Mechanical Force Enables an Anomalous Dual Ring-Opening Reaction of Naphthodipyran

Molly E. McFadden, Skylar K. Osler, Yan Sun, and Maxwell J. Robb*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

ABSTRACT: Multimodal mechanophores that exhibit complex mechanochromic behavior beyond the typical binary response are capable of distinguishing between multiple stress states through discrete changes in color. Naphthodipyran photoswitches contain two pyran rings fused to a central naphthalene core and represent a potentially promising framework for multimodal reactivity. However, the concurrent ring opening of both pyran moieties has previously proven inaccessible via photochemical activation. Here, we demonstrate that mechanical force supplied to naphthodipyran through covalently bound polymer chains generates the elusive dual ring-opened dimerocyanine product with unique near-infrared absorption properties. Trapping with boron trifluoride renders the merocyanine dyes thermally persistent and reveals unusual sequential ring-opening behavior that departs from the reactivity of previously studied mechanophores under the high strain rates imposed by ultrasound-induced solvodynamic chain extension.

Mechanical force has been demonstrated to promote unusual reaction pathways that often diverge from those obtained under more conventional thermal or photochemical processes.[1–3] Stress-sensitive molecules termed mechanophores are designed to selectively transduce mechanical force into a wide variety of productive chemical transformations.[4] The development of mechanochromic mechanophores in particular has attracted significant interest as these molecular force probes enable the straightforward detection of stress and/or strain in polymers through changes in color. Naphthopyrans are molecular switches that undergo a ring-opening reaction upon external stimulation to generate intensely colored merocyanine dyes.[5] The photochemical reactivity of naphthopyrans has been studied extensively, producing a rich array of structurally diverse and commercially important photoswitches.[6] More recently it was discovered that the ring-opening reaction of naphthopyrans can be achieved using mechanical force.[7–9] While relatively rare, multimodal mechanophores that exhibit more complex mechanochromic behavior beyond a binary on–off response are capable of distinguishing between different stress states through discrete visual cues.[10–12] To this end, our group previously developed a bis-naphthopyran mechanophore incorporating two separate naphthopyran subunits joined by a conjugated linker that displays transient changes in color via a force-dependent dynamic equilibrium.[13]

Naphthodipyrans are compounds that contain two separate pyran rings fused to a central naphthalene nucleus. In contrast to bis-naphthopyrans, however, concurrent ring opening of both pyran units is inaccessible upon photochemical activation (Figure 1a).[14–16] Given the proclivity for mechanical force to facilitate otherwise unattainable reactions, we hypothesized that mechanochemical activation of naphthodipyran could enable the ring-opening reactions of both pyrans to produce the elusive dimerocyanine species with extended π-conjugation. The potential reactivity of naphthodipyran endowed with two mechanochemically active pyran rings and distinctly colored merocyanine states would render it an alluring new multimodal mechanophore.

The 3*H*-naphthodipyran scaffold was identified as an ideal target as it possesses the requisite geometry for transmitting force selectively across the C–O bonds in each pyran ring (Figure 1b). We initiated our investigation by examining the computationally predicted mechanochemical reactivity of a series of 3*H*-naphthodipyran derivatives using the *ab initio* constrained geometries simulate external force (CoGEF) method.[17,18] The calculations revealed that several substituted naphthodipyran derivatives were predicted to undergo a dual ring-opening reaction upon mechanical elongation, including a model incorporating aryl substituents with *para*-pyrrolidine groups (Figure 1c and Figures S1 and S2). Conveniently, merocyanine dyes derived from simple 3*H*-napthopyrans containing similar tertiary amines on the aryl substituents can be trapped using $BF_3 \cdot Et_2O$,[19] precluding possible complications in reaction analysis due to fast thermal reversion processes.[9]

With these insights, we set out to experimentally investigate the mechanochemical reactivity of naphthodipyran using solution-phase ultrasonication for direct comparison to the photochemical reactivity under ultraviolet (UV) light. Polymers in dilute solution subjected to high intensity ultrasound undergo rapid extension with elongational forces maximized near the chain midpoint.[20] Therefore, we designed and synthesized a naphthodipyran bis-initiator that

