Functionalization of Diamond-Like Carbon Surfaces to Access High Rupture Forces in Single-Molecule Force Spectroscopy of Covalent Bonds

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1. Introduction

By supplying external energy to chemical systems, reactions can be triggered. Typically, energy is provided in the form of photons, thermal energy or electrical energy. There is, however, also the possibility of using mechanical force to activate bonds and thus induce reactions. In this case, mechanical force affects bond lengths, angles and thus atomic interactions within a molecule, changing a molecule’s reactivity.[1] This mechanochemistry has received increasing interest, as it allows various alternative approaches to chemical synthesis, characterization and innovation of functional materials, in addition to opening up new reaction pathways e.g. using selective activation of single bonds or solvent-free synthesis.[2] These principles have been applied to industrial scale extrusion, benchtop ball milling and sonication experiments and even in single molecule activation in basic research.[3]

In this work, we focus on the aspect of covalent attachment of single molecules. Using atomic force microscopy (AFM), we can investigate the mechanical activation of a single polymer molecule covalently bound between a surface and the cantilever of the AFM. By moving the cantilever away from the surface, the molecule is stretched, with the distance between cantilever and surface controlling the mechanical force exerted on the molecule.

Due to the precise control of the mechanical force, these single molecule force spectroscopy (SMFS) experiments allow for the investigation of various force-induced reactions, e.g. the folding and unfolding of proteins[4,5] or conformational changes such as the chair-boat transition in sugars at lower forces,[6,7] up to covalent bond scission, e.g. in cyclopropanes[8] and cyclobutanes.[8]

For this aim, however, the molecule first has to be attached to the surface and cantilever. The two most common approaches are the incorporation of a means of attachment into the sample molecule itself or the introduction of so-called anchors on substrate surface and cantilever tip, to which the mechanophore can be attached using coupling chemistry. The first approach is for example employed by Craig et al., who embed multiple mechanophores in a polymer backbone and either copolymerize them with mono-epoxidized cyclooctadiene or introduce epoxides post-synthetically with meta-chloroperbenzoic acid.[7] The epoxides increase adhesion with the surface substantially, practically “glueing” parts of the polymer to surface and cantilever. If enough epoxides are attached to the surface, this attachment can withstand forces in the nN-regime. Due to the amount of mechanophores within
the polymer, a large number of rupture events can be observed each time the surface attachment is strong enough.

The second approach utilizes the formation of self-assembled monolayers (SAMs) as anchors on surface and cantilevers. The SAMs are terminated with functional groups to which the mechanophore can be attached, with a large variety being commercially available, varying in attachment to the surface, size and functional groups. A general overview of the types of SAMs used is given by Pujari et al.\[31\] Since cantilevers typically are made of silicon or silicon nitride, anchors used in SMFS usually attach to Si species. For the same reason glass surfaces, mica or silicon wafer are mostly used as substrate material. This invites the use of functionalized silanes as SAMs to establish anchors, as they allow rapid formation of monolayers using various organosilanes.\[31\]

Typically, two different approaches are taken, one in liquid and one in gas phase, influencing the formation of the SAMs. In liquid, silanes are solvated in a solution of ethanol and water and subsequently activated by curing the surface at elevated temperatures. As silanes a wide variety can be chosen, changing in activity and cross-linking capability. Established anchors consist of covalent Si–C and Si–O bonds, easily allowing investigation of interactions in the sub-nN-regime, such as protein unfolding, but also nN forces have been reported.\[13,39\]

The second possibility, leading to a denser, more closely packed monolayer, is gas-phase silanization. Based on the work of Lyubchenko et al.\[10\] for silanization of mica substrates, Reiner et al.\[11\] also implemented gas-phase silanization in the preparation of AFM tips.\[12\] A nowadays widely used approach is using APDMS (aminopropyltrimethoxysilane) in a dry N\(_2\) atmosphere in a desiccator to silicon wafer and AFM tips and activates surface radicals by UV irradiation, see Figure 1.\[17\] In comparison, gas phase silanization is more complex, yet leads to more cross-linking and thus higher rupture forces, while silanization in solution shows a lower functionalization density.

