

Mechanochemical Transduction of Externally Applied Forces to Mechanophores

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Abstract: We present a theoretical study on the role played by aliphatic polymer chains in the transduction of external forces to mechanophores being at the heart of force spectroscopy and sonication experiments. Upon introducing a rigorous approach rooted in catastrophe theory, we demonstrate that the rupture force of a cis 1,2-disubstituted benzocyclobutene features a remarkable dependence, including odd–even effects, on the length of attached polymer chains. This unexpected finding is furthermore rationalized by establishing a correlation between the rupture force and local distortions of the mechanophore at its junctions with the transducing chains. The force-transformed Hessians unveil a surprising force-dependence of harmonic force constants associated with relevant structural parameters of these chains. Not only do our findings highlight the necessity of taking into account the polymer chains explicitly when thinking about mechanochemical manipulation, but they also announce the possibility of tuning the properties of mechanoresponsive polymers by tailoring the force-transducing chain molecules.

Introduction

Among the most common methods of accelerating chemical reactions are the use of heat, light, or electricity. In the past decade, however, a wealth of novel experimental techniques has been developed that allow for the application of external mechanical forces to specific covalent bonds within molecules. This enables a fundamentally different paradigm of initiating, accelerating, and controlling chemical reactions, thus opening the doors to an exciting emerging research field, namely, molecular nanomechanics or covalent mechanochemistry (CMC).^{1,2}

In the exploitation of atomic force microscopy (AFM), the rupture of *covalent* bonds has been pioneered at the single molecule level.^{3–6} In the force-clamp mode,⁷ the stretching force is controlled by a feedback mechanism and transmitted via long (bio)polymer chains to reactive molecular cores dubbed mechanophores. Since the force is roughly constant within experimental limitations, such “isotensional” experiments have been analyzed with the help of phenomenological models in terms

of structural distortions of transition states,⁸ in addition to measuring the influence of constant external forces on the kinetics of complex reactions.^{9,10} In all such AFM-like setups, anisotropy is introduced by suspending the macromolecules between a surface and the AFM tip. In recent years, forces have also been applied in isotropic solution by means of sonochemical techniques.¹¹ Within this realm, targeted cleavage and rearrangement of covalent bonds has been achieved in mechanophores incorporated into polymer chains.^{12–18} Most recently, yet another ingenious approach relying on cyclic chain molecules under tailored strain has been devised to apply forces in solution upon photoswitching.^{19,20}

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On account of this wide experimental scope, it is now well appreciated that mechanical forces can not only promote but can also redirect complex chemical reactions, even if such reactions might be regarded as impossible in the context of “traditional” chemistry. CMC thus has the potential for great impact not only in synthetic chemistry but also in the design and preparation of mechanoresponsive materials.^{2,21,22}

These experimental advances also initiated theoretical studies of CMC,^{23–41} helping to arrive at a broad molecular-level understanding by complementing experimental insights. Most recently, we have devised a conceptual framework³⁶ to investigate CMC that relates isotensional (force-clamp) techniques to earlier isometric setups^{23–29} by exploring how a potential energy surface (PES) changes as a function of applied forces; related computational approaches have been introduced concurrently by Martinez and co-workers,³⁵ followed by others.³⁹

Common to *all* current practical CMC manipulation techniques is the use of polymer chains as a means to transduce mechanical forces from some environment into the chemically reactive mechanophore unit. Obviously, the lack of a thorough fundamental understanding of the nature of mechanochemical transduction,² let alone technical problems, constitutes a significant difficulty which imposes limitations. However, despite a plethora of theoretical CMC studies^{23–41} the very role played by polymer chains in the transduction of externally applied nano-Newton forces up to the point of enabling chemical reactions remains fully unexplored. It is thus clear that the emerging field of controlled CMC at the nanoscale would immensely benefit from a detailed and quantitative knowledge on how mechanical stress is transmitted to a target bond in order to trigger desired reactions.²

Here, we elucidate the mechanochemical transduction of external forces from the termini of attached chain molecules to the mechanophore itself. Transcending earlier work, our present

