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A systematic workflow for mechanophore design

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Abstract

Advancing mechanoresponsive materials require novel mechanophores, though clear and structured design guidelines are still emerging. In this work, we present a systematic workflow aimed at facilitating the design and discovery of new mechanophores. By integrating the classic iso-metrical CoGEF approach with our innovative iso-tensional Tension Model of Bond Activation (TMBA) simulation, the workflow described herein enables comprehensive evaluation of mechanophore candidates prior to experimental implementation, with a practical case study included for detailed illustration. This predictive capability allows computational screening, efficient identification and filtering away unexpected issues while providing valuable insights for potential structural optimization.

Introduction

What happens at the molecular level when a polymeric material fails? This fundamental question has captivated chemists and materials scientists for over a century, laying the groundwork for the research field known as polymer mechanochemistry.[1] Early investigations demonstrated that deformation and subsequent failure of polymers—whether linear polymers in solutions or bulk polymeric materials—result in the cleavage of chemical bonds within the polymer backbone.[2] Understanding the chemical nature of these resulting species provides critical insights into the polymer's behavior after failure. Entering the twenty-first century, research in polymer mechanochemistry has shifted significantly from destructive chemistry to productive applications.[1] By incorporating mechanophores into polymer backbones, researchers can precisely control the location of bond cleavage and the nature of the resulting chemical species. This strategy allows mechanophore activation to be intentionally designed and experimentally characterized to provide productive results. Incorporation of various mechanophores facilitates the advent of mechanoresponsive materials enabling diverse applications across numerous fields, including fundamental research,[3–5] material reinforcement,[6] fracture detection,[7,8] force sensing,[9] drug delivery,[10] cancer therapy,[11] controlled release of small molecules,[12–14] and reaction catalysis.[15] The rapid development and expanding utility of polymer mechanochemistry highlights its vast potential for further innovation and applications across multiple scientific and technological domains.

To further broaden the scope of polymer mechanochemistry applications, design and development of new mechanophores are sometimes required. However, developing a systematic workflow for mechanophore design remains a significant challenge for researchers, which makes it an evolving area of science. Traditionally, verifying the feasibility of a newly designed mechanophore requires extensive preliminary experimentation, including organic synthesis, polymerization and activation trials. These initial experiments are often time-consuming and occasionally frustrating due to unforeseen outcomes. Although computational simulations have been explored as a partial solution,[16,17] existing methods sometimes suffer from drawbacks such as being excessively time-consuming, having steep learning curves, or yielding unreliable predictions that fail to provide meaningful guidance for experiments. Consequently, researchers still frequently depend on their personal experience and chemical intuition when designing new mechanophores. This situation underscores the need for a better, more systematic and reliable workflow to streamline mechanophore design and validation prior to conducting resource-intensive experimental studies.

One of the most developed and widely used simulation methods for mechanophore pre-experimental analysis is the Constrained Geometries simulated External Force (CoGEF) method.[18,19] As implied by its name, CoGEF is an iso-metrical simulation approach involving geometry optimization and energy calculations of mechanophore molecules under constrained distances at specific "handle" positions. Recently, another approach named Tension Model of Bond Activation (TMBA) has been introduced to simulate mechanophore activation.[20,21] Unlike the classic CoGEF approach, TMBA employs an iso-tensional methodology, focusing primarily on activation energy calculations for bond cleavage and molecular geometry optimization integrated with an additional tension energy function for force-coupling analysis. Due to the complementary mechanisms underlying CoGEF and TMBA, combining these two methods promises comprehensive and reliable pre-experimental analyses.

In the method reported here, we propose a systematic mechanophore design workflow integrating CoGEF and TMBA simulations (Fig. 1). This pre-experimental analysis workflow leverages simulations that are both efficient and accessible, offering detailed guidance for mechanophore design and effectively addressing potential drawbacks prior to actual experimentation. We believe this structured workflow will significantly enhance the efficiency and rationality of mechanophore discovery. To demonstrate the practicality and effectiveness of this method, we also include a case study drawn from our recent research on gaseous-molecule-releasing mechanophores. We hope that this workflow will help overcome existing challenges in mechanophore design and further promote the development of polymer mechanochemistry.

Mechanophore hypothesis & primary feasibility analysis (CoGEF)

The primary feasibility analysis aims to verify whether a mechanophore can be activate through the intended pathway upon applying mechanical force at the designated handle positions. A common challenge with newly designed mechanophores is the occurrence of unexpected processes leading to side products upon activation. Based on prior research and our experiences, the two predominant reasons for such side reactions are competitive bond cleavage [Fig. 2(a), (b)] and unexpected side reactions [Fig. 2(c)]. For instance, the trans-sulfolene isomer in Fig. 2(b) was initially expected to undergo a cheletropic elimination similar to the cis-sulfolene isomer in Fig. 2(a). However, CoGEF simulations revealed premature cleavage of the handle before the anticipated reaction could occur. Similarly, in the case shown in Fig. 2(c), the molecule was designed to undergo a retro [4+2] cycloaddition reaction to yield a quinone product. Simulation results instead showed that after the initial C-O bond cleavage, a rapid 1,5-hydrogen shift led to a stable intermediate, effectively prevent progression along the intended reaction pathway. Similarly, previous work has also revealed failed generation of ketene from tension-activated retro [2+2] cycloaddition from cyclobutadiones.[22] These examples highlight the crucial role of preliminary feasibility analysis to reveal unforeseen complications before experimental validation.

