Furan–Maleimide Mechanophores: Competitive Activation Experiments and Mechanically Triggered Drug Delivery Applications

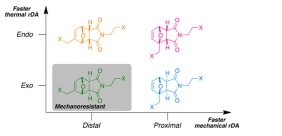
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Mechanochemistry of Diels–Alder Adducts

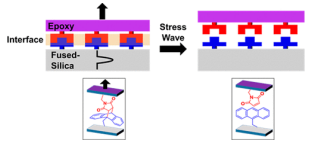
Mechanical force is a unique external stimulus for controlling specific chemical reactions of stress-sensitive molecules known as mechanophores. **Furan–maleimide (FM) and anthracene–maleimide (AM) Diels–Alder adducts** are widely studied mechanophores that undergo retro-Diels–Alder reactions upon mechanical activation in polymers. These mechanophores have been developed for a wide range of applications such as stress visualization and the triggered release of small molecules.

Mechanochemical reactivity of FM adducts controlled by geometry



Stevenson, De Bo, *J. Am. Chem. Soc.* **2017**, *139*, 16768

Laser-induced mechanochemical activation of interfacial AM adducts

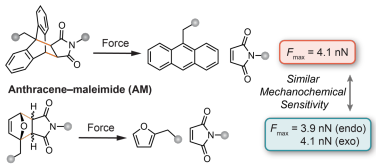


Sung, Robb, White, Moore, Sottos, *J. Am. Chem. Soc.* **2018**, *140*, 5000

Comparing Reactivities of Mechanophores

Mechanophore candidates are typically evaluated with density functional calculations using the **CoGEF method**, which is a good predictor of mechanochemical reactions and their corresponding rupture force. Experimental evaluation of mechanophore reactivity typically relies on measuring the **rate of mechanophore activation** upon ultrasound-induced mechanochemical activation of polymers in solution.

CoGEF evaluation:



Klein, Husic, Kovács, Choquette, Robb, *J. Am. Chem. Soc.* **2020**, *142*, 16364

Ultrasonication Experiments:

Limited due to variation in:
- Polymer **dispersity**
- Mechanophore **chain-centeredness**

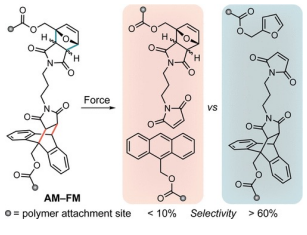
Multiple polymer samples required

Overholts, Robb, *ACS Macro Lett.* **2022**, *11*, 733

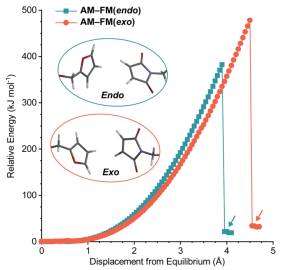
Overholts, McFadden, Robb, *Macromolecules* **2022**, *55*, 276

Challenge: Investigate a reliable methodology to resolve differences in mechanochemical reactivity for mechanophores with similar predicted F_{max} values.

Design of a Bis-Adduct Mechanophore



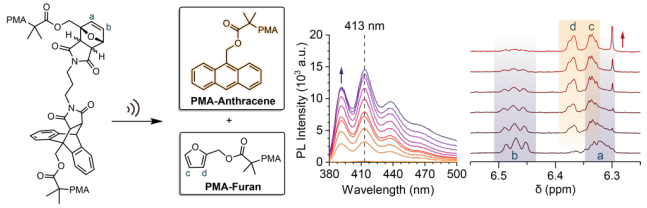
Each adduct is exposed to the **same mechanical forces** when tethered covalently, providing **direct comparison** of their reactivities.



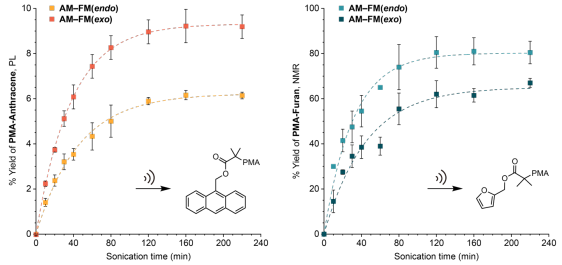
CoGEF predicts the retro-Diels–Alder reaction of the FM subunit at F_{max} values of 4.0 nN for **AM–FM(*endo*)** and 4.2 nN for **AM–FM(*exo*)**

Competitive Activation Experiments

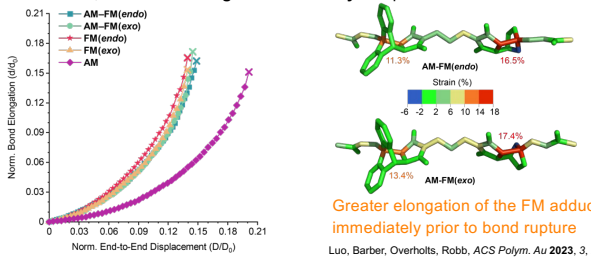
Poly(methyl acrylate) polymers incorporating **AM–FM(*endo*)** and **AM–FM(*exo*)** bis-adducts near the center were were subjected to **pulsed ultrasonication**. Formation of the anthracene product and the furan product was quantified by **photoluminescence (PL) spectroscopy** and **^{1}H NMR spectroscopy,** respectively.