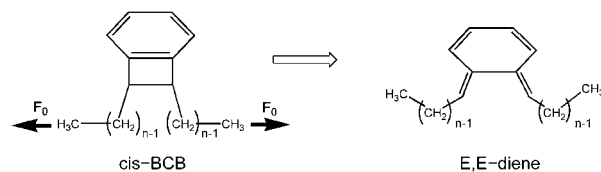


Figure 1. Schemes depicting the molecular species underlying this study. The constant external force F_0 is applied to a cis 1,2-disubstituted benzocyclobutene mechanophore core covalently linked to two aliphatic chains, each of them consisting of $n = 1–10$ carbon atoms yielding BCB- C_n (left). The force is invariably applied to the two methyl end groups along the interconnecting line between the two terminal carbon atoms of the polymer chains as indicated by the arrows. The mechanochemical reaction product of the force-induced ring-opening reaction is the corresponding *E,E*-diene (right) instead of the “thermochemically expected” *E,Z*-diene.

approach draws on catastrophe theory,⁴² which not only provides a proper language and qualitative insights but also accurate rupture forces and breaking (yield) points. Specifically, we will show that the rupture force features a remarkable dependence, including odd–even alternation effects, on the length of the polymer chains. A clear and simple correlation between the rupture force and the local distortion of the mechanophore will be established, thus explaining this striking finding. Furthermore, we will uncover a hierarchy of structural changes taking place in the sense of a cascade of events involving the composite system, i.e., mechanophore plus chains, upon mechanical stress before reaching its yield point. Particular attention will be paid to the most surprising nonmonotonous dependence of (harmonic) force constants associated with key structural parameters on the exerted stretching force. Let us stress already at this stage that since the main focus here is the rupture of covalent bonds, which requires forces of several nano-Newton, the initial conformational unfolding of long (bio)polymer chains, occurring at much lower forces and being largely entropy-dominated, needs no consideration.

Results and Discussion

The selected model system consists of benzocyclobutene (BCB) cores functionalized for CMC by covalently linking them in cis arrangement at the 1,2-positions to two polyethylene-like chains consisting of $n = 1$ to 10 carbon atoms each, i.e., cis 1,2-disubstituted benzocyclobutenes (BCB- C_n) according to Figure 1. This choice responds to the facts that BCB and closely related molecules have been repeatedly demonstrated to be powerful mechanophores^{12,13,17,19,20,35–37} in addition to polyethylene being the simplest polymer known, thus reducing the chemical complexity to the lowest useful level. The rationale for using such short chains is that the forces which induce conformational transitions in real polymers (and thus noncovalent mechanochemistry) are at least 1 order of magnitude smaller than those required to induce covalent chemical reactions and thus CMC. At the same time, the length scales are very different, e.g., on the order of 0.1 nm for CMC, whereas the nanometer scale and beyond is relevant for the relaxation of conformational degrees of freedom. The vastly different character of conformational degrees of freedom, and even more so of supramolecular and elastic contributions, compared to covalent bonds is illustrated most clearly in Figure 8 of ref 1 in the realm of mechanochemical manipulation. Thus, our assumption is that once nano-Newton forces and thus the strong

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stretching regime is reached for a real polymer, most of the conformational and entropic contributions are eliminated. In addition, the relevant changes in this regime will occur on the local Ångström scale, which is, precisely, the situation captured by our specific model, in conjunction with our computational approach.

Given the system depicted in Figure 1, the first aim is to determine if there is a dependence of the *rupture force*, F_{\max} , on the chain length. From the chemical point of view, F_{\max} is the force required such that *cis*-BCB rearranges into the corresponding *E,E*-diene product in the sense of a mechanochemically barrierless process, i.e., in the absence of any additional thermal activation. It is well-understood that this occurs via a concerted *disrotatory* ring-opening reaction^{12,35–37} sketched in Figure 1. F_{\max} is readily calculated as an application of the conceptual framework we have recently presented for CMC;³⁶ see refs 35 and 39 for related computational approaches. The central concept of our *isotensional* formalism is the force-transformed potential energy surface (PES), which, given a constant external force \mathbf{F}_0 , is rigorously defined as

$$V_{\text{EFEI}}(\mathbf{x}, \mathbf{F}_0) = V_{\text{BO}}(\mathbf{x}) - \mathbf{F}_0 \mathbf{q}(\mathbf{x}) \quad (1)$$