With increasing mechanical stability of the mechanophore, SMFS experiments become exceedingly challenging as the attachment is more likely to break before the mechanophore is activated, making investigations using SMFS in the nN-range scarce. In our previous work with stronger mechanophores by Schütze et al.\[13\] and Pill et al.,\[14\] this limitation leads to almost all bond scissions being attributed to the breaking of the attachment of the investigated molecule rather than mechanophore activation. Both these works used attachment based on silanes in PBS buffer, able to withstand forces in the low nN regime. Schmidt et al.\[15\] investigated the durability of silane anchoring under near neutral and acidic conditions.\[16\] To assign rupture events to successful binding of a sample between the silane anchors, carboxymethylated amylose (CMA) was used. Upon stretching, the CMA undergoes chair-boat transition at forces around 300 pN, showing a characteristic plateau in force-distance curves. Binding to the silane on the surface was carried out either at pH 7.4 in PBS buffer, using carbodiimide coupling chemistry or at pH 2 after acidification of the buffer using hydrochloric acid by means of acid-catalyzed condensation. Results showed that at pH 7.4 siloxane and amide bond scissions being attributed to the breaking of the attachment of the investigated molecule rather than mechanophore activation. Both these works used attachment based on silanes in PBS buffer, able to withstand forces in the low nN regime. Schmidt et al.\[15\] investigated the durability of silane anchoring under near neutral and acidic conditions.\[16\] To assign rupture events to successful binding of a sample between the silane anchors, carboxymethylated amylose (CMA) was used. Upon stretching, the CMA undergoes chair-boat transition at forces around 300 pN, showing a characteristic plateau in force-distance curves. Binding to the silane on the surface was carried out either at pH 7.4 in PBS buffer, using carbodiimide coupling chemistry or at pH 2 after acidification of the buffer using hydrochloric acid by means of acid-catalyzed condensation. Results showed that at pH 7.4 siloxane and amide bond are prone to force-induced hydrolysis, stating that the former is the most likely to dissociate.\[14a,d\] At pH 2, rupture forces were recorded to be lower than at pH 7.4,\[14b\] showing a predominance of silyl ester cleavage by means of acid-catalyzed hydrolysis\[14b,a\] due to the formation of a protonated species, supported by calculations by Pill et al.\[17\]

In this work we take a closer look at the functionalization protocol used recently by Pill et al.\[16\] based on the work of Stavis et al.\[18\] and Drew et al.\[19\] on the functionalization of diamond-like carbon surfaces. We present a fairly low-cost functionalization protocol and show the performance of this attachment compared to liquid phase silane-based attachment. Furthermore, the influence of various modifications to the protocol, such as acid treatment and functionalization times, as well as the possibility of re-using functionalized surfaces will be discussed.

2. Results and Discussion

Diamond-like carbon (DLC) substrates and cantilevers were washed in 2-propanol, dried, placed in petri dishes and immersed in the respective functionalization solutions containing 10-undecanoic acid for surfaces and allylamine for cantilevers. The petri dishes were then transferred to a functionalization chamber (see Figure S1 in the Supporting Information) flooded with N\(_2\) and irradiated by UV light (254 nm) for three hours. In previous work, the surface functionalization is described as photoactivated grafting.\[20\] However, since we have strong evidence for oligomerization, we suggest that surface radicals are generated by UV irradiation, see Figure 1. Since DLC is commonly assumed to be hydrogen terminated,\[21\]

![Figure 1. Schematic view of the functionalization of DLC-surfaces.](image-url)

