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Mechanophores

Pinpointing Mechanochemical Bond Rupture by Embedding the Mechanophore into a Macrocycle**

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Dedicated to Professor Hermann E. Gaub on the occasion of his 60th birthday

Abstract: *Mechanophores contain a mechanically labile bond that can be broken by an external mechanical force. Quantitative measurement and control of the applied force is possible through atomic force microscopy (AFM). A macrocycle was synthesized that contains both the mechanophore and an aliphatic chain that acts as a "safety line" upon bond breaking. This ring-opening mechanophore unit is linked to poly(ethylene glycol) spacers, which allow investigation by single molecule force spectroscopy. The length increase upon rupture of the mechanophore was measured and compared with quantum chemical calculations.*

A wide variety of mechanochemical reactions have been demonstrated through the deliberate incorporation of mechanophores[1–3] into long polymers,[3,4] with the aim of developing mechanoresponsive materials. Several cycloreversion mechanophores are have been reported.[5–7] A 1,2,3-triazole moiety embedded in poly(methyl acrylate) appeared to undergo mechanochemical cycloreversion,[6,7] which would seem to demonstrate that "click" chemistry is mechanically reversible. However, the validity of these experimental data is currently under debate.[8]

In order to address the putative mechanochemical cycloreversion of 1,2,3-triazoles with a different experimental approach, we designed a ring-opening mechanophore that allows the investigation of the mechanochemical activation of a 1,2,3-triazole on the single-molecule level. In contrast to simple bond-breaking mechanophores, which lead to polymer rupture at a defined site, ring-opening mechanophores lead to an elongation of the polymer upon activation. The ring-opening mechanophore with the largest known elongation, at 0.4 nm, is a bicyclo[3.2.0]heptane.[9] Herein, we report the synthesis of a ring-opening mechanophore with an elongation of more than 1.0 nm. The elongation was directly measured by single-molecule force spectroscopy (SMFS)[10,11–14] and compared to quantum chemical calculations.

The design of the mechanophore was inspired by the work of Fernandez and co-workers, who used an engineered protein to study the force-dependence of bimolecular disulfide reduction by SMFS.[15] In our ring-opening mechanophore **14**, the bond to be cleaved is in the shorter branch of the macrocycle, namely that containing the triazole moiety. The longer branch is an alkyl chain, which constitutes the "safety line". The carboxylic acid end groups allow us to incorporate the mechanophore in between poly(ethylene glycol) (PEG) spacers, which are required for SMFS.

Triazole **14** was synthesized in 10 steps, starting with protection of the carboxylic acid of **1** as the corresponding methyl ester.[16] Etherification of **2** with hex-5-en-1-ol (**3**) through a Mitsunobu reaction gave **4**. For the reduction of the nitro group, stannous dichloride dihydrate was used and the desired amine **5** was obtained. Amine **5** is needed to produce both the azide **7** and the iodide **8**.

First, aniline **5** was transformed into the corresponding diazonium salt **6** by adding hydrochloric acid and sodium nitrite at 0°C. After the addition of sodium azide, product **7** was obtained. The diazonium salt **6** could also be used to produce iodide **8** through a Sandmeyer analogous reaction. To convert **8** into the alkyne **10**, a Sonogashira coupling with trimethylsilyl acetylene was performed. The silylated alkyne **9** was deprotected and **10** was obtained (Scheme 1).

Starting from alkyne **10** and azide **7**, triazole **11** was produced in a copper-catalyzed [3+2] cycloaddition (click reaction) by employing microwave irradiation. The safety line was introduced through ring-closing metathesis and macrocyclic alkene **12** was isolated. Hydrogenation of the double bond was carried out with platinum(IV) oxide and hydrogen to yield the saturated macrocycle **13**. Ester cleavage as the final step led to dicarboxylic acid **14** (Scheme 2 and the Supporting Information).