where $V_{\text{BO}}(\mathbf{x})$ is the usual Born–Oppenheimer PES as a function of all nuclear Cartesian coordinates \mathbf{x} . In this framework, \mathbf{q} is a mechanical coordinate, i.e., some generalized coordinate in terms of \mathbf{x} , to which the fixed force is conjugate in the sense of a Legendre transform relation.³⁶ By locating the stationary points of this function, in which the “external force is explicitly included” (EFEI), one can evaluate, without invoking any further approximation, properties such as force-distorted structures and reactions pathways as a function of \mathbf{F}_0 . It must be stressed that both computational approaches, i.e., isotensional and isometric, are idealized theoretical frameworks, which are introduced in order to compute properties obtained by controlling either force or distance, respectively. This is analogous to the isobaric and isochoric formalisms of statistical mechanics that are used to describe bulk experiments where pressure or volume, respectively, is controlled.

The Topological Viewpoint. With this formalism at hand, it is in principle straightforward to compute F_{\max} . By locating the stationary points corresponding to the reactant basin of BCB- C_n at different magnitudes, $F_0 = |\mathbf{F}_0|$, we will observe that as F_0 increases, the system, in its reactant configuration, will become more and more strained. Let $F_{0-\Delta}$ be a value of F_0 for which the system can still sustain the mechanical stress such that it stays in the reactant basin configuration. Let us now consider that we slightly increase the value to $F_{0+\Delta}$, for which the system can no longer sustain the associated stress and hence spontaneously undergoes mechanochemical ring-opening. Then, it is obvious that the *rupture force* of the system, F_{\max} , will be contained in the interval defined by $F_{0-\Delta}$ and $F_{0+\Delta}$. Major drawbacks of this simple procedure are its iterative character together with its dependence on the finite force interval inducing numerical instabilities in conjunction with geometry optimizers, in addition to not being elegant. Having reached this point, obviously, we would prefer to devise a superior procedure.

In the following, we establish a profound approach based on catastrophe theory.⁴² As such, it is rooted in the topological properties of the force-transformed PES, with F_0 acting as the *control parameter*, in catastrophe theory language. In order to set the stage, let us consider first the trivial case of stretching a diatomic molecule subject to a standard anharmonic one-

dimensional PES where a constant stretching force acts along its bond axis. Two simple parameters characterize mechanochemical rupture: the *breaking point* distance and the *rupture force*, F_{\max} . Both physical quantities have an unambiguous mathematical definition, the former being the inflection point of the potential energy curve whereas the latter is the first derivative at the inflection point. These definitions can be readily used to investigate multidimensional polyatomic systems with the *isometric* COGEF method introduced by Beyer²⁴ as a means to determine the mechanochemical strength of covalent bonds.³⁸

How do these concepts generalize to the multidimensional force-transformed PES? According to catastrophe theory, the breaking points on the force-transformed PES are, in the context of Morse theory of differential topology, *non-Morse critical points* or *degenerate critical points*. In our context, such points are stationary points of the force-transformed PES in which at least one of the eigenvalues of the force-transformed Hessian matrix vanishes (apart from the trivial translational and rotational modes). The force-transformed Hessian is the matrix of second partial derivatives of $V_{\text{EFEI}}(\mathbf{x}, \mathbf{F}_0)$ with respect to the nuclear Cartesian coordinates. Once the breaking point has been located, the calculation of F_{\max} is trivial. Since the mechanical coordinate (i.e., the generalized coordinate $\mathbf{q}(\mathbf{x})$ conjugate to the control parameter \mathbf{F}_0) is the distance between the terminal carbon atoms of the polymer chains, F_{\max} is given by the absolute value of the projection of the gradient vector of the terminal carbon atoms onto their interconnecting line at the breaking point; in this projection only the gradient coming from $V_{\text{BO}}(\mathbf{x})$ of (eq 1) is taken into account. As the breaking point itself is a stationary point, it follows that F_0 must be equal to the projection of the internal gradient of the terminal atoms along their interconnecting line, so that the total force acting on the terminal carbon atoms is zero. We stress that these rupture forces are exact within the electronic structure method employed to evaluate $V_{\text{BO}}(\mathbf{x})$.