In this work we take a closer look at the functionalization protocol used recently by Pill et al.\[16\] based on the work of Stavis et al.\[18\] and Drew et al.\[19\] on the functionalization of diamond-like carbon surfaces. We present a fairly low-cost functionalization protocol and show the performance of this attachment compared to liquid phase silane-based attachment. Furthermore, the influence of various modifications to the protocol, such as acid treatment and functionalization times, as well as the possibility of re-using functionalized surfaces will be discussed.
the leaving group $Y$ would be H. However, the suppliers of the DLC-coated germanium window and cantilever do not specify how the DLC coatings are produced. Depending on the manufacturing process, DLC coatings may differ in their chemical composition and morphology, such that the DLC coated cantilever and germanium window may actually feature differing DLC types. Moreover, DLC coatings are usually rich in defects, and far from a single-crystal structure. There may be sp$^2$ hybridized carbon present, as well as a series of dopants like metals, silicon, oxygen, nitrogen, fluorine, or boron. We also do not know precisely where the functionalization occurs, and it may very well take place at steps or other defects in the material. The process of surface radical generation with a leaving group $Y$ therefore illustrates the generation of a surface radical, but the exact mechanism, in particular the nature of the leaving group, is not known.

Subsequently, the DLC coated specimens were placed in a solution containing $\alpha$-tocopherol as radical scavenger, washed and stored in a vacuumized desiccator. A schematic view of the processes assumed to occur is given in Figure 1.

The strength of the attachment was investigated using dynamic SMFS experiments, during which heterobifunctional polyethylene glycol (PEG) was bound to functionalized surface and cantilever using NHS/EDC coupling. Obtained force-distance curves were investigated, mainly focusing on rupture forces from single molecules. Reference measurements based on silane attachment are described in the experimental section and the supporting information. A schematic view of systems using DLC-based and silane-based attachment is given in the Figure and an exemplary force-distance curve is shown in Figure S3 in the Supporting Information. Furthermore, modifications to functionalization and preparation of DLC substrates were carried out to investigate the DLC-based attachment. An overview of the modifications is given in Table 1.

2.1. Comparison to Silane-Based Attachment

To determine the influence of DLC-based attachment, rupture forces obtained from SMFS experiments were compared to liquid phase silane-based attachment using silane-PEG-amine as reference (preparation described in Supporting Information, page S6). The respective rupture force distributions are given in Figure 2. The DLC-based attachment clearly shows significantly higher rupture forces and a larger distribution, with an average rupture force of 1751 pN and a standard deviation of 721 pN as compared to 819 pN with a deviation of 253 pN for the reference.

In the case of the DLC-based attachment, rupture events are assigned to force accelerated hydrolysis of the amide bond, which is established by NHS/EDC coupling, as recently published by Pill et al.$^{[16]}$ For reference measurements using the silane anchor, bond dissociation can also occur via force induced siloxane hydrolysis resulting in the detachment of the silane, as shown by Schmidt et al.$^{[14a,b]}$ The significant amount of rupture events at higher forces when using DLC anchors therefore stem from the change in the DLC-based attachment, with C–C-based bonds being significantly stronger than the Si–O and Si–C from the silane and not being susceptible to hydrolysis.

Table 1. Attempted modifications to the DLC functionalization on surfaces and respective investigated effects.

| Modification | Purpose/Motive                      |
|--------------|-------------------------------------|
| Time         | Determine timeframe/time-dependence |
| Re-use       | Long term stability, sustainability |
| Caro’s acid  | Induce defects on surface           |
| UV in air    | React with defects prior to functionalization |
| DMSO         | Solvent influence on hydrophobic surface during activation |

Figure 2. Rupture force distribution (bin size 250 pN) for DLC-based attachment (left) after three hours of functionalization and for conventional liquid phase silane attachment (right). Only rupture events with $F > 500$ pN were considered as potential covalent bonds. Force loading rates were in the range of 39–602 nN/s for DLC-based attachment and 23–57 nN/s for silane-based attachment (see Figure S4 in the Supporting Information).
2.2. Modifications

To determine the influence of the modifications described above on DLC-based attachment, SMFS experiments were carried out under the same conditions as for the “standard” procedure (S). The results are given in Table 2.

First, the interaction of cantilever and surface are investigated by comparing strength and range of the unspecific adhesion for all respective tests, regardless of whether a single rupture event was observed or not. Histograms for the distance from the surface at which unspecific interaction is observed (range of the unspecific adhesion) are given in the Supporting Information (Figure S5 in the Supporting Information). With this aim, the retrace of all measurements was investigated and the distance determined at which interaction decreased to a value lower than 100 ± 50 pN for the first time. The strength of the unspecific adhesion was determined to be around 1250 pN on average for the standard procedure (S).

