

Mechanically Assisted Organic Transformations

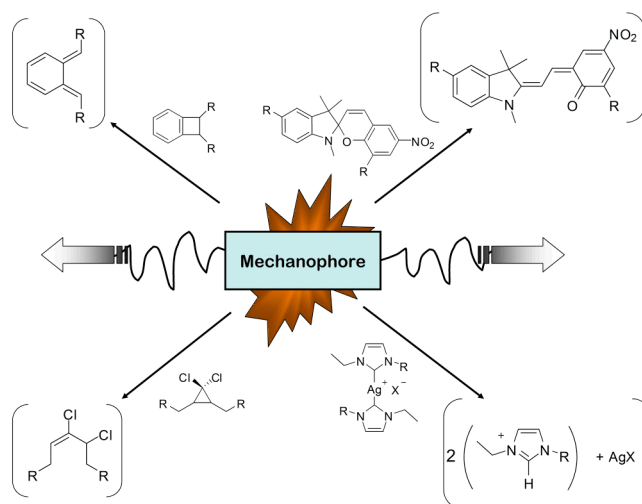
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ABSTRACT



Chemists traditionally rely on the use of thermo-, photo-, and electrochemistries in combination with optimized reactant and catalyst structure to push the forefront of new organic syntheses, but the last two years have seen landmarks in the use of mechanical force as a non-traditional and productive mechanism for directing chemical reactivity. Mechanically activated transformations offer unique capabilities relative to other methods, and they motivate the need for an improved, fundamental understanding of how mechanical forces induce and participate in chemical reactivity. These recent developments and their implications are reviewed here.

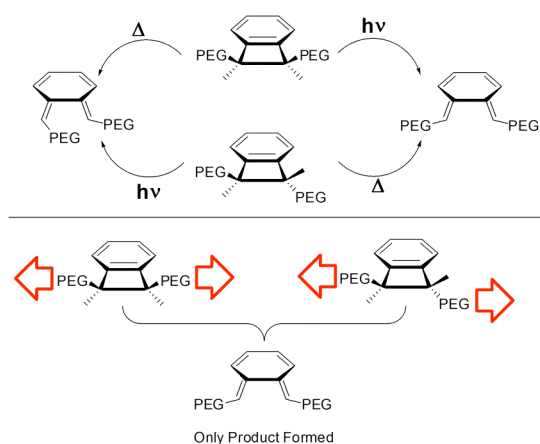
Mechanical forces typical of daily life have the potential to induce dramatic reactivity at the molecular level. The force exerted by the human body on the earth is, in fact, more than ten billion times greater than the force required to break a C-C bond! While these forces are many orders of magnitude greater than those between atoms, they are also directional, in a way that is fundamentally different than conventional stimuli such as heat and light. In the past two years, several studies have demonstrated that macroscopic mechanical forces can be harnessed at the molecular level, creating a new tool for

the organic and materials chemist alike. These studies have suggested potential utility in stoichiometric reactivity, catalysis, and stress responsive polymers. Some recent highlights, their potential impact, and primary challenges and opportunities are reviewed here.

Perhaps the primary reason that mechanical forces are unconventional stimuli in organic chemistry is the difficulty of applying a directional restoring force to small molecules, which translate away from a highly stressed region by biased diffusion. Solids and large molecular weight polymers do not translate as efficiently and remain

in high stress regions long enough to affect their molecular structure. These mechanical effects on solids and polymers vary from simple conformational changes, to bond stretching and deformation, and finally to homolytic bond cleavage at sufficiently high stresses. Such studies include the force-induced *cis/trans* isomerization of proline¹, bond deformations in polymer films under elongational tension², and the degradation of polymer solutions from homolytic bond scission under ultrasonication-induced shear forces³. The ability to physically break covalent bonds is noteworthy, because it suggests that with the strategic coupling of a mechanical force of the correct magnitude, one might be able to direct almost any organic transformation of interest.

Scheme 1: Mechanochemical selectivity in the ring opening of benzocyclobutene.



