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First Principles Dynamics and Minimum Energy Pathways for Mechanochemical Ring Opening of Cyclobutene

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Electrocyclic ring opening of cyclobutene is a textbook example of a pericyclic reaction whose structural outcome is governed by the Woodward–Hoffmann (WH) rules.[1] Under thermal conditions, the ring opening occurs with conrotatory stereochemistry, in contrast to disrotatory stereochemistry after photoexcitation. Recent experiments have shown that these rules can be circumvented by the application of external force.[2] Benzocyclobutene (BCB) was bifunctionalized and used as a seed for polymerization, leading to a long chain polymer with the BCB moiety covalently bonded to the chain on opposing sides and located roughly in the middle of the chain. Using chemical methods, the two ends of the polymer chain were selectively attached to the BCB unit either *cis* or *trans* relative to each other. Sonication of a solution containing these polymers leads to large mechanical forces due to the collapse of cavitation bubbles, and the stereochemistry of the ring-opening product depended on whether the flanking polymer strands were attached to the BCB unit in *cis* or *trans* fashion. Surprisingly, *cis* attachment leads to disrotatory ring opening, in violation of the WH rules.

The first conceptual description of mechanochemistry in molecular terms was presented some time ago.[3] However, conventional wisdom has been that mechanical forces would lead to largely nonspecific covalent bond rupture. The advent of the atomic force microscope enabled many experiments in the biological context, most of which involve the mechanically induced rupture of hydrogen bonds.[4] These processes can be modeled effectively with empirical force fields, and there have been many simulation studies of force-induced unfolding of biological molecules.[5] A recent resurgence of interest in covalent bond mechanochemistry[6] is connected to the notion of "mechanophores"—compliant, force-sensitive chemical elements that can be designed into a material to alter its reaction to stress. Using the mechanophore concept, it may be possible to avoid the nonspecific rupture typically seen at forces large enough to break covalent bonds. However, an accurate description in this case requires going beyond empirical force fields. Thus, there has been considerably less theoretical work on covalent bond-breaking mechanochemistry.[7]

In this paper, we model the response of the cyclobutene (CB) molecule (a simplified model of the BCB moiety) to applied external force. We first investigate the mechanical response using an *ab initio* molecular dynamics approach. Computational expense limits these studies to short time scales. Thus, we also investigate the potential energy surface as modified by external force to locate transition states and the associated barrier heights as a function of force. We show that both barrier heights and transition state geometries are modified by the application of external force. This leads to the possibility of designed mechanophores where the reaction path depends on the strength and nature of the applied force.

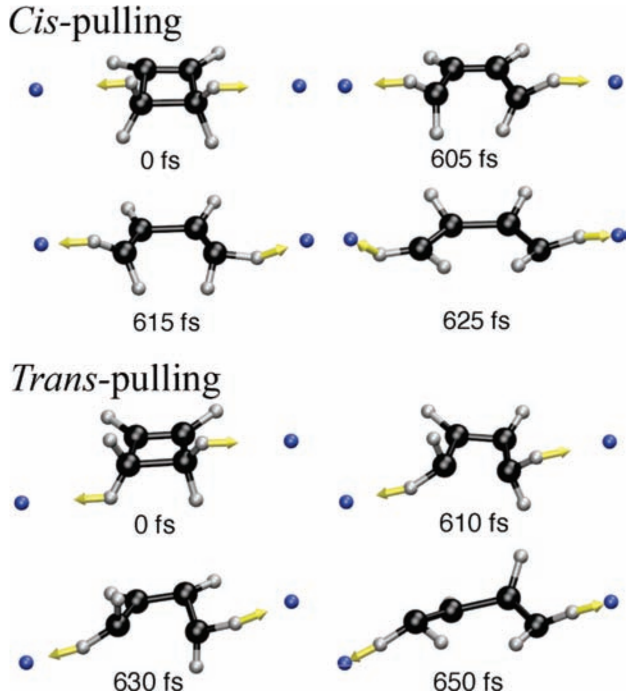

Figure 1. Snapshots from representative AISMD runs of CB using an external force of 2.5 nN. Fixed pulling points and instantaneous external force are depicted as blue spheres and yellow arrows, respectively. When the external force is applied to *cis* H atoms (upper panel), the ring opens in a disrotatory fashion, in violation of the WH rules. In contrast, ring opening proceeds with conrotatory stereochemistry when the external force is applied to *trans* H atoms (lower panel).