Re-used surfaces (M3), acid treated surfaces (M4) and surfaces activated in DMSO show similar values (M5). For the shorter functionalization time (M1) and surfaces irradiated with UV in air prior to functionalization (M6), the average unspecific adhesion was determined to be lower, with around 1000 and 800 pN, respectively. In the case of the increased functionalization time (M2), the strength of the unspecific adhesion almost quintupled, as compared to the standard procedure. Similarly, the range of the unspecific adhesion increased close to twelve-fold. This can be attributed to extensive radical polymerization on the surface during functionalization. As the irradiation time increases, substantial amounts of undecanoic acid from the solution can polymerize as well as bind to the functionalized surface, as shown in Figure 1. These changes are so substantial that they can be easily seen in AFM images, shown in the Supporting Information (Figure S8 in the Supporting Information).

All other modifications (M1, M3-6) only had a small impact on the range of the unspecific adhesion, most noteworthy being the increase in range of the unspecific adhesion of approximately 30% and 50% for activation in DMSO (M5) and acid pre-treatment (M4), respectively.

Second, clearly distinguishable and specific single rupture events obtained from said tests were compared, focusing on the absolute and relative number of events being observed with respect to the number of tests, the average rupture forces and average distances from the surface. The probability of observing single rupture events is highest for the standard procedure and surfaces treated by irradiation with UV-light in air prior to functionalization (M6), with 2.6 and 2.7% of tests respectively leading to the desired events. For a shorter functionalization time of 1 h (M1), as well as acid pre-treated surfaces (M4) and activation in DMSO (M5), the likelihood of observing single rupture events decreases by about a third to 1.7–2.0%. In the case of re-used surfaces (M3), a reduction to 0.8% is attributed to degeneration, such as hydrolysis of amide bonds between PEG and surface anchor, during storage. However, single rupture events are still observable even without adding new PEG to the surface. For long functionalization times (M2), almost no single rupture events were observed, due to the large range of unspecific adhesion, covering specific interactions in the force distance curves. Average single bond rupture forces were highest for surfaces treated with caro’s acid (M4, 1800 pN) and standard functionalization procedure (S, 1750 pN). Other modifications (M1, M3, M5, M6) showed – with exception of the 10 h functionalized sample (M2) – average single bond rupture forces between 1500 and 1600 pN, which is still significantly higher than for silane functionalization.

The distribution of the rupture forces is given in Figure 3. A comparison of standard procedure and modifications taking into account the probability of observing single molecule rupture events is given in the Supporting Information (Figure S6A in the Supporting Information). For the standard procedure (S), more than half of the rupture events occur between 1000 and 2000 pN, followed by each 15–20% in the range of 500–1000 and 2000–2500 pN. About 15% of the rupture events are recorded at forces higher than 2500 pN, with 5.7% even exceeding 3000 pN. For surfaces treated with caro’s acid (M4), the distribution looks similar, but with a larger amount of rupture events between 2000 and 3000 pN compared to the standard procedure, accounting for the slightly higher average rupture forces. Taking into account that about 34% fewer single rupture events were observed using this modification compared to the standard procedure, the overall performance is lower. The distribution of rupture forces for samples which were activated in DMSO (M5) is almost identical to the standard procedure at forces higher than 1000 pN. It does, however, show a significant increase in rupture events between 500 and 1000 pN. For short functionalization times (M1) and substrate pre-treated with UV in air (M6), the general...