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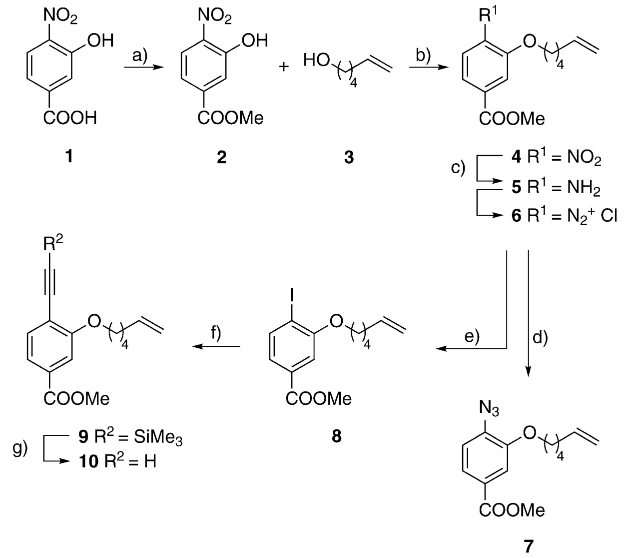
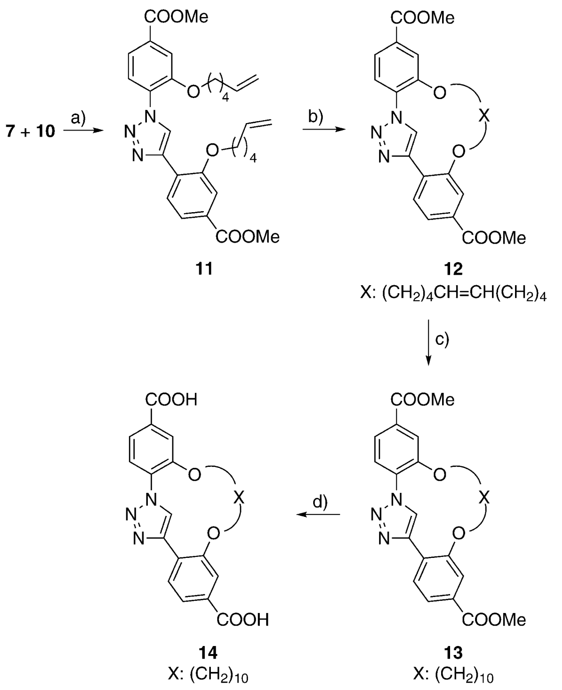
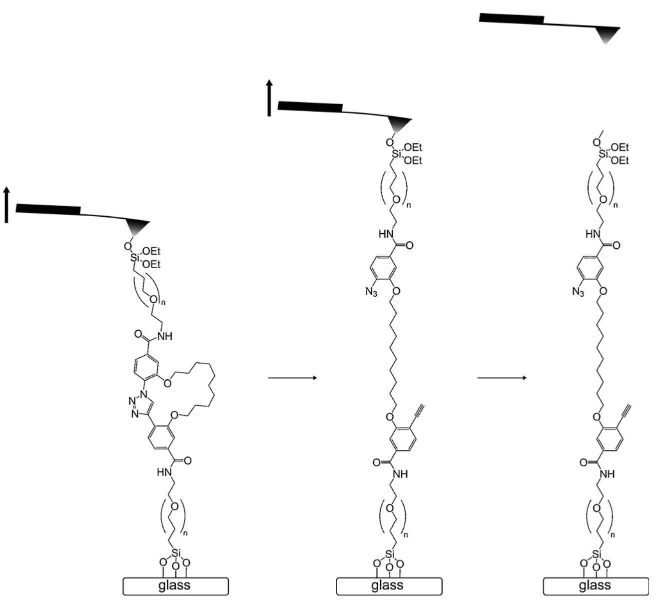


Scheme 1. Synthesis of azide **7** and alkyne **10**: a) MeOH, H_2SO_4, 24 h, reflux, 99%; b) 1. THF, PPh_3, 2. DIAD, 30 min, 0°C, 3. 22 h, RT, 83%; c) EtOH, $SnCl_2{\cdot}2H_2O$, AcOH, 1 h, 75°C, 87%; d) 1. H_2O, HCl, 0°C, 2. $NaNO_2$, 20 min, 0°C, 3. NaN_3, 30 min, 0°C, 57%; e) 1. Acetone, HCl, 0°C, 2. $NaNO_2$, 2 h, 0°C, 3. KI, 30 min, 0°C, 15 min, 80°C, 81%; f) $Me_3SiC{\equiv}CH$, THF, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, 20 h, RT, 74%; g) $CHCl_3$, Bu_4NF, 16 h, RT, 95%.