We first investigate the response of CB under applied forces using steered molecular dynamics[8] (SMD) combined with *ab initio* quantum chemistry, which we call *ab initio* SMD (AISMD). The electronic Schrödinger equation is solved during the dynamics to determine the forces on the atoms, allowing arbitrary bond rearrangement. We simulate the effect of external force by defining space-fixed "pulling points" (PPs) and molecular attachment points (APs). An external force is added to the *ab initio* internal forces. This external force is of constant magnitude F_0 and acts only on the AP atoms, directed toward the PPs:

$$\mathbf{F}_{ext} = \sum_{i}^{N_{attach}} F_0\,\mathbf{n}_i \qquad (1)$$

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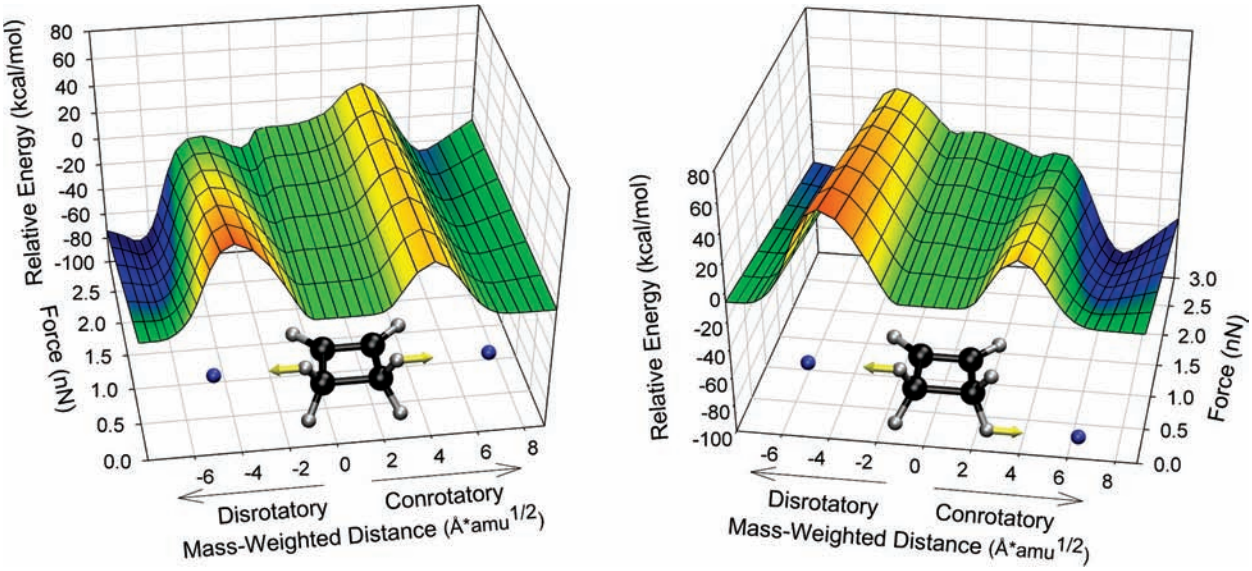

Figure 2. Force-modified potential energy surface for cyclobutene ring opening. Left panel shows the FMPES obtained by *cis*-pulling. Right panel shows the FMPES obtained by *trans*-pulling. The blue spheres and arrows in the inset denote the fixed PPs and molecular APs, respectively. When there is no applied force, the ring opening occurs through a conrotatory pathway, as predicted by the WH rules. At large applied forces, the ring opening occurs through a disrotatory pathway for *cis*-pulling (left panel) but through a conrotatory pathway for *trans*-pulling (right panel).

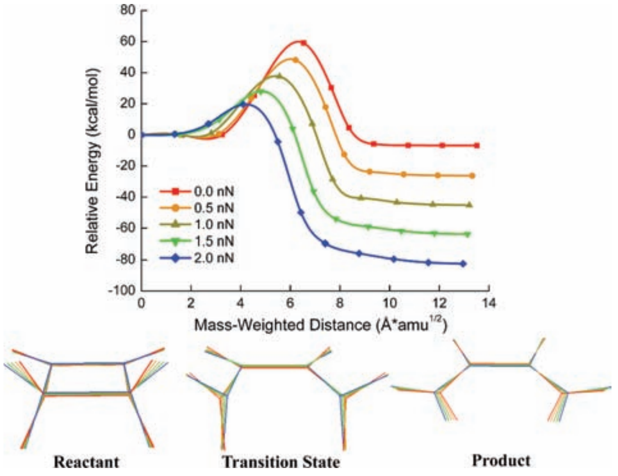

Figure 3. Optimized MEPs for disrotatory ring opening under a range of external forces and *cis*-pulling. Superpositions of the reactant, transition state, and product geometries under a range of external forces are shown below (color scheme matches the one used in plotting the MEPs).