Topological Analysis of Functionalized Mechanophores. Using this machinery, we investigated the topological properties of the breaking points of functionalized BCBs. Interestingly, they are all found to follow the same scenario irrespective of chain length up to $n = 10$, which is exemplified in Figure 2 using BCB- C_{10} . In particular, at the breaking point, the corresponding force-transformed Hessians are found to feature a single zero eigenvalue, which means that they are *doubly degenerate critical points*. If the force-transformed PES, i.e., the EFEI energy, is evaluated at fixed $F_0 = F_{\max}$ along a pathway obtained by following the normal mode associated with zero eigenvalue, one generates the black curve in Figure 2. It features a plateau in close vicinity of the breaking point at $\xi = 0$, which reflects the fact that it is a stationary point. If we now take the very same pathway and evaluate the EFEI energy at a fixed force F_0 slightly smaller than F_{\max} , the energies obtained (red line) feature a qualitatively different behavior. Indeed, the 2-fold degenerate critical point at $\xi = 0$ is split here into two isolated critical points. From the chemical point of view, the minimum at $\xi < 0$ is related to the optimized structure of the reactant configuration at this particular value $F_0 < F_{\max}$. At $\xi > 0$ there is a maximum instead, which, in turn, is associated with the transition state structure connecting the reactant configuration of *cis*-BCB- C_{10} to the product configuration of *E,E*-diene at this F_0 . The behavior obtained for $F_0 > F_{\max}$ (blue line) is again qualitatively different. The curve does not possess any critical point at all, which is a consequence of the fact that for $F_0 > F_{\max}$ the system can no longer exist in its reactant configuration. Analysis of the normal mode at criticality (shown by the red

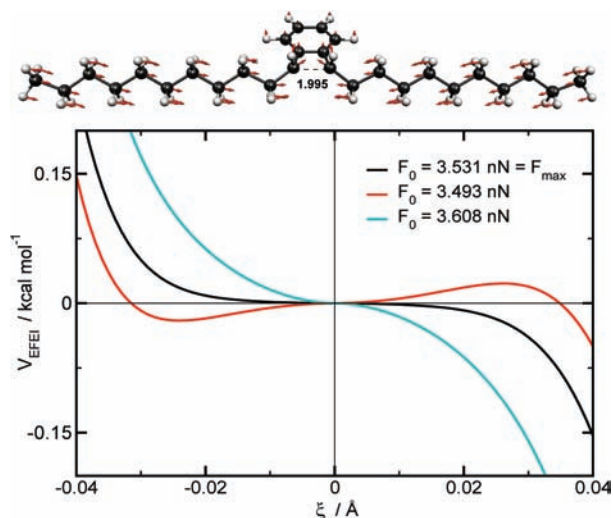


Figure 2. Topological analysis in the vicinity of the breaking point of BCB- C_{10} for several values of the fixed control parameter F_0 . The evolution of the force-transformed PES in terms of EFEI energies according to eq 1 is shown along the trajectory following the normal mode with zero eigenvalue at the critical point. The abscissa measures the displacement of the molecular structure with respect to that at the breaking point; thus $\xi = 0$ Å refers to the molecular structure at breaking, negative ξ -values indicate evolution toward the reactant configuration, and $\xi > 0$ implies approaching the product configuration. EFEI energies are plotted at breaking, $F_{\max} = 3.531$ nN, (black line), and at slightly smaller (red) and larger (blue) forces. The inset depicts the isotensionally optimized structure at the breaking point, where the chemical bond that yields upon mechanical stress at a length of 1.995 Å is marked by the dashed line, and the red arrows indicate the atomic displacements along the corresponding normal mode obtained from the force-transformed Hessian.

arrows in Figure 2) reveals furthermore that the internal coordinates undergoing most of the change are the length of the C–C single bond that yields upon stretching in conjunction with rehybridization of the associated carbon atoms from sp^3 to sp^2 as the bond opens (sketched in Figure 1).