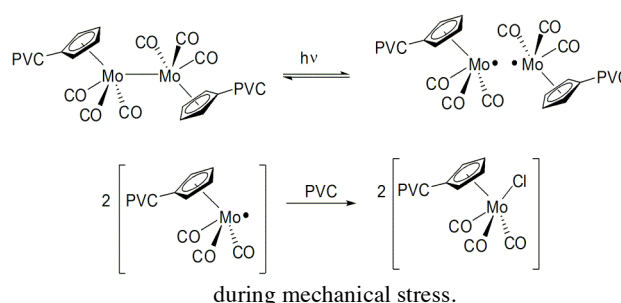
The potential of a mechanochemical approach was recently demonstrated for the ring opening of benzocyclobutene.⁴ Hickenboth *et al.* showed that a directional, mechanical force induced reactivity to yield products not obtainable from either light or heat alone. Ultrasonication of solutions of benzocyclobutene (BCB) centered polymers led to formally disrotatory (*cis*-BCB) and conrotatory (*trans*-BCB) ring opening confirming that the mechanochemical process is neither thermal nor photochemical in nature (Scheme 1). For the organic chemist, this result highlights a critical aspect of mechanically-initiated reactions—that a mechanical force can alter a potential energy surface such that a ‘forbidden’ process becomes accessible, even to the extent that it is the sole detectable reaction pathway. This type of control, realized in forcing both *cis* and *trans* benzocyclobutene to

proceed through the *E,E*-intermediate, cannot be achieved by adjusting any chemical or physical parameter of the system. The reaction is simply biased towards the transition state which best relieves the applied stress.

Hickenboth *et al.*'s results speak more generally to the potential utility of mechanically assisted rate accelerations. Indeed, the allowed (~ 40 kcal/mole) and disallowed (~ 60 kcal/mole) benzocyclobutene ring openings have activation energies that are comparable to or exceed those that of thermal processes that are useful on the lab bench. Under shear-induced mechanical stretching, however, both reactions proceed in a matter of minutes at less than 10°C . Even more interesting is that the disallowed disrotatory ring opening of *cis*-benzocyclobutene (~ 60 kcal/mole) proceeds as fast or slightly faster than the allowed conrotatory opening of the *trans*-adduct (~ 40 kcal/mole), despite the fact that thermolysis of *cis*-benzocyclobutene leads not to diene products, but to a complex mixture of degraded products.

History shows, however, that an applied force does not always accelerate reactivity. An excellent example of the complexity of mechanochemical phenomena comes from work on Mo-Mo crosslinked polymer networks and their photochemical degradation during elongational strain⁵. Mo-Mo bonds are susceptible to photochemical degradation to diradicals that are trapped by poly(vinyl chloride). Under elongational stress, photogenerated radicals initially separate more rapidly and increase the photochemical degradation by chlorine abstraction from the PVC backbone. At higher stresses, however, alignment in the PVC creates local rigidity so that the radicals simply recombine. This result spotlights the complex processes that occur during material deformation by mechanical force and the need to be able to monitor the exact nature of how macroscopic forces are translated to molecular constituents, discussed further below.

Scheme 2: Photochemical degradation of Mo-Mo cross-links



A mechanistic understanding of chemical reactivity (“physical organic chemistry”) has driven the development of traditional organic reactions. Such analyses will also be necessary for mechanochemical

¹ Valiaev, A.; Lim, W.W.; Oas, T.G.; Chilkoti, A.; Zauscher, S. *J. Am. Chem. Soc.* **2007**, *129*, 6491.

² Vettegren, V.I.; Novak, I.I. *J. Polym. Sci. Polym. Phys.* **1973**, *11*, 2135.

³ Berkowski, K.L.; Potisek, S.L.; Hickenboth, C.R.; Moore, J.S. *Macromolecules.* **2005**, *38*, 8975.

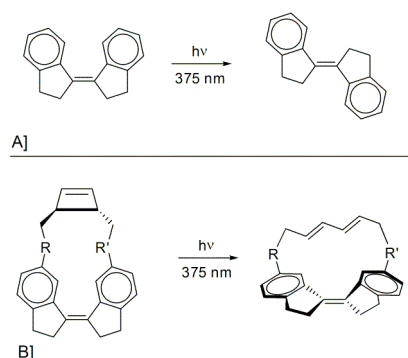
⁴ Hickenboth, C.R.; Moore, J.S.; White, S.R.; Sottos, N.R.; Baudry, J.; Wilson, S.R. *Nature.* **2007**, *446*, 423.

⁵ Chen, R.; Tyler, D.R. *Macromolecules.* **2004**, *37*, 5430.

phenomena, and important and very fundamental questions are raised by these results. For example, “what is the appropriate reaction coordinate?”, and “how do mechanical forces actually drive chemical reactivity?”. The contributions of the magnitude and direction of the applied force have been well-documented, especially in the context of single molecule studies with the atomic force microscope (AFM), but very recent work has mapped the coupled restoring force formalism onto reactivity in isolated small organic molecules.

Probing the effects of force on single molecule reactivity has generally been approached by incorporating *mechanophores* within polymer chains. A new technique has made use of the photochemical switching of E and Z states of the molecule stiff stilbene (Scheme 3, A) to efficiently induce the ring opening of cyclobutene⁶. By tethering the cyclobutene functionality at the C6-C6' ends of stilbene with different tether lengths, (Scheme 3, B: R and R') the authors were able to change the amount of force translated to the mechanophore upon opening stilbene to its Z conformer. Interestingly, using a combination of calculated and experimentally determined reaction energies, the authors noted that the calculated internal force in the molecule is a better indicator of reactivity than is a molecule's overall strain energy.