where N_{attach} is the number of APs (two in the following) and $\mathbf{n}_i$ is a unit vector directed from the ith AP to its corresponding PP:

$$\mathbf{n}_i = \frac{\mathbf{r}_i^{fix} - \mathbf{r}_i}{\|\mathbf{r}_i^{fix} - \mathbf{r}_i\|} \tag{2}$$

The positions of the APs and PPs are denoted as $\mathbf{r}_i$ and $\mathbf{r}_i^{fix}$, respectively. The total force is then given as the vector sum of the *ab initio* internal forces and the external force:

$$\mathbf{F}_{total} = \mathbf{F}_{ab\ initio} + \mathbf{F}_{ext} \tag{3}$$

Here, we choose idealized fixed pulling points which are consistent with forces that would act on the CB molecule embedded in a polymer which was being elongated.

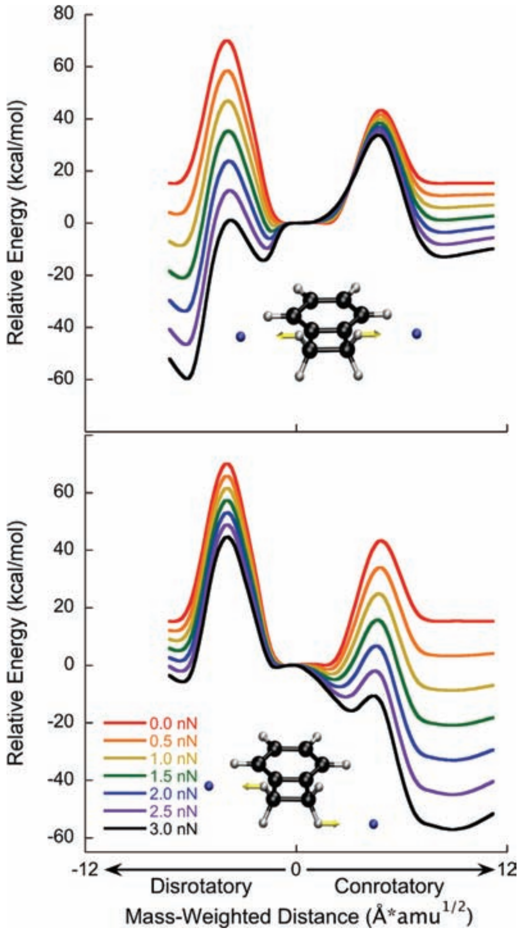

Figure 4. MEP for conrotatory and disrotatory ring opening in BCB with external force correction for a variety of applied forces. The *cis*-pulling case is shown in the upper panel, and the *trans*-pulling case is shown in the lower panel. Qualitative features are similar to those seen in CB.

We have carried out AISMD simulations using the complete active space self-consistent field (CASSCF) method[9] with second-order perturbation theory corrections,[10] i.e., CAS(4/4)-PT2, and the 6-31G** basis set in a modified version of the AIMS-MolPro code.[11] Twenty trajectories were followed for each of the *cis* and *trans* attachment cases. Representative results with an applied force of 2.5 nN are shown in Figure 1. When the APs and PPs are chosen to model the *cis* attachment of the CB moiety to the surrounding polymer strands, we find that the ring opening proceeds exclusively in a disrotatory fashion. When the APs and PPs are chosen to model the *trans* attachment, the ring opening instead proceeds exclusively in a conrotatory fashion. Our simulations start with initial conditions appropriate for a temperature of 280 K and proceed for 1 ps after the initial application of the external force. As shown in the Supporting Information, bond rupture is not observed within the 1 ps time frame for applied forces less than 1.5 nN. However, bond rupture is expected on a longer time scale, and it is furthermore expected that the preference for the reaction outcome will largely follow the indications from our AISMD results with large forces.