As a well-established and widely applied method in polymer mechanochemistry studies, CoGEF has proven particularly suitable for feasibility analyses, specifically in ruling out unintended chemical reactions under mechanical tension.[19] Details related to CoGEF calculation method were well developed and can be found in previous work, but briefly, the CoGEF method involves

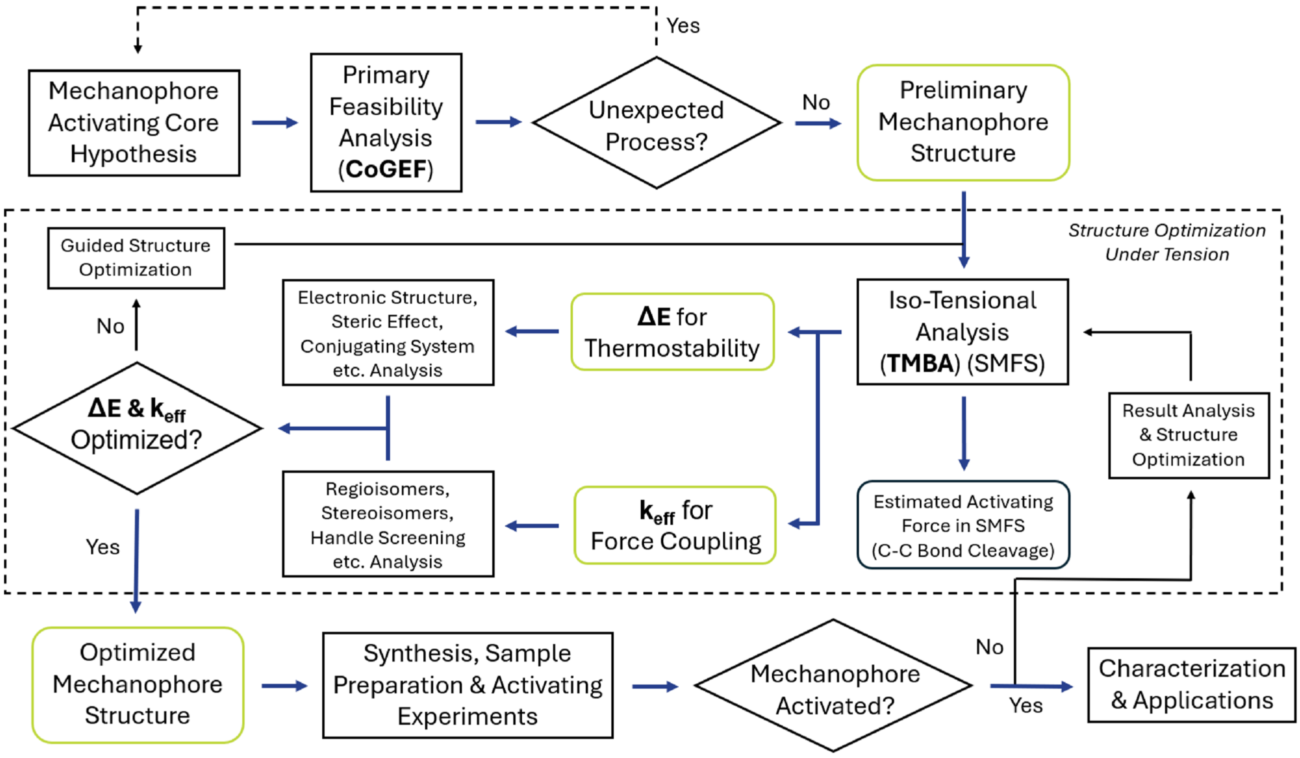


Figure 1. Systematic workflow for mechanophore design. Blue arrows indicate the main sequence of the workflow, while green frames indicate the important productive results from simulation. The workflow can be roughly separated into three parts: Mechanophore hypothesis & feasibility analysis (CoGEF); Structure optimization under tension (TMBA); Final modification and activating experiments. Specifically, CoGEF appeared to be not straightforward at some case, which leads to the dash backward arrow with unexpected process from CoGEF.