Scheme 3: Stiff stilbene, a single molecule force probe.



An important conclusion of the stilbene work relates to the challenge of defining an appropriate reaction coordinate. In particular, the rate enhancements of cyclobutene ring opening with increasing force were found to reflect not the elongation of the scissile C-C bond, as typically assumed in most mechanochemical models, but rather with the increased separation between the two methylenes that link the cyclobutene ring to the photochemical actuator. For the first time, a physical description of the effect of mechanical force relating to a single internuclear bond distance was established. It seems likely that the appropriate reaction coordinate that should be considered in the mechanochemical setting will

⁶ Yang, Q.-Z.; Huang, Z.; Kucharski, T.J.; Khvostichenko, D.; Chen, J.; Boulatov, R. *Nature Nanotech.* **2009**, *4*, 302.

change significantly both with reaction and its coupling to the applied force. Importantly, the most useful reaction coordinate may or may not coincide with the coordinate that most efficiently describes the force-free reaction in other contexts.

This point is further driven home by the Hickenboth⁴ work, in which the *cis*-benzocyclobutene reacts slightly faster under mechanical stress than the *trans* analogue. By viewing the migrating methylene groups as mechanically directing handles, the significance becomes clear. The distance traveled by the *cis*-methylene groups in relation to *trans* is longer, acting as a more efficient ‘lever’ in opening the cyclobutene ring. The idea of efficient “levers” as tools for efficiently directing chemical reactivity is both intriguing and potentially useful. It is also effectively untapped to date.

In light of the proliferation of data on the covalent mechanochemistry of cyclobutenes, there is a requirement for the development of better theoretical frameworks for covalent bond activation. The initial model for describing increased rates of non-covalent bond dissociation by mechanical force was developed by Eyring⁷ and Bell,⁸ and estimated that the energy landscape of the reaction did not change in the presence of a force. Further work resulted in a ‘tilted potential energy surface (tPES)’ model⁹ though this model did not take into account any force-induced distortion of the underlying potential energy surface. Recently, COGEF (COstrained Geometries simulate External Force) calculations have been used to probe an entire reaction coordinate—therefore one can evaluate reactant and transition state structures as well as activation energies as a function of the applied force¹⁰. In comparing these three models for the covalent mechanochemistry of benzocyclobutene, both the Bell and tPES models failed to accurately portray the behavior of benzocyclobutene ring opening at forces larger than ~1.5 nN; covalent mechanochemistry occurs for forces between 2.6 and 13.4 nN for C-C bonds¹¹. These results accentuate the need to synthesize, design, and quantify the activity of mechanically responsive molecules to aid the development of a comprehensive, working theory of covalent mechanochemistry.

While stoichiometric mechanochemistry could be very useful in stress-responsive polymers, there is an issue of scale that likely prevents its utility in synthesis. If mechanochemical effects could be amplified via catalysis, however, efficient turnover would lead to a new, and potentially synthetically useful, breed of mechanocatalytic reagents. Two main approaches to mechanocatalysis can be envisioned: the mechanical alteration of the catalyst structure and/or coordination sphere, and the mechanical displacement of a ligand to provide an empty site for reagent coordination.

⁷ Kauzmann, W.; Eyring, H. *J. Am. Chem. Soc.* **1940**, *62*, 3113.

⁸ Bell, G.I. *Science.* **1978**, *200*, 618.

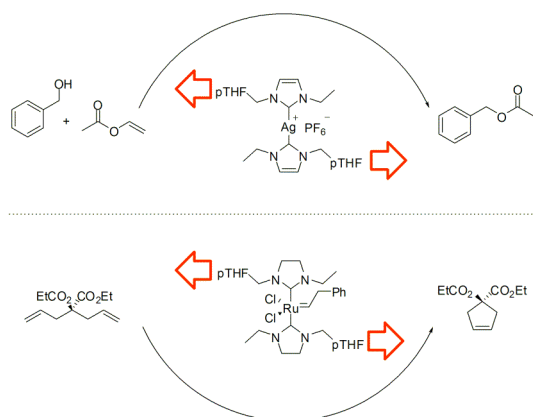
⁹ Evans, E.; Ritchie, K. *Biophys. J.* **1997**, *72*, 1541.

¹⁰ Ribas-Arino, J.; Shiga, M.; Marx, D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4190.

¹¹ Beyer, M.K.; Clausen-Schaumann, H. *Chem. Rev.* **2005**, *105*, 2921.