Scheme 2. Synthesis of macrocycle **14** from azide **7** and alkyne **10**: a) MeCN, CuI, EtN*i*Pr$_2$, MW, 10 min, 100°C, 120 W, 71%; b) CH_2Cl_2, Grubbs' catalyst 1st gen., 36 h, RT, 77%; c) $CHCl_3$, PtO_2, H_2, 24 h, RT, 97%; d) THF, MeOH, H_2O, $LiOH{\cdot}H_2O$, 1. 5 min, 50°C, 2. 15 h, RT, 96%.



Scheme 3. **14** is covalently anchored between two PEG chains, which in turn are covalently attached between a glass substrate and a Si_3N_4 cantilever. Upon stretching of the molecule, a double rupture event is observed if bond rupture occurs first in the triazole branch of **14** (cycloreversion shown), and a characteristic length increase is measured by AFM.

To investigate the mechanochemical ring-opening behavior of **14**, the molecule was covalently attached via an amide bond to a PEG chain, which was covalently attached through silane anchors to a glass substrate (Scheme 3). SMFS was employed in fly-fishing mode.[17] The PEG-silanized cantilever repeatedly approached the glass substrate, with the tip continuously covered by the solution. In less than 10% of the approaches, a second amide bond was formed between the amine end group of the PEG and the second carboxylic acid of **14**. The force–extension curve, where extension refers to the piezo element of the cantilever, exhibited the characteristic shape of a stretched PEG molecule[18] (Figure 1).

In the vast majority of successful attachments, only a single rupture event was observed, which is associated with rupture of the silane surface anchor.[11–14,19] In about 5%

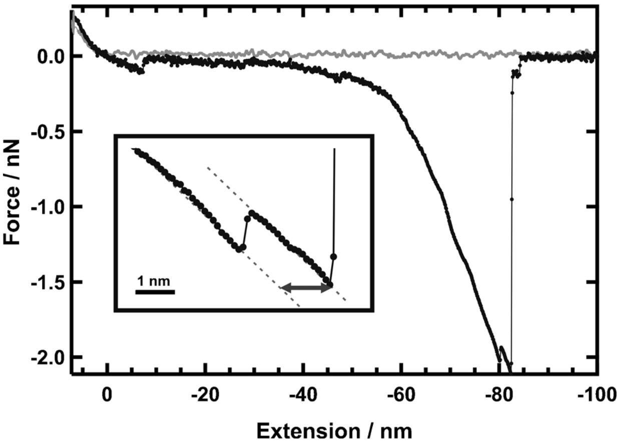


Figure 1. Force–extension curve with one of the rare double rupture events assigned to the rupture of **14** (curve 3 in Table 1). The inset shows that the slope of the force-extension curve is the same before and after the rupture. The length change is read from the figure as the horizontal displacement of the force–extension curve.

of the recorded force–extension curves, however, two rupture events were observed. These double rupture events were due either to the mechanochemical ring opening of macrocycle **14** or to the attachment of two polymer chains. In the case of mechanochemical ring opening, the same polymer chain was stretched before and after the first rupture event, thus resulting in identical slopes of the curve (Figure 1). If multiple polymer chains were attached, the slope of the force–extension curve changed after the first rupture, and these curves were discarded. After close examination of all of the force–extension curves with double ruptures, only three curves remained in which the slope was the same before and after the first rupture event. In these curves, the length increase is measured as described in Figure 1. The results are summarized in Table 1, with a conservative uncertainty of ± 0.2 nm for the length change, based on the uncertainty of positioning the parallel fit lines in the force–extension curves.

Table 1: Rupture force and elongation measured from force–extension curves featuring a double rupture event.

Force–extension curve	Rupture Force [nN]	Elongation Δx (exp) [nm]	Elongation Δx (COGEF) [nm]
1	1.11 ± 0.01	1.2 ± 0.2	1.01 ± 0.20
2	1.21 ± 0.02	1.2 ± 0.2	1.01 ± 0.20
3	2.05 ± 0.03	1.4 ± 0.2	1.05 ± 0.20

According to Bielawski and co-workers,[6,7] this length increase should be assigned to a mechanochemical retro-click reaction of macrocycle **14**. However, bond ruptures between the triazole unit and its phenyl anchors, with the triazole ring remaining intact, would lead to the same AFM response. These events thus cannot be distinguished here, and the single-molecule nature of the experiment precludes the use of standard spectroscopic techniques to further differentiate between the possible products.