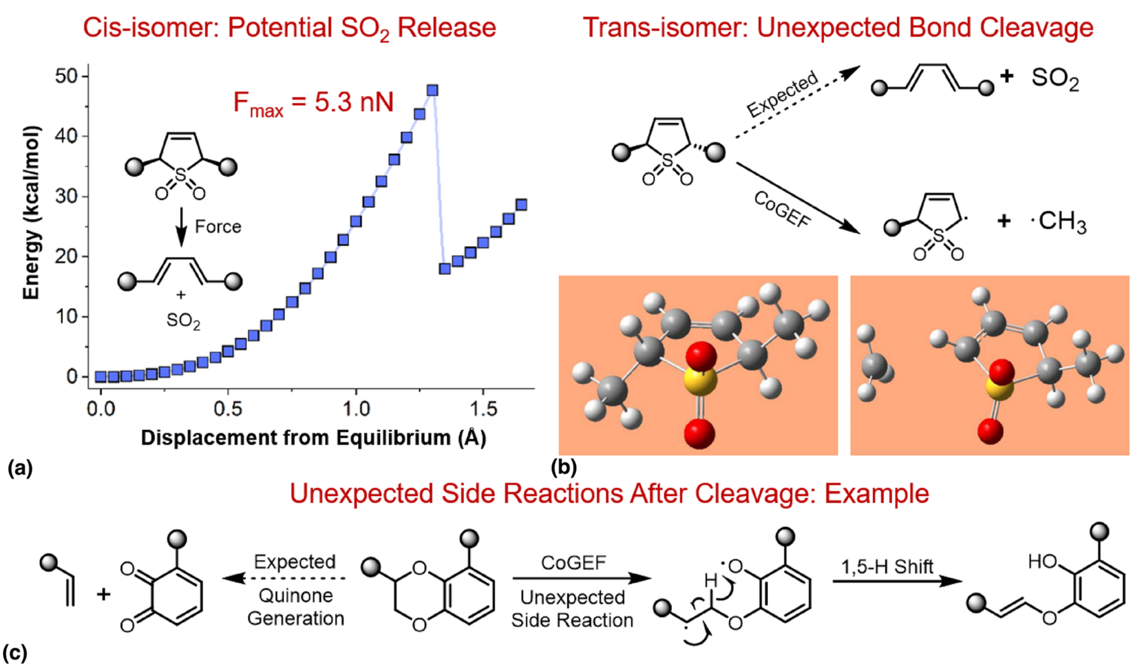


Figure 2. Preliminary feasibility analysis based on CoGEF. (a) Simulation result for the cis-sulfolene mechanophore based on cheletropic elimination. (b) Unexpected bond cleavage for the trans-sulfolene isomer. (c) Unexpected side reaction for purposed quinone-generating mechanophore.

optimizing molecular structures under constrained handle distances while calculating their associated energies in parallel. By progressively increasing the constrained distance, CoGEF simulations effectively mimic the mechanical stretching of mechanophore, as exemplified in Fig. 2(a). Due to its iso-metrical nature, CoGEF is capable for predicting chemical transformations during deformation but lacks the assistive role of thermal activation (transition state theory) CoGEF requires the external force to promote complete bond scission. Although researchers have attempted to estimate an "activation force" by deriving values from CoGEF simulations, these obtained numbers have limited physical relevance and have been demonstrated to significantly deviate from experimental results obtained through Single Molecule Force Spectroscopy (SMFS), which is one of the most widely accepted and used methods for quantitative measurement of mechanophore activation force. The main reason for discrepancies is the lack of consideration for thermal energy, indicating that CoGEF simulates reactivity as to the zero activation barrier is approached, which is far from realistic experimental conditions. Consequently, to gain meaningful insights into mechanical properties directly related to applied force and activation energies, the complementary iso-tensional TMBA method is necessary.

Mechanophore structure optimization under tension (TMBA)

While CoGEF is valuable for feasibility studies and ruling out unintended chemical reactions under mechanical tension, it cannot reliably provide energetic and tensional information necessary for optimized mechanophore design.[20] Specifically, CoGEF struggles to accurately determine the force coupling efficiency through the handles and lacks effective consideration of activating energy related to bond cleaving energy. To address these limitations, an iso-tensional approach is required. In 1940, The Force-Modified Potential Energy Surface (FMPES) method developed by Eyring et al. addressed this requirement by integrating a force potential into the classical diatomic Morse potential.[23] Although effective for providing reliable energy and force-related insights, the original FMPES method is primarily applicable to simple diatomic systems. When extended to complex molecular systems, the original FMPES fails to capture realistic molecular features (e.g., stereochemistry), thus limiting its utility for pre-experimental mechanophore evaluations.

Inspired by the classic FMPES method and recent developments in mechanophore design, Moore, Kulik and Craig et al. introduced the Tension Model of Bond Activation (TMBA) in 2024.[20] This approach significantly simplifies the External Force Explicitly Included (EFEI) simulation process, making it accessible to a broader research community while providing valuable insights and guidance. EFEI simulation method can always provide relatively accurate and reliable information about transition states of mechanophore under tension, but its accuracy and reliability come together with its time-consuming nature, which is not suitable and inefficient for pre-experimental design.[20] Details related to TMBA calculation method can be found in previous work, but briefly, the TMBA method simplifies the first derivative of the Morse potential under force into a triangular shape known as the Restoring

Force Triangle (RFT)[21] [Fig. 3(a)]. By reducing the complexity of the restoring force curve, TMBA intuitively captures the relevant molecular parameters, **ΔE** and $\mathbf{k_{eff}}$ [Fig. 3(b)]. Under the framework of TMBA, **ΔE** was defined as the energy difference between the mechanophore far before (ground state) and right after activation, while $\mathbf{k_{eff}}$ indicates the effective Hookean constant of the cleaving bond when tension was applied on handles. The detailed computational steps required to determine these parameters have been previously discussed.[20] Analysis of the RFT allows researchers to obtain crucial energy- and force-related insights, facilitating both feasibility assessment and optimization of mechanophore designs.

In TMBA simulation results, the parameter **ΔE** is directly related to the area of the Restoring Force Triangle (RFT) and physically represents the energy required to cleave the initial bond necessary for mechanophore activation [Fig. 3(b)]. To calculate the **ΔE** parameter, geometry optimization of the mechanophore is conducted before and after the bond cleavage event (activation), and the energy difference between these two optimized states is determined. It is important to note that no