Table 2. Overview of results from MSFS experiments for DLC-functionalization using standard procedure and modifications. Given are the amount of measurements, the average of the maximum force and range of the unspecific adhesion, the absolute and relative number of single rupture events recorded with respect to the number of tests as well as average rupture forces and distance from the surface for single rupture events.

| Modification | Description | Short | Measurements [n] | Unspec. Adhesion [pN] | d_range [nm] | Single Events [n] | % | Average Frupture [pN] | drupture [nm] |
|--------------|-------------|-------|-----------------|---------------------|-------------|----------------|-----|-------------------|-------------|
| Standard (3 h) | S           | 5     | 15744           | 1247                | 15.8        | 404            | 2.6 | 1751              | 43.5        |
| Short (1 h)  | M1          | 7696  | 1004            | 17.4                | 152         | 2.0            | 1552 | 44.4              |             |
| Long (10 h)  | M2          | 1680  | 5842            | 187.6               | 7           | 0.4            | 829  | 95.6              |             |
| Re-use       | M3          | 3302  | 1250            | 15.7                | 28          | 0.8            | 1575 | 31.2              |             |
| Caro’s Acid  | M4          | 6990  | 1273            | 23.3                | 124         | 1.8            | 1799 | 45.1              |             |
| Act. in DMSO | M5          | 7334  | 1147            | 20.5                | 126         | 1.7            | 1516 | 44.3              |             |
| UV/Air       | M6          | 6637  | 789             | 13.7                | 180         | 2.7            | 1599 | 30.2              |             |
distribution pattern is similar, but shows a decrease in rupture events between 1500 and 2500 pN. For re-used samples (M3) and those with long functionalization times (M2) there are too few events to give any statistically relevant information on the distribution pattern.

Since the PEG employed in these experiments has a MW of 10 kDa, distances of 60–90 nm from the substrate surface are to be expected for single molecule bond ruptures. However, coupling reactions of the cantilever amine with remaining surface groups to which the PEG did not bind remain possible, resulting in smaller rupture distances. Therefore, changes in the average rupture distances for the modifications can give an indication regarding changes in the amount of just PEG bound to the surface (lower average distances) or degree of radical polymerization occurring during the functionalization and giving rise to a length increase of the spacer between AFM tip and substrate. The distribution of the rupture distances is given in the Supporting Information (Figures S6B and S7 in the Supporting Information). Standard functionalization procedure, short functionalization times (M1), as well as acid-treated (M4) and surfaces activated in DMSO (M5) show highly comparable average rupture distances around 45 nm. In the case of re-used samples (M3) and such irradiated with UV-light in air prior to substrate functionalization (M6), the average distance decreases by about a third. In the former case we assume that this results from PEG being removed during washing or storage. For the irradiated sample (M6) this could originate from changes in the degree of polymerization, but also from the shorter, weaker unspecific adhesion, making single events more easily distinguishable close to the surface. For the long functionalization time of 10 h (M2), the few single events observed are very far away from the surface. Due to the range of the unspecific adhesion, this is a prerequisite to any event observed and rupture events closer to the surface could be hidden within the unspecific adhesion. Therefore, these special events could be outliers and cannot be assumed to be representative for all rupture events taking place.

3. Conclusion

In this work we investigate a DLC-based attachment for SMFS experiments. Conventionally used functional groups for coupling chemistry, such as terminal carboxy or amine groups, can easily be covalently bound to the DLC surface. Different variations in the surface preparation were carried out, varying functionalization times and pre-treatment of surfaces. DLC-based attachment showed significant improvement in the mechanical stability compared to a liquid silane-based functionalization. Best results were obtained without treatment of surfaces prior to functionalization and 3 h of functionalization time, with single molecule rupture forces averaging around 1750 pN and about 2.6% of the experiments yielding single rupture events. Thus, this type of DLC-based attachment allows investigation of stronger covalent bonds in the nN range.

Experimental Section

Functionalization

Diamond-like carbon (DLC) coated germanium windows (UQG Optics, Cambridge, UK) were used as substrate surfaces in combination with DLC coated AFM cantilevers (μmash, HQ:CSC17/ hard/Al BS; 0.2 N/m). The surfaces were cut into pieces of desired size for the experiments using a glass cutter and, together with the cantilevers, placed in a glass petri dish filled with 2-propanol for 30 minutes.