Ultrasonication of the PMA polymers revealed that **FM activation outcompetes AM activation** by a ~7:1 ratio for **AM–FM(*exo*)**, and by a ~13:1 ratio for **AM–FM(*endo*)**



Computational modeling indicates **more efficient mechanochemical coupling** for the FM adduct, which results in **greater reactivity** compared to the AM unit.

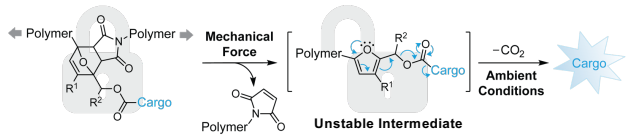


Greater elongation of the FM adduct immediately prior to bond rupture

Luo, Barber, Overholts, Robb, *ACS Polym. Au* **2023**, *3*, 202

Mechanically Triggered Small Molecule Release

A mechanically gated cascade reaction enables molecular release



Masked 2-furylcarbinol derivative (FM mechanophore)

Force unmasks an unstable intermediate that decomposes to release its cargo

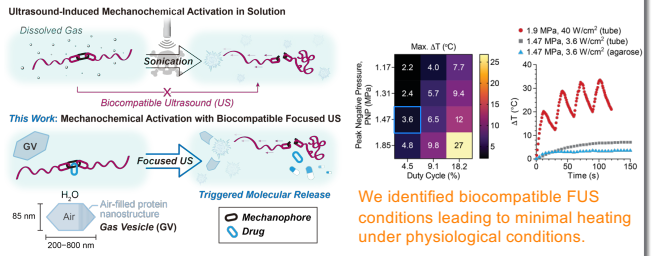
Hu, Zeng, Husic, Robb, *J. Am. Chem. Soc.* **2019**, *141*, 15018

Hu, Zeng, Husic, Robb, *ACS Cent. Sci.* **2021**, *7*, 1216

Goal: Drug delivery applications using ultrasound as an external mechanical trigger.

Ultrasound-Induced Drug Delivery

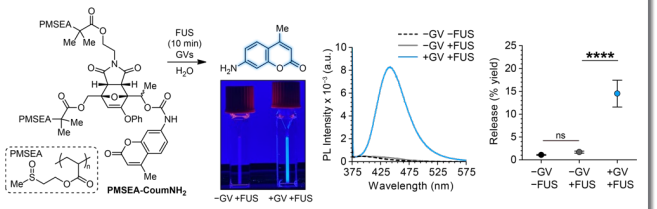
We report a synergistic system where the **selective mechanochemical activation** of mechanophore-functionalized polymers is achieved using **biocompatible focused ultrasound (FUS)** by leveraging **pressure-sensitive gas vesicles (GVs)** as acousto-mechanical transducers.



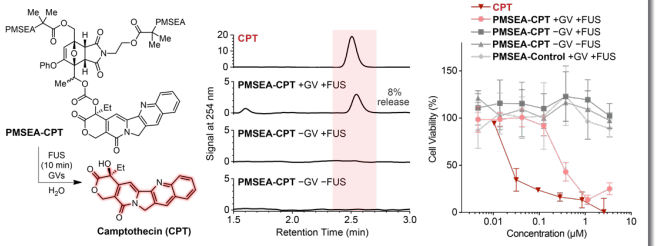
We identified biocompatible FUS conditions leading to minimal heating under physiological conditions.

For more about GVs, see: Bar-Zion, Nourmahnad, Mittelstein, Shivaei, Yoo, Buss, Hurt, Malounda, Abedi, Lee-Gosselin, Swift, Maresca, Shapiro, *Nat. Nanotechnol.* **2021**, *16*, 1403

A dilute solution of **PMSEA-CoumNH$_2$** was subjected to 330 kHz FUS under the conditions identified above in the presence of GVs (1.4 nM), resulting in **15% release** after 10 min of FUS exposure, as quantified by PL spectroscopy.



The triggered release of camptothecin from **PMSEA-CPT** was achieved using the same FUS conditions, as evidenced by quantitative HPLC measurements. The mechanochemically activated polymer exhibits **significant cytotoxicity** to Raji cells.



Yao, McFadden, Luo, Barber, Kang, Bar- Zion, Smith, Jin, Legendre, Ling, Malounda, Torres, Hamza, Edwards, Shapiro, Robb, *Proc. Natl. Acad. Sci. U.S.A.* **2023**, *120*, e2309822120

Future research aim to translate these proof-of-principle results to *in vivo* settings for drug delivery and other biomedical applications.

Acknowledgments

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