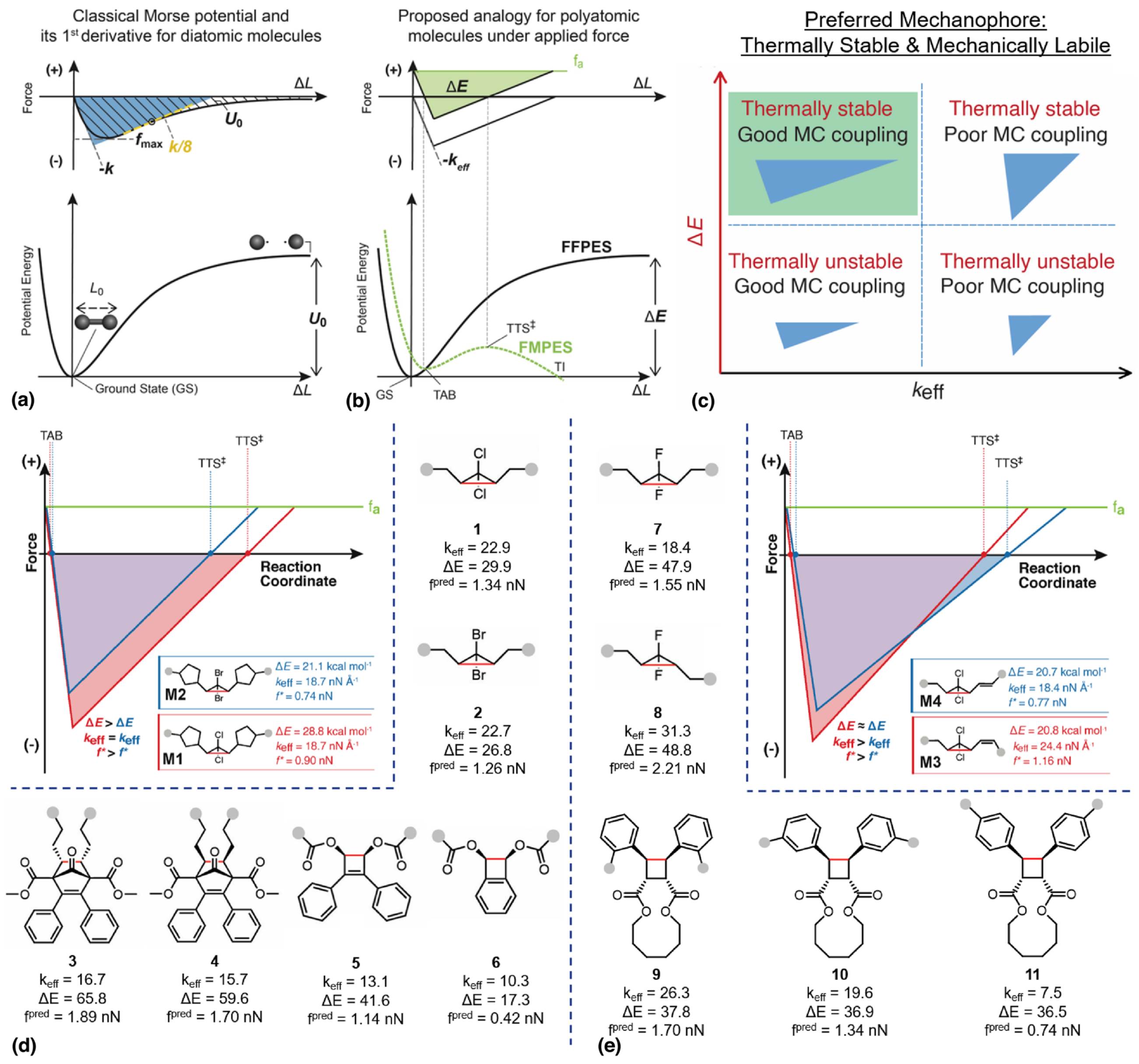


Figure 3. Structure optimization under tension based on TMBA method. (a) the 1st derivative of Morse potential and how it is approximated to Restoring Force Triangle (RFT). (b) Morse potential and RFT with force (f_a) applied, indicating the two determining factor $\mathbf{k_{eff}}$ & **ΔE**. (c) Schematic diagram of the mechanophore activity matrix, a quad chart for mechanochemistry. (d) RFTs for mechanophores with nearly identical $\mathbf{k_{eff}}$ but different **ΔE**, together with some examples. (e) RFTs for mechanophores with nearly identical **ΔE** but different $\mathbf{k_{eff}}$, together with some examples. This figure was reorganized from previous publications.[20,21]

tension is applied during this calculation (a force-free analysis), indicating that the **ΔE** parameter itself is intrinsic to the bond itself. Consequently, the **ΔE** parameter obtained from TMBA simulations not only reflects the mechanochemical activation energy but also potentially correlates with the mechanophore's thermal stability if the thermal decomposition pathway aligns with the mechanochemical activation route (and this alignment can be reflected by $\mathbf{k_{eff}}$, which will be discussed later). Considering its physical and chemical meaning, **ΔE** is closely related to the electronic structure and steric effects of the mechanophore both before and immediately after activation, as illustrated in Fig. 3(d). By tuning the electronic structure [**1** & **2** in Fig. 3(d)], conjugation system [**5** & **6** in Fig. 3(d)] and/or steric environment [**3** & **4** in Fig. 3(d)] around the cleaving bond, researchers can adjust the shape of RFT and effectively control and optimize the ΔE parameter, guiding further structural optimization of mechanophores. However, if analyzed solely from the perspective of **ΔE**, a potential dilemma emerges: mechanophores that are easily activated mechanically might inherently lack thermal stability. Fortunately, TMBA simulations distinguish the thermal and mechanochemical contributions from tension by introducing $\mathbf{k_{eff}}$. A comprehensive analysis involving both **ΔE** and $\mathbf{k_{eff}}$ can thus help resolve this dilemma and provide improved strategy for better mechanophore design.

Unlike **ΔE** calculations, $\mathbf{k_{eff}}$ values are calculated under systematically varying tensile force (in the low force region). Inspired by the classical diatomic Morse potential[24]—which models chemical bonds as springs obeying Hooke's Law—TMBA similarly employs a Hookean approximation for bond activation analysis.[21] To consider the force transmission process from remote handles to the scissile bonds, the TMBA method introduces the effective Hooke's constant, $\mathbf{k_{eff}}$, representing the effective force transduction and coupling to the cleaving bond [Fig. 3(e)]. Consequently, $\mathbf{k_{eff}}$ strongly depends on the mechanophore's topological structure and can vary significantly between constitutional [**9** & **10** & **11** in Fig. 3(e)] or stereoisomers [**7** & **8** in Fig. 3(e)], providing further opportunities for precise tuning of mechanochemical properties through topology design and/or handle screening. Meanwhile, since there are no transition states searching in all TMBA simulations, the time efficiency and the learning barrier is also suitable for most researchers.