The observation of only three ring-opening events in several thousand force–extension curves clearly shows that the aryl–triazole–aryl region is mechanically stronger than the silane surface anchor.[11] In force-ramp experiments, the rupture forces are scattered over a range of more than 1 nN,[12] so it is entirely reasonable that in rare cases the mechanically stronger bond breaks first. With the safety line concept described here, we can unambiguously identify these events and measure the rupture force. Unfortunately, the events were so rare in this case that a quantitative statistical analysis was not possible.

Among the quantum-chemical methods available to describe covalent mechanochemistry,[2,20,21] the constrained geometries simulate external force (COGEF) method[20] is ideally suited to describe AFM experiments performed in force-ramp mode. In this study, COGEF calculations were used to determine the expected elongation associated with mechanochemical ring-opening of **14** and subsequent stretching of the $(CH_2)_{10}$ safety line. Since only the length difference before and after mechanochemical ring-opening was of interest here, only the force-induced structural deformability of the initial and final states was modelled.

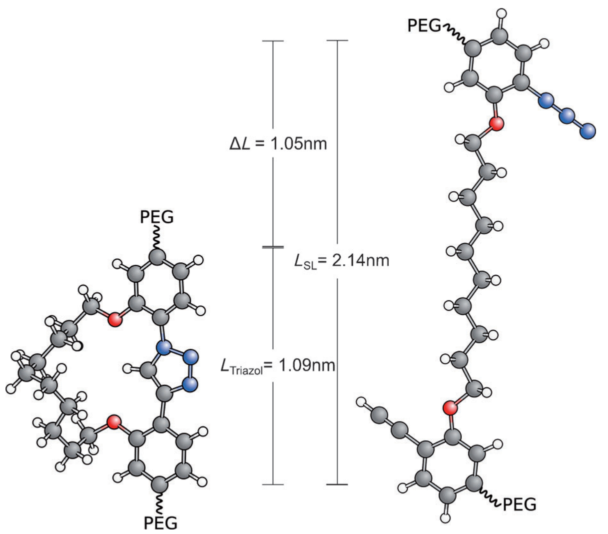


Figure 2. COGEF calculation of the length increase resulting from mechanochemical ring opening of macrocycle **14**.

The initial state was represented by two phenyl rings linked by a 1,2,3-triazole; the final state by two phenyl rings linked by the safety line (Figure 2). The PEG chains were not included in the calculations. For both configurations, a series of relaxed scans was performed. The pulling forces were obtained from the first derivatives of the energy–distance curves. From the resulting force–distance curves, the length difference between the initial and final configurations, taken at the experimental force value, yielded our theoretical estimate for the length change upon mechanochemical ring-opening. This theoretical estimate is 1.05 ± 0.20 nm for a force of 2.05 nN, which is slightly shorter than the experimental value. However, there are several effects that contribute to significant uncertainties. The conditions for the calculations were set as under vacuum at 0 K, while the experiments were performed in solution at room temperature. Rupture of the C−N bond instead of triazole cycloreversion will slightly change the geometry of the aryl groups. The high force of 2.05 nN applied to the bond deforms the binding potentials and increases their anharmonicity, which in turn leads to thermal expansion of the PEG chain. The effect of the lever arms was also shown to be significant.[22] These effects justify a conservative estimate of ± 0.20 nm for the uncertainty.

The described combination of tailor-made mechanophore synthesis, AFM experiments, and quantum chemical calculations shows that arbitrary bonds can be embedded in a macrocycle and selectively addressed through an external mechanical force applied through PEG linkers. Even very few rupture events of the mechanophore can be unambiguously identified through the characteristic length increase together with the unchanged slope of the force–extension curve before and after the rupture event. With the present molecular design, we cannot determine whether it was really mechanochemically induced retro-click reactions of the 1,2,3-triazole ring that took place or merely bond ruptures next to it. We can state, however, that the force required to induce either of the two reactions is in the nN region. The present technique opens a wide range of possibilities for the design of mechanophores. By changing the length of the safety line in **14**, ring-opening mechanophores with arbitrary elongation can be synthesized. By replacing the 1,2,3-triazole linkage, for example with cyclobutane or disulfide, the response of the mechanophore can be finely tuned to a specific range of mechanical strain. These two degrees of freedom make a wide variety of mechanophores accessible for the design of functional materials.

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