Nevertheless, there is a clear need to be able to understand these mechanochemical processes in the limit of low force, where the reaction is activated and may be best thought of in the language of transition state theory. Thus, we point out that one can extend the model[3] of Kauzmann and Eyring and construct a force-modified potential energy surface (FMPES) that is consistent with the AISMD forces defined above:

$$V_{total}(\mathbf{r}) = V_{ab\ initio}(\mathbf{r}) + \sum_{i}^{N_{attach}} F_0\left(\|\mathbf{r}_i^{fix} - \mathbf{r}_i\| - \|\mathbf{r}_i^{fix} - \mathbf{r}_i^0\|\right) \tag{4}$$

where $\mathbf{r}_i^0$ is the initial position of the APs. Using the nudged elastic band method,[12] we located the minimal energy pathways (MEPs) for conrotatory and disrotatory ring opening of CB without any external force. Along this pathway, we added the force modification (second term in eq 4) to generate the FMPES. The resulting FMPESs are shown in Figure 2, where the left and right panels depict the FMPES under *cis*- and *trans*-pulling, respectively. Mass-weighted distances are used in accord with conventional practice in plotting reaction paths,[13] where zero denotes the reactant structure. The *y* axis represents the magnitude of the applied force, and thus these plots show how the energetic profile of the conrotatory and disrotatory MEPs changes under the application of external forces. It is readily apparent that the barrier heights for the two competing reactions are affected differently by the applied force. This leads to mechanoselectivity, even when the applied force is small. For example, the barrier heights for disrotatory and conrotatory ring opening under *cis*-pulling (left panel) become nearly equal at an applied force of 1 nN. Thus, one expects that a mixture of conrotatory and disrotatory reaction products will be observed under these external force conditions. It is also notable that the geometry of the ring-closed minimum shifts under external force, which is clearly visible at forces exceeding 2.5 nN for both the *cis*- and *trans*-pulling cases. In some cases, it is apparent that the barrier along one of the MEPs can be removed completely; for example, the barrier to conrotatory ring opening vanishes at ~2.0 nN for *trans*-pulling. These FMPES plots explain the AISMD results; subpicosecond bond rupture is observed in the regime where the barrier to reaction has fallen below the available thermal energy.

Once the problem is cast in terms of an FMPES, it is possible to bring the optimization machinery of conventional quantum chemistry to bear directly in the presence of external applied force. The reactant and product minima on the FMPES can be located directly, and the resulting geometries will be a function of the applied force. Likewise, we can optimize MEPs directly on the FMPES, thereby determining whether the reaction pathway changes in the presence of an external force. For illustration, we have carried out these procedures for the case of *cis*-pulling of CB. The resulting MEPs are shown in Figure 3, as a function of the external force. We also show the force-dependent reactant and product minima and transition state geometries. Note that the reactant and product geometries are more affected by the external force than the transition state. It is clear from Figure 3 that the application of external force in the *cis*-pulling case lowers the barrier to ring opening along the disrotatory path. It is also clear that the transition state geometry shifts earlier along the reaction path with increasing external force. It will be interesting to apply the present methodology to other mechanophores where larger changes in the reaction path induced by mechanical force may be observed.

Finally, one might ask whether there is any significant difference between CB and BCB. We carried out MEP calculations for conrotatory and disrotatory pathways in BCB using B3LYP density functional theory (DFT) with the 6-31G** basis set. The external force correction is added to the MEP at each point for both *cis*- and *trans*-pulling. As shown in Figure 4, the qualitative features are similar to CB. In the *cis*-pulling case, the barrier heights for the conrotatory and disrotatory pathways become equivalent at an applied force of 1.5 nN. This provides a theoretical prediction for the minimum magnitude of the applied force which is exerted in the sonication experiments. This remains to be quantitatively verified, for example by experiments in a flow field or perhaps by single molecule AFM pulling experiments. It is also possible that the stereochemistry induced by *cis*-pulling in the sonication experiments is set *after* the ring-opening reaction, and this more subtle explanation is currently under investigation using MEP calculations on the FMPESs.

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Supporting Information Available: Evolution of key bond lengths for *cis*- and *trans*-pulling at a variety of forces. Cartesian coordinates and energies of important geometries. Details about FMPES and different pulling limits. This material is available free of charge via the Internet at http://pubs.acs.org.

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