Overall, Figure 2 clearly reveals the effect of the external force on the topological properties of the force-transformed PES which governs mechanochemical ring-opening of all BCB- C_n mechanophores. For $F_0 < F_{\max}$, both the reactant state configuration of BCB- C_n and the transition state connecting it with the corresponding *E,E*-diene product state feature a stationary point on the force-transformed PES. At $F_0 = F_{\max}$, the external force makes these two critical points collapse into a 2-fold degenerate critical point corresponding to the breaking point, thus giving rise to the catastrophic failure of BCB- C_n toward a disrotatory ring-opening chemical reaction. Noteworthy, the topological properties embodied in Figure 2 uncover that these enforced ring-openings are so-called “ A_2 ” or “fold catastrophes”.

Force Transduction along Polymer Chains. Next, we will tackle the important issue of the role played by the polymer chains in tuning the rupture force. Not only does the dependence of F_{\max} on chain length n exhibit an unexpected striking odd–even behavior according to Figure 3, but it also reveals that the convergence of $F_{\max}(n)$ is not reached until about $n > 6$. The latter highlights the necessity of taking the polymer chains explicitly into account when it comes to the prediction of accurate rupture forces; indeed, $F_{\max}(n)$ varies by about half a nano-Newton! Therefore, consideration of isolated mechanophores has clear limitations when exploring mechanoresponsive polymers, the long-chain limit being the most relevant to experiment. The good news from the computational point of

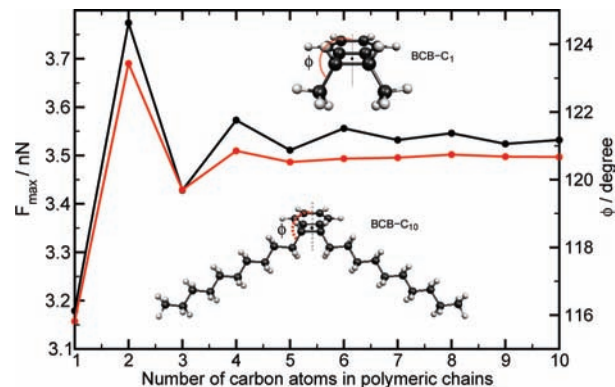


Figure 3. Analysis of force transduction in BCB- C_n as a function of chain length n . The black line (scale at left y-axis) shows the dependence of the breaking force F_{\max} on the polymer length n . Insets show the optimized molecular structures of BCB- C_1 (top) and BCB- C_{10} (bottom) both at $F_0 = 0$ together with the out-of-plane angle ϕ being a relevant structural parameter; see inset of Figure 2 for BCB- C_{10} optimized at $F_0 = F_{\max}$. The red line (right y-axis) shows the value of ϕ at the breaking point as a function of n . Lines connect the data points linearly to guide the eye.

view, though, is that converged F_{\max} values can be obtained with modestly long chains and, most importantly, that the topological features as such are independent of chain length. In relation to providing guidelines for experiments, the phenomenon uncovered in Figure 3 suggests that the properties of mechanoresponsive systems can be tuned by tailoring polymer chains as a means for transducing external forces to a given mechanophore. We anticipate that this concept in conjunction with chemical modification of the monomeric building blocks will play an important role in future design and preparation of more efficient mechanoresponsive polymers with increased functionality.

Why is the rupture force not monotonous as a function of chain length but features instead a most surprising odd–even alternation? After a thorough analysis of how structural parameters change as a function of force, a clear correlation emerges between F_{\max} and a simple internal coordinate of the mechanophores itself at breaking. It is the out-of-plane distortion angle ϕ (see Figure 3) as determined by analyzing the force-transformed PES at F_{\max} . The nonmonotonous odd–even behavior of $F_{\max}(n)$, including its most pronounced oscillations in the short-chain limit and the leveling off for long chains of about $n > 6$, correlates perfectly with the optimized $\phi(n)$ angles in Figure 3. Another surprising observation is that $\phi(n)$ is always larger at even chain lengths n compared to the neighboring odd values, $n \pm 1$. This indicates that the rupture force is governed by local structural distortions close to the junctions between the mechanophore itself and the force-transducing chains.