Based on TMBA simulation results using the parameters **ΔE** and $\mathbf{k_{eff}}$, researchers can gain a deeper understanding of the mechanochemical behavior of a designed mechanophore. Specifically, **ΔE** generally reflects thermostability and captures non-tensional contributions, while $\mathbf{k_{eff}}$ represents force-coupling efficiency and encapsulates the mechanical aspects. The separation and analysis of thermally related and mechanically related contribution allows a more intuitive and comprehensive evaluation of a mechanophore's molecular characteristics. Ideally, a well-designed mechanophore should exhibit a relatively high **ΔE** to ensure thermal stability and a low $\mathbf{k_{eff}}$ to maximize mechanochemical coupling—i.e., thermally stable but mechanically labile.[21] Furthermore, for mechanophores that undergo C–C bond cleavage during activation, the availability of extensive experimental data enables the prediction of activation force (**f***) under Single-Molecule Force Spectroscopy (SMFS) experiments.[4] This predicted **f*** can further provide overall evaluation of mechanophore lability related to experimental environments.

Ultimately, calculated values of **ΔE** and $\mathbf{k_{eff}}$ guide both the structural optimization of mechanophores and deeper feasibility analyses from energetic and mechanical perspectives. By combining the iso-metrical CoGEF method with the iso-tensional TMBA approach, researchers can obtain a systematic and comprehensive evaluation of mechanophore candidates, helping to identify and eliminate potential issues before proceeding to synthesis and experimental testing.

Final modification, polymerization and activating experiments

While systematic feasibility analysis using CoGEF and TMBA simulations can eliminate many potential pitfalls in mechanophore design, it is important to note that a successful simulation does not guarantee positive experimental outcomes. Simulation can significantly narrow the design space and provide optimized structures, but experimental validation—including synthesis, polymer incorporation, and activation testing—is essential for confirming mechanophore performance and realizing functional applications.

Due to computational limitations, most simulations focus mainly on the mechanophore units, and thorough simulation of bulk system with hundreds of atoms still remains challenging for general researchers with limited access of calculating power. However, successful mechanophore activation in practical polymer systems depends on the incorporation of the mechanophore into a polymer matrix and the appropriate method to apply mechanical force for activation. Activation techniques vary significantly depending on the context and polymer platform, ranging from Single-Molecule Force Microscopy (SMFS) for isolated polymer strands, to ultrasonication for polymers in solution, and to bulk mechanical deformation in solid-state polymer materials. The effectiveness of mechanophore activation also depends heavily on the design of the polymer environment, including polymer architecture, synthetic accessibility, and chemical compatibility with the mechanophore. These parameters influence not only force transduction efficiency but also the overall success of achieving the target function.

In summary, mechanophore and polymer system design should be guided by the intended application. While simulation provides essential insights and design criteria, the realization of mechanophore functionality ultimately requires a holistic approach that incorporates molecular design, polymer integration, and mechanical activation conditions. Only through the combined optimization of these factors can mechanochemical performance be reliably achieved and translated into practical use.

Case study: Mechanically triggered signaling gaseous molecules release

To offer a more specific and intuitive illustration of the systematic workflow, we ground the process in a real example completed and published in recent years from our laboratory.[12,13,25] Although the workflow presented underwent stages of evolution, it guided us toward achieving the desired mechanochemical functionality. The project's successful outcome ultimately motivated us to organize our approach into the workflow outlined in this letter.

As described in the following sections, the path to success included numerous setbacks and false starts. Nevertheless, by adhering to an iterative process, we were able to learn from each failure and make consistent progress toward our target. We hope that by detailing the real-world application of this workflow, it becomes clearer how each step plays a role in guiding the evolution of a mechanochemical system—from design, simulation and structure optimization to synthesis, activation, final performance validations and improved understanding.

Motivation & system design

Signaling gaseous molecules represent a class of endogenous gases that serve as chemical messengers, inducing physiological or biochemical changes within organisms, tissues, or cells.[26] These molecules—including nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S), oxygen (O_2), and sulfur dioxide (SO_2)—are collectively known as gasotransmitters, a subclass of neurotransmitters. In biological systems, such gases may be synthesized internally or absorbed from the external environment, such as atmospheric or aquatic sources, as in the case of oxygen. Notably, the 1998 Nobel Prize in Physiology or Medicine was awarded to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad for their discovery of nitric oxide as a key signaling molecule in the cardiovascular system, highlighting the societal and scientific importance of these compounds.

Recent research has explored the potential of exogenously introduced signaling gases to modulate biological behaviors in various organisms, including humans.[27] However, one of the major challenges in this area is the intrinsic toxicity of many of these gases. For example, NO, CO, and H_2S are all highly toxic at concentrations exceeding 100 ppm, posing immediate risks to health and life.[26,27] Therefore, achieving precise control over the local concentration and targeted delivery of these gasotransmitters is critical for their safe and effective use. This need for controlled release underlies the motivation for developing mechanophore systems capable of timely and spatially controlled gas release.

