[76]

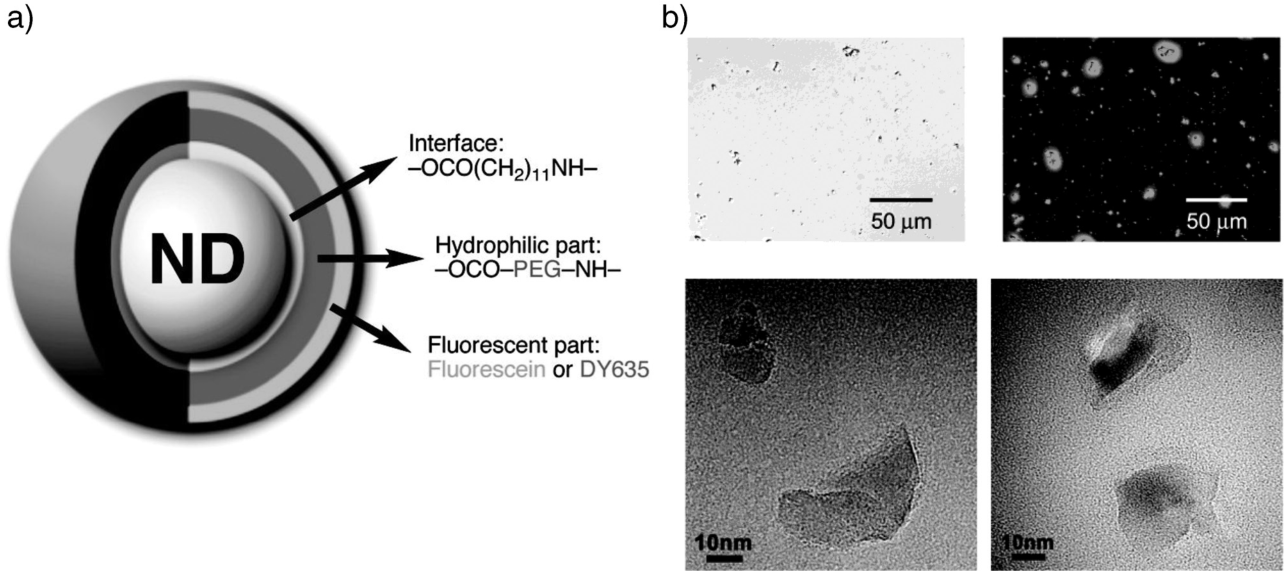

Figure 14. a) The covalent immobilization of PEG chains and fluorescent dyes leads to ND samples with a multilayer organic shell that are fully dispersible in PBS buffer; b) They can be used e.g., for the fluorescence imaging in HeLa cells (bright field image and luminescence image are shown. Below: HRTEM images of the multishell ND from a)). Reproduced with permission from.[149] Copyright 2010, American Chemical Society.

Although the reported yields and selectivities are not yet satisfactory for the large-scale application of such ND-catalyst conjugates it shows the feasibility of the concept. Enantioselective reactions performed using a suitable catalyst include also the application of ND-conjugated enzymes. The reaction of acetophenone to the enantiomerically pure phenoxyethanol can be carried out using an alcohol dehydrogenase covalently immobilized on ND.[160] The enantioselectivity of the ND conjugate did not differ from the one of the free enzyme (ee > 99%), but the reaction efficiency was reduced to ~50%. This problem is common for many kinds of immobilized enzymes on various supports. It can be related to agglomeration or partial unavailability of the reactive site of the enzyme due to non-specific adsorption of the proteins on the diamond surface (see above).

5. Conclusions

In summary, the possibilities for a versatile and reproducible surface modification of nanoscale diamond have become numerous during the past few years. Various methods for the production of functional nanodiamond particles have been reported and the availability of surface groups for all kinds of subsequent grafting reactions has significantly improved. Most of the organic functional groups can be established on the diamond surface. Especially the oxygenated groups are easily available and can be used as versatile anchor groups for the immobilization of larger moieties. Other groups (e.g., amino, thiol, halogens etc.) require more complex procedures for the direct attachment on the diamond lattice. Therefore, these groups are most often established as the terminal moiety of a short and inert linker molecule, like an alkyl chain or an aromatic ring. In all cases, the functional groups enable the immobilization of polymer chains, drug molecules, biomolecules or catalysts–be it by simple adsorption of the functional unit or by directed covalent grafting. Both approaches are useful in their own right, depending on the envisaged application. In the future even stricter requirements for the homogeneity and the flexibility of the functional platforms built on nanoscale diamond particles will occur. The ever more complex and sophisticated applications of nanodiamond in biomedical or high-tech materials demand a deep understanding and control of the surface properties of nanodiamond.

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