The next obvious question is why different polymer lengths support such distinct distortions? We will address this issue with the help of Figure 4, its inset showing the optimized structure of BCB- C_5 close to breaking. Consider a structural distortion where ϕ is decreased while keeping all other internal coordinates frozen for simplicity. Due to the zigzag chain conformation, obviously, the distances between odd-numbered carbon atoms from one chain to the other is *increased* while the even–even distances *decrease*; note that the terminal methyl group is carbon number 5 in Figure 4. Taking now into account that the mechanical coordinate $q(\mathbf{x})$ is the carbon–carbon distance between the terminal methyl groups, it is clear that for the odd cases a decrease of ϕ close to breaking is accompanied, to first order, by an *elongation* of q , which facilitates stretching of the

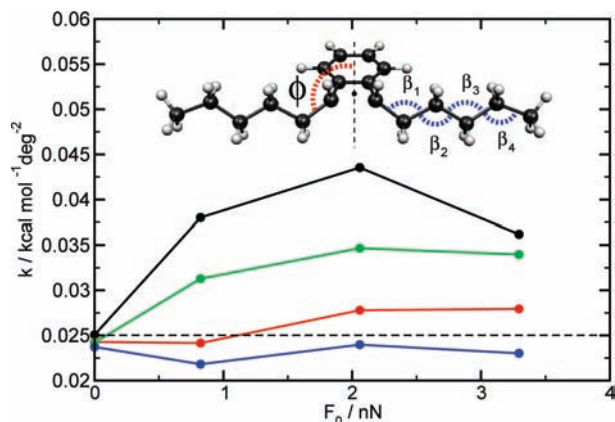


Figure 4. Analysis of bending force constants of BCB-C₅. The values of the harmonic spring constants k_i associated with $C_{i-1}-C_i-C_{i+1}$ bending motion as measured by the bond angles β_i are shown as a function of the magnitude of the external force, F_0 . The molecular structure close to the critical point, together with the relevant structural parameters β_1 (black line), β_2 (red), β_3 (green), and β_4 (blue) is depicted in the inset. Lines connect the data points linearly to guide the eye.

entire system. In stark contrast, for even chains the same distortion goes hand in hand with a *compression* of q , which requires *work against* the external stretching force! It follows from this qualitative argument that $\phi(n)$ at the breaking point of even systems n must be larger than for neighboring odd cases $n \pm 1$, and hence $F_{\max}(n)$ of the former is expected to be larger than $F_{\max}(n \pm 1)$, in agreement with the odd–even alternation in Figure 3.

Analysis of the change of bending force constants k_i associated with the angles β_i due to force-transforming the PES and thus the Hessians uncovers another surprising result, see Figure 4. At zero force, all spring constants have essentially the same value (dashed line). Upon stretching, quite remarkably, the force constant of β_1 , which governs the stiffness of the junctions between the force-transducing chains and the mechanophore, is the one which undergoes the largest alteration. Not only that, but β_1 becomes by far the stiffest bend of all the β_i angles along the chain up to breaking, and it nearly doubles around $F_0 \approx 2$ nN. With that in mind, the largest value of ϕ at breaking of BCB-C₂, and consequently, its largest value of F_{\max} , are no longer a mystery: since the force constant of β_1 becomes so large, this angle cannot open enough to allow for a smaller value of ϕ . This distinct behavior of β_1 might be due to the fact that this angle involves a carbon atom of the bond which cleaves upon stress, rehybridizes from sp^3 to sp^2 as the bond opens, and is extremely stretched at the breaking point. Regarding BCB-C _{n} with $n > 2$, their F_{\max} value is smaller than in the BCB-C₂ case because the longer polymer chains provide more flexibility in terms of extra degrees of freedom to accommodate a smaller value of ϕ at breaking. The BCB-C₁ case, in its turn, has the lowest value of ϕ (and hence the smallest value of F_{\max}) because, in absence of other degrees of freedom which can be deformed easily, the external force can solely stretch the system by decreasing ϕ and, obviously, by elongating the C–C bond that yields. The unexpectedly rich dependence of bending force constants along polymer backbones on the magnitude of the applied mechanical force is in itself a remarkable feature most relevant to understanding single-molecule force spectroscopy experiments of mechanoresponsive polymers.