The prepared surfaces and cantilevers were then functionalized and terminated with carboxylic and amine groups, respectively. A schematic view of the functionalization reactions is given in Figure 1. Functionalization solutions of 10% 10-undecanoic acid in 2-propanol for the surfaces and 10% allylamine in 2-propanol for the cantilevers were prepared and mixed for 10 minutes. Cantilevers and surfaces were then placed in separate petri dishes and immersed in their respective solutions as to ensure adequate coverage of about 2 mm liquid. They were then placed under a UV lamp (Ultra-Violet Products Ltd, Cambridge, UK, Model 115C-1) in the functionalization chamber (see S1) filled with nitrogen (Nitrogen 5.0, Linde) using an overpressure of 2 bar. The surfaces and cantilevers were then irradiated with UV light (254 nm) for the desired functionalization time (3 hours). To account for any nitrogen loss, the chamber atmosphere was regenerated with nitrogen for 1–2 minutes in 30 minute intervals.

Figure 3. Histogram showing rupture force distribution (500 pN bin size) for single rupture events obtained from SMFS experiments for standard procedure and modified DLC-based attachment. Only rupture events with \( F_{rupture} > 500 \text{ pN} \) were considered.
Chemistry—Methods

After UV irradiation, the cantilevers and surfaces were immersed in a 5% solution of α-tocopherol in 2-propanol in the functionalization chamber under nitrogen atmosphere for 15 minutes to remove any remaining radicals. They were then washed twice in 2-propanol and twice in ethanol, dried in the fume hood and stored under vacuum in a desiccator with silica gel.

Activation

During the activation process, surface carboxylic groups were activated using a solution of N-(3-dimethylaminopropyl)-N-ethyl-carbodiimide hydrochloride (EDC) and N-hydroxy succinimide (NHS) in phosphate buffered saline solution (PBS). Subsequently, heterobifunctional polyethylene glycol (PEG) was terminated on one end with a carboxylic and on the other with an amine group (RAPP MFP and HCS acknowledge financial support through the CANTER Research Focus of the Bavarian State Ministry for Science and Education. MSS, SS and MKB acknowledge financial support through FFG R&D Infrastructure Funds, Project No. 870523, co-financed by the State of Tyrol. This article/publication is based upon work from COST Action CA18112 Mechanochemistry for Sustainable Industry, supported by COST (European Cooperation in Science and Technology).

Conflict of Interest

The authors declare no conflict of interest.

Keywords: covalent bond rupture · force spectroscopy · mechanochemistry · surface functionalization · single-molecule studies

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SMFS

To determine the mechanical stability of the attachment using DLC surfaces and DLC coated cantilevers, dynamic SMFS experiments were carried out using a Nanowizard 4 by JPK. All experiments were conducted in PBS at room temperature. Cantilever spring constants were determined using the thermal noise method.[10]

Cantilevers were approached to the surface until a setpoint of 500 pN was reached, dwelled for three seconds allowing the activated surface to react with the terminal amine on the cantilever, thus forming an amide bond. The cantilever was subsequently retracted at a constant velocity of 1 μm/s leading to bond ruptures and detachment of the cantilever from the surface. The cantilever was then moved to the next point of a predefined grid and the aforementioned procedure was repeated.

Reference measurements using previously reported silane-PEG-amime to form a silane-based attachment[9] on both Si-based surface and cantilever as well as adipic acid[14] to establish a connection between cantilever and surface attachments were performed under the same conditions. Detailed information on the functionalization and activation are given in the Supporting Information. This method was chosen as it shows little to no cross-linking of silanes on the surface, giving a better comparability of silane- and DLC-based attachment.

Modifications

Furthermore, modifications (Table 1) to the aforementioned preparation were carried out to investigate the DLC-based surface attachment. The irradiation time was varied, activated and used surfaces were washed with double distilled water and ethanol, dried in the fume hood and stored there. They were then re-used one week later to determine if the PEG remained bound to the surface. Here, the terminal carboxylic groups from the PEG from the initial test were re-activated using NHS/EDC. Additionally, different types of surface treatment prior to functionalization were investigated. Surfaces were either left for one hour in caro’s acid or irradiated for one hour with UV light at atmosphere. Lastly, by way of comparison to PBS, dimethyl sulfoxide was tested as a non-aqueous solvent for activation solutions.

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