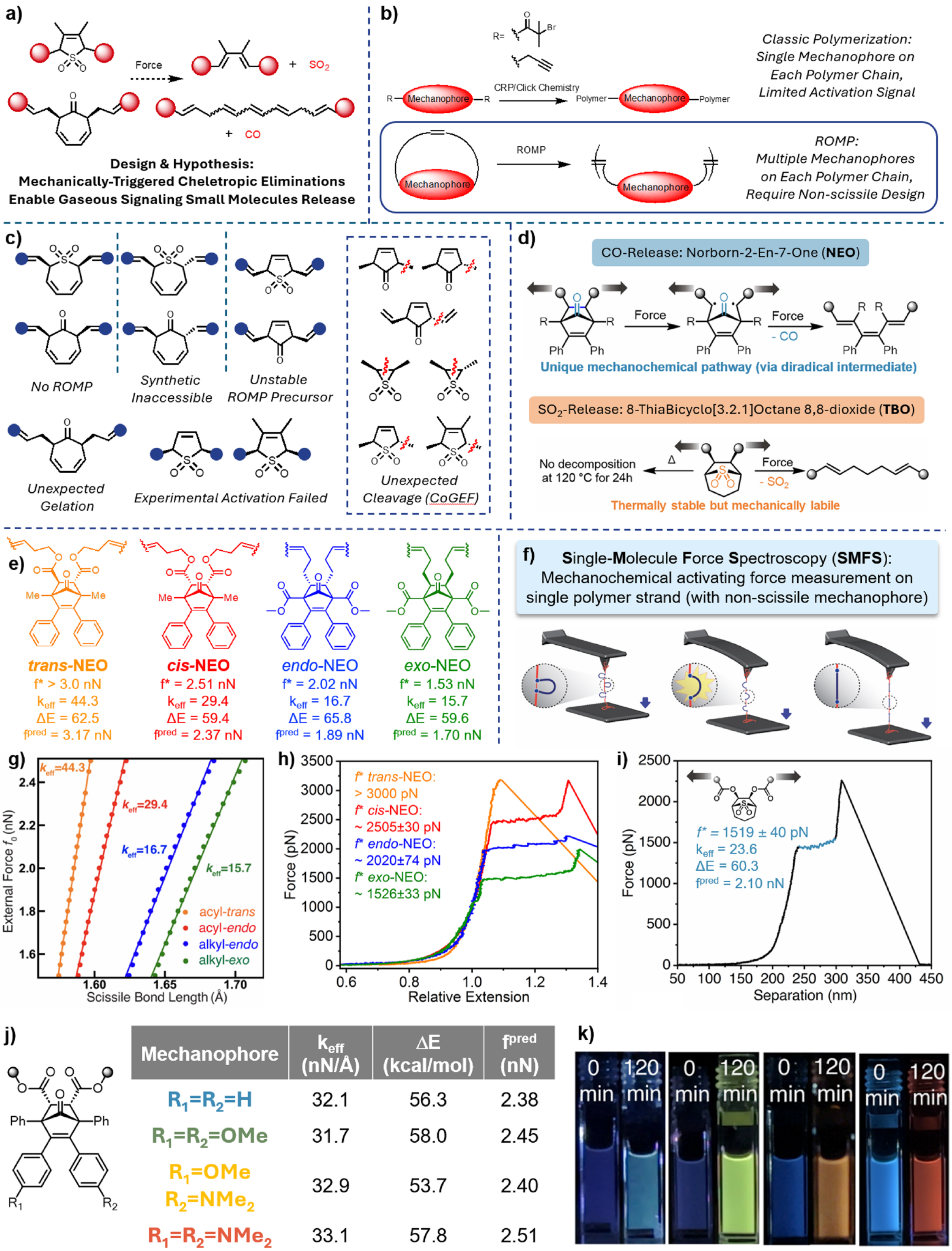
To address this challenge, our previous work focused on the development of a series of mechanophores capable of mechanically triggered release of signaling gases such as CO[12] and SO_2.[13] Once incorporated into polymer backbones, these mechanophores release small molecules upon ultrasonic (US) treatment—a widely adopted method for applying mechanical force to polymers in solution. Spatial precision can be enhanced using focused ultrasound (FUS),[28] while concentration control can be achieved by adjusting the ultrasound power, exposure duration, and the degree of polymerization.

To achieve both efficient release and compatibility with US activation, we designed our system to incorporate multiple mechanophores within a single polymer chain using a non-scissile mechanophore topology.[6] Based on this strategy, we selected cheletropic elimination as the key mechanism for molecular release at the beginning of this project [Fig. 4(a)], coupled with Ring-Opening Metathesis Polymerization (ROMP) as the polymerization technique [Fig. 4(b)]. Cheletropic elimination is a well-established mechanism for small-molecule release,[29] while ROMP is known for its capacity to incorporate numerous mechanophores into individual polymer chains.[4,20] Importantly, the non-scissile design ensures that polymer strands remain intact even as multiple mechanophores are activated, enabling continuous and efficient molecular release upon ultrasound exposure.

Mechanophore hypothesis & preliminary feasibility check via CoGEF

Based on previous analysis, several of our initial mechanophore designs are illustrated in Fig. 4(c). Although none of these early candidates yielded successful results, each provided critical feedback that contributed to the eventual success of the project. CoGEF simulations played a vital role in identifying and eliminating candidates with undesired bond cleavage, helping to prioritize the most promising structures. Additionally, our choice of polymerization method and monomer topology will also eliminate some designs incompatible with synthesis, thus conserving experimental resources. Nevertheless, some candidates that passed both simulation and synthetic feasibility assessments encountered unexpected issues during polymerization or activation under ultrasound. These experimental setbacks highlighted an important insight: while CoGEF simulations and function-guided design can significantly improve the efficiency of mechanophore screening, there are still inherent uncertainties that can only be revealed after experimental trials. These challenges further highlight the necessity of integrating simulation with iterative experimental feedback to refine mechanophore systems toward real-world functionality.