Enzyme catalysis was the first example of mechanical modification in catalytic activity. Klibanov *et al.* modified elastomeric supports with trypsin or α -chymotrypsin and performed catalysis while the support was stretched or unstretched¹². Changes in activity were observed, but linking those changes to structural perturbations of the enzyme is both experimentally and intellectually challenging. Mechanical grinding has also been used to generate heterogenous catalysts *in situ*¹³. A clearer example of the ligand displacement strategy for catalyst activation involves Sijbesma's report of sonochemical ligand displacement from latent *bis*-N-heterocyclic carbene (Ru and Ag) complexes in solution¹⁴. On sonication, the shear forces arising from collapsing cavitation bubbles induce ligand dissociation and initiate catalysis.

Scheme 4: Sonochemical activation of latent catalysts; *Mechanocatalysis*



Looking ahead, the success of mechanically initiated catalysis raises several interesting questions and challenges. For example, how might one alter catalyst reactivity and/or selectivity without ligand dissociation, e.g. influencing coordination chemistry towards determining the most efficient 'bite angle' of a coordinating bidentate ligand. Notably mentioned in the work of Sijbesma¹⁴ is the eventual inactivation of the reaction, so can future latent catalysts be repeatedly cycled on and off? More interestingly, can they be tuned *in situ* during the catalytic cycle?

While solution mechanochemistry is an efficient route for producing mechanochemical phenomena, more efficient mechanical transduction would likely be found in heterogenous supports. In many bulk polymers, sufficiently large mechanical forces lead to covalent bond

¹² Berezin, I.V.; Klibanov, A.M.; Samokhin, G.P.; Martinek, K. *Methods Enzymol.* **1976**, *44*, 558.

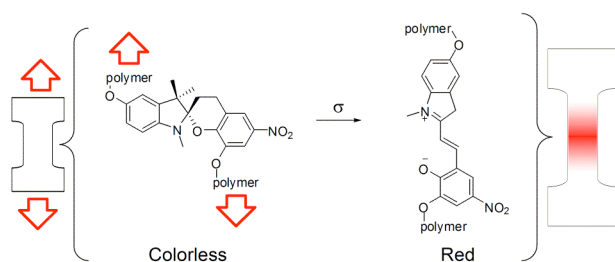
¹³ Ikeda, S.; Takata, T.; Komoda, M.; Hara, M.; Kondo, J.N.; Domen, K.; Tanaka, A.; Hosono, H.; Kawazoe, H. *Phys. Chem. Chem. Phys.* **1999**, *1*, 4485.

¹⁴ Piermattei, A.; Karthikeyan, S.; Sijbesma, R.P. *Nature Chem.* **2009**, *1*, 133.

scission, damage, and eventual failure of the network. It would be useful both to take advantage of these forces in catalysis, and also to create materials that respond to mechanical forces constructively, including: (1) signal generation to warn of ensuing failure, (2) structural modification to extend or slow the rate of failure, or (3) repairing the damage altogether. In each case, the rational design of synthetic mechanophores is of the utmost importance.

But, as discussed previously in the context of the Mo-Mo dissociation, the relationships between macroscopic forces and molecular behavior is often complex. To help clarify those relationships, a spiropyran-incorporated polymer was recently shown to respond to mechanical force through a ring-opening mechanism leading to a highly colored merocyanine product¹⁵. This article emphasized that molecular processes can be triggered in bulk materials under both tensile and compressive stress, but more importantly, the colored transition from spiropyran to merocyanine provides a mechanism for mapping molecular stress distributions. Ideally, one would like to do this in a ratiometric way (e.g., by FRET), but it is clear that truly quantitative mechanochemical mapping should be possible.

Scheme 5: Mechanical force activates spiropyran in a polymer network.



With respect to the variety of techniques available to the synthetic chemist for molecular manipulation, the use of mechanical force holds great promise as a next generation method for molecular remodeling. A fundamental understanding of the mechanism/s of molecular response to mechanical force requires the synthesis and quantification of responses of still more mechanophores. While much work has focused on mechanophores with significantly weak bonds, relying instead on torsional forces may provide an additional route of bond activation by taking advantage of large conformational changes between the reactant and product. Influencing conformational changes in organometallic chemistry may also provide for further examples of reactions susceptible to bite angles or other coordination effects towards the preparation of mechanocatalysts.

¹⁵ Davis, D.A.; Hamilton, A.; Yang, J.; Cremer, L.D.; Gough, D.V.; Potisek, S.L.; Ong, M.T.; Braun, P.V.; Martinez, T.J.; White, S.R.; Moore, J.S.; Sottos, N.R. *Nature.* **2009**, *459*, 68.