Hierarchical Structural Responses. The last aspect is a “cascading behavior” of structural changes found upon stretching

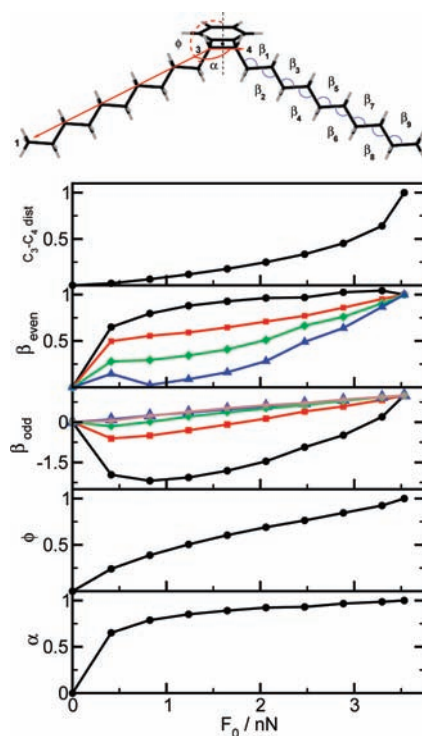


Figure 5. Hierarchical cascade of force-induced structural changes of BCB-C₁₀ from $F_0 = 0$ up to breaking. The relative distortion of each parameter P is reported as $(P_{F_0} - P_0)/(P_{F_{\max}} - P_0)$, where P_{F_0} is its value at external force F_0 , P_0 is its value at zero force, and $P_{F_{\max}}$ is its value at breaking; all P are defined in the scheme, and the last data points correspond to P at breaking. The panels labeled β_{odd} and β_{even} collect the β_i angles with odd or even i . Color code: β_1 (black), β_3 (red), β_5 (green), β_7 (blue), and β_9 (brown); β_2 (black), β_4 (red), β_6 (green), and β_8 (blue). Lines connect the data points linearly to guide the eye.

BCB-C _{n} ’s compiled in Figure 5 for BCB-C₁₀. On one extreme, we find the angle α between the aliphatic chain and the C₃–C₄ bond undergoing most of its deformation already at sub-nanomolar forces. On the other extreme, the C₃–C₄ distance associated with the bond that finally yields suffers most of its deformation only at high forces close to breaking, $F_0 > 3$ nN. In between, the out-of-plane angle ϕ changes near linearly up to breaking, whereas the bond angles β_i along the polymer backbone do feature a complex nonmonotonous behavior. Two of the odd angles, β_1 and β_3 , appreciably decrease already in the low-force regime. A close inspection of the structure of BCB-C₁₀ in Figure 5 helps to understand why: assuming again for simplicity that the rest of internal coordinates are kept frozen, a decrease of β_1 and β_3 at the optimized structure at $F_0 = 0$ results in an increase of the mechanical coordinate q , thus facilitating stretching of the entire system. In fact, the rapid increase of α in the sub-nanomolar regime is correlated with the behavior of β_1 and β_3 in this range of forces and also to the changes of ϕ .

Conclusions

Upon introducing a rigorous approach rooted in catastrophe theory, we provide a set of clear evidence that polyethylene-like chains are far from being inactive “transmission belts” that transduce external mechanical forces down to the mechanophore core unit. On the contrary, even such simple polymers do *induce* significant changes of the mechanophore’s properties and thus affect its breaking behavior. In the limit of short chains, this not only results in a remarkable dependence (including odd–even

effects of rupture forces) on the length of the polymer backbone but offers a practical way to tailor synthetic mechanoresponsive materials. This can be achieved, for instance, by exploiting the idea of a hierarchical cascade of “yield points” in polymer strands by interleaving mechanophore units with oligomeric linkers of varying length. An even richer nanomechanical behavior is expected when transducing forces to mechanophores via biomolecular macromolecules such as peptides or polysaccharides.

Methods

All calculations were performed using the B3LYP⁴³ density functional together with Ahlrichs’s SVP basis set.⁴⁴ All techniques were implemented in Turbomole or interfaced with it.⁴⁵ This cost-

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efficient electronic structure method has been shown^{35,36} to be accurate enough for our purposes as judged by CASPT2 data. In addition, B3LYP has been shown to perform well for computing breaking points and rupture forces of other polyatomic molecules.³⁸

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Supporting Information Available: Structures of the breaking points of all BCB- C_n systems and their corresponding energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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