After several additional failed attempts, we noticed that mechanophore designs relying solely on cheletropic elimination inherently suffer from poor force-coupling efficiency. This limitation arises possibly because the applied tension is distributed symmetrically across two bonds at the cleavage center, significantly reducing the mechanical activation potential. To overcome this, we introduced a design strategy involving diradical intermediates prior to the final molecular release step—a concept inspired by earlier work in our group.[30] Based on our previous experimental findings, diradical intermediates generated mechanically differ from those produced *via* traditional thermal or chemical methods. These force-induced diradicals are often highly energetic and can follow unique, non-classical reaction pathways, leading to distinct products not accessible



Mechanophore	k_{eff} (nN/Å)	ΔE (kcal/mol)	f^{pred} (nN)
R_1=R_2=H	32.1	56.3	2.38
R_1=R_2=OMe	31.7	58.0	2.45
R_1=OMe R_2=NMe_2	32.9	53.7	2.40
R_1=R_2=NMe_2	33.1	57.8	2.51

Figure 4. Case study based on previous publications (signaling gaseous small molecule release) (a) Original idea about mechanically triggered CO & SO_2 release based on cheletropic elimination. (b) Polymerization method selection: Why ROMP is better for the target function. (c) Examples of failed hypothesis attempt based on CoGEF simulation and unexpected experimental results. (d) Mechanophore designs which provide positive results for CO & SO_2 release, named as NEO & TBO. (e) Mechanophore optimization based on TMBA simulation. (f) Schematic illustration about the mechanism of SMFS. (g) TMBA simulation results (**k_{eff}**) of four NEO mechanophores. SMFS experimental results of (h) NEO mechanophores and (i) TBO mechanophore. (j) Mechanophore designs and TMBA analysis about mechanically triggered adjustable AIE, a following project inspired by the NEO system. TMBA helps check feasibility before further experiments (k) Different color of AIE observed from different systems after activation & aggregation. Part of Fig. 4 is reorganized from previous publications.[12,13,25]

through conventional activation. Utilizing this principle, we successfully achieved targeted gas release using two specific mechanophore scaffolds: Norborn-2-en-7-one (NEO) for CO release and 8-Thiabicyclo[3.2.1]octane 8,8-dioxide (TBO) for SO_2 release [Fig. 4(d)]. Notably, these two mechanophores displayed dramatically different behavior under thermal versus mechanical activation due to the involvement of diradical intermediates. For NEO scaffolds, thermal activation led to cheletropic elimination followed by oxidation and aromatization to yield benzene derivatives, which are significantly different from mechanically activated pathways.[12] In contrast, TBO scaffolds showed exceptional thermal stability, exhibiting no detectable degradation after 24 h at 120℃.[13] This thermal stability, combined with mechanical lability, represents an ideal characteristic profile for effective and selective mechanophores.

Structure optimization under tension (TMBA)

For further energetic and tension-related analysis of NEO mechanophores, iso-tensional TMBA simulations were conducted for four NEO derivatives [Fig. 4(e)]. For each mechanophore, **ΔE** values were calculated without additional tension function, and $\mathbf{k_{eff}}$ values were derived *via* linear regression of the cleaving C–C bond length against the applied force at the handles [Fig. 4(g)]. Additionally, based on the established simulation model for C–C bond-cleaving mechanophores, predicted activation forces ($\mathbf{f^{pred}}$) were calculated using the derived **ΔE** and $\mathbf{k_{eff}}$ values.

The TMBA simulation results offered valuable insights into the mechanochemical characteristics of the NEO-based systems. For example, when comparing cis-NEO and trans-NEO, the primary difference in their predicted activation forces stems from variations in force-coupling efficiency ($\mathbf{k_{eff}}$), rather than bond dissociation energy (**ΔE**). This suggests that trans-NEO exhibits greater resistance to mechanical activation due to less effective force transmission. In contrast, the comparison between endo-NEO and exo-NEO highlights a different mechanism: the difference in predicted activation force is more closely tied to **ΔE**, implying that the exo isomer experiences slightly destabilized ground-state energy—likely due to steric hindrance from its molecular scaffold—resulting in lower bond activation energy. Overall, the TMBA simulations predicted an activation force trend of trans-NEO > cis-NEO > endo-NEO > exo-NEO, which closely aligns with experimental observations from Single-Molecule Force Spectroscopy (SMFS) studies discussed later. This consistency validates the predictive value of TMBA analysis and reinforces its utility for both mechanophore selection and interpretation of experimental outcomes. Finally, taking both TMBA results and synthetic accessibility into account, cis-NEO was selected for further experimental validation. Subsequent tests confirmed its successful activation, thereby demonstrating the reliability of the systematic design and simulation-guided selection process.

Experimental results: Activation on single strand polymer (SMFS) and more

Single-Molecule Force Spectroscopy (SMFS), pioneered by Craig et al. in evaluating mechanophores, is a powerful experimental technique for probing the mechanochemical activation of mechanophores on single polymer strands.[4] It is widely recognized as one of the most reliable systems for quantitatively measuring the activation force of mechanophores. A schematic overview of the SMFS mechanism is shown in Fig. 4(f). As indicated, SMFS experiments are conducted using an atomic force microscope (AFM) operating in tension mode. In a typical setup, a mechanophore-embedded, epoxy-functionalized polymer strand is anchored to a substrate and attached to the AFM tip. As the tip is gradually retracted, mechanical force is applied to the polymer strand, leading to elongation and progressive mechanophore activation. This process continues until the point of maximum activation is reached. Furthermore, when the embedded mechanophores are arranged in a non-scissile topology and multiple mechanophores are incorporated along a single polymer chain, the SMFS force-extension curve exhibits a characteristic plateau. This plateau corresponds to the repeated activation of mechanophores and enables a direct, quantitative determination of the activation force. SMFS thus provides a crucial experimental benchmark for validating predictions made through TMBA simulations and for deepening our understanding of mechanophore mechanics at the molecular level.

Following the feasibility analysis and structural optimization under tension, SMFS experiments were conducted on four NEO scaffolds and one TBO mechanophore to quantitatively evaluate their activation forces and assess the accuracy of predictions from TMBA simulations. As shown in the experimental data for the NEO systems [Fig. 4(h)], the TMBA-predicted activation forces are in good agreement with the measured values. Notably, no activation was observed for trans-NEO, suggesting either that its activation force exceeds the detachment threshold of the AFM tip–polymer interface (typically around 3 nN) or that activation does not proceed following the expected pathway—both consistent with the high activation force predicted by TMBA. In addition, activation of the TBO mechanophore was successfully observed in SMFS experiments, exhibiting a lower activation force compared to the NEO scaffolds.

These results reinforce earlier conclusions that TMBA simulations provide valuable insights into the mechanical properties of mechanophores, with $\mathbf{k_{eff}}$ describing force-coupling efficiency and **ΔE** reflecting bond-cleavage energy. Furthermore, TMBA enables the prediction of activation forces in SMFS experiments, particularly for C–C bond-cleaving mechanophores. Based on our experience, the combined use of TMBA simulations and SMFS experiments is strongly recommended prior to conducting bulk activation studies. This dual approach provides both theoretical predictions and experimental validation of mechanochemical properties, offering a powerful toolkit for evaluating newly designed mechanophores that have not yet undergone mechanical activation studies.

Last but not least, we would like to briefly share how the study of the CO-releasing NEO mechanophore inspired a new direction in our research.[25] During activation experiments, we observed not only the successful release of CO but also an interesting phenomenon: the activated NEO mechanophore exhibited significant Aggregation-Induced Emission (AIE). This behavior, attributed to the formation of a highly conjugated structure upon activation, prompted us to explore whether the emission wavelength could be tuned by modifying the substituent groups on the conjugated core.

Motivated by this insight, we designed four new mechanophores with varied substituents and applied the same systematic workflow for feasibility assessment and structure optimization. TMBA simulations [Fig. 4(j)] confirmed that these structural modifications had negligible impact on the mechanical properties of the mechanophores, which is consistent with our hypothesis. Subsequent synthesis, polymerization, and activation experiments (*via* ultrasound in solution) demonstrated strong AIE behavior in all four systems, with clearly distinguishable emission wavelengths [Fig. 4(k)]. This result not only validated the design but also highlighted the potential for developing a new class of mechanophores with tunable optical properties for sensing or display applications.

The success of this project illustrates how careful observation of "side results" can lead to new research directions. While target functions should guide experimental design, some other incidental but interesting findings can also lead to exciting and fruitful outcomes and this is part of what makes scientific research so exciting and rewarding.

Conclusion

In this work, we established and illustrated a systematic workflow for the design and pre-experimental feasibility analysis of mechanophores. By integrating the classic iso-metrical CoGEF simulation method with the innovative iso-tensional TMBA simulation approach, the workflow provides reliable insights into key mechanophore characteristics—including potential side reactions, bond cleavage energies (**ΔE**), and force-coupling efficiencies ($\mathbf{k_{eff}}$)—prior to any laboratory-based activation studies. To validate the predictive capability of the TMBA approach, we employed Single-Molecule Force Spectroscopy (SMFS) as a benchmark method for quantitatively measuring activation forces. The consistency observed between TMBA predictions and SMFS measurements underscores the robustness of the simulation-based workflow.

To further demonstrate the utility of the workflow in practical scenarios, we presented a detailed case study from our recent work involving CO and SO_2-releasing mechanophores. This case study not only exemplified the application of the workflow in guiding design decisions and troubleshooting failures but also led to an unexpected discovery—mechanically induced Aggregation-Induced Emission (AIE)—which opened a new direction in our research.

Time-consuming and repetitive feasibility checks are often cited as a major barrier in the development of new mechanophores, primarily due to the lack of accessible and reliable simulation tools coupled with clear design guidance. We hope that this systematic workflow, combining CoGEF and TMBA simulations, can serve as a valuable resource for researchers. By reducing the experimental burden and providing mechanistic insight, it has the potential to accelerate innovation and advance the broader field of polymer mechanochemistry.

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Author contributions

Fangbai Xie contributed to workflow design, data organization and original draft writing. Yunyan Sun contributed to project design and data collection of all projects included in case study. Jeffrey S. Moore contributed to funding acquisition and manuscript submission. Yunyan Sun and Jeffrey S. Moore both contributed to manuscript editing, revision and review.

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Data availability

The data supporting this study's findings are available from the corresponding author and the first author upon reasonable request. Any discussions about this publication are welcomed by the authors.

Declarations

Conflict of interests

The authors declare no conflict of interest.

Declaration of AI use

ChatGPT was used only to assist improving the language and providing concise and accurate expressions for better reading experience. All contents revised by ChatGPT were further carefully examined and reviewed by the authors to eliminate any misinterpretation of original expressions, and the authors take full responsibility for the content included in this publication. Final editing and proofreading were done without any assistance from ChatGPT.

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