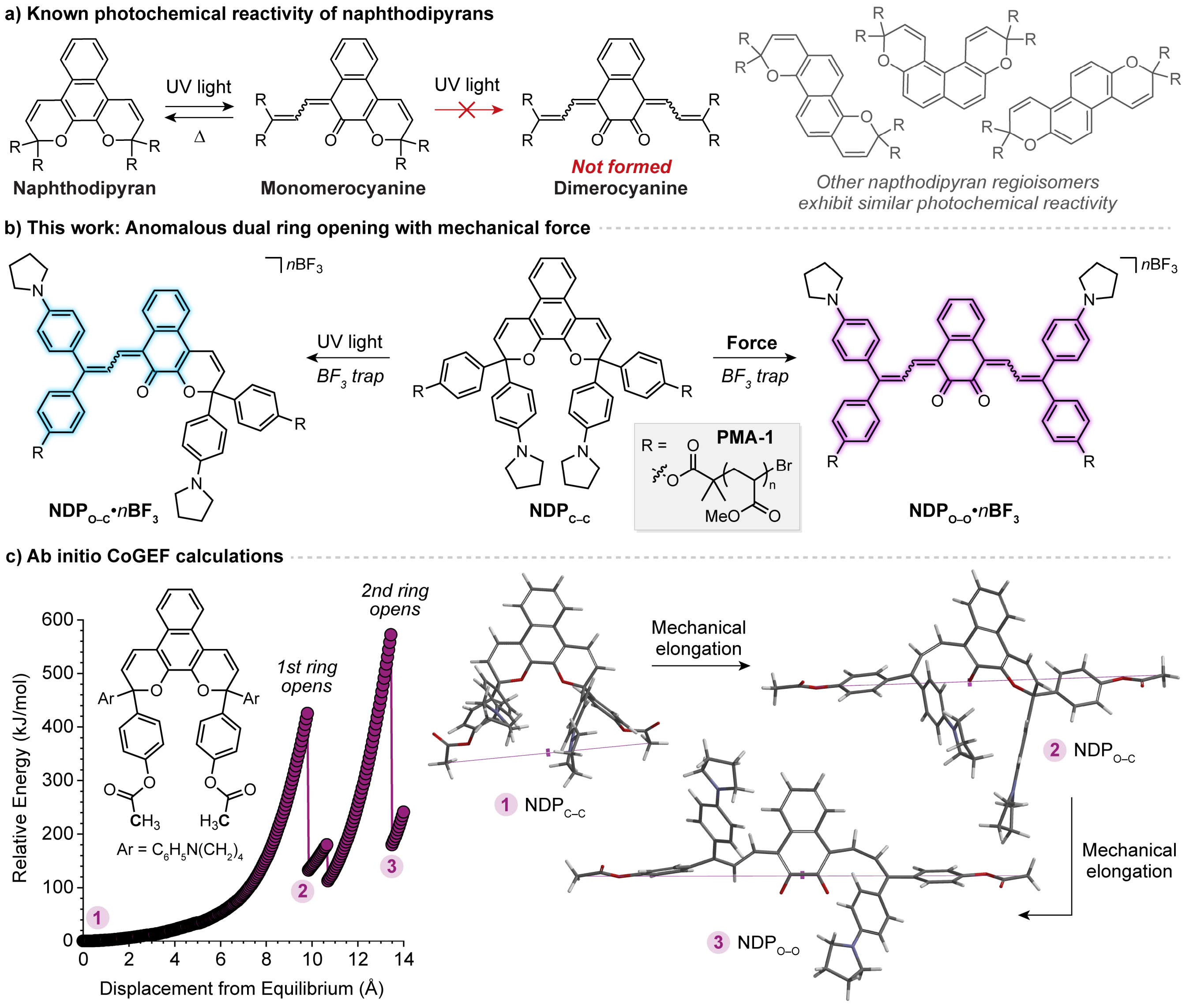

Figure 1. a) Naphthodipyran photoswitches undergo a single ring-opening reaction with UV light. b) Divergent photochemical and mechanochemical reactivity of a 3*H*-naphthodipyran moiety incorporated near the center of a polymer chain. c) CoGEF calculations (B3LYP/6-31G*) performed on a naphthodipyran model predict ring opening of both pyran units upon mechanical elongation.

was used in the controlled radical polymerization of methyl acrylate to generate linear **PMA-1** (M_n = 185 kDa, $Đ$ = 1.23) incorporating the naphthodipyran motif near the center of the polymer chain (Figure 1b, see SI for details). A continuous flow setup enabled monitoring of both mechanochemical and photochemical reactions in real-time by UV–vis–near-infrared absorption spectroscopy.[13,21] Photoirradiation of **PMA-1** (5.8 μM in CH_3CN stabilized with 30 mM BHT) with 365 nm UV light in the presence of $BF_3{\cdot}Et_2O$ (1.5 mM) generates a thermally persistent merocyanine dye with a single visible absorption peak at 625 nm (Figure 2a and Figure S3). Additional irradiation with UV light does not produce any further spectral changes (Figure S4). The absorption spectrum is consistent with the expected BF_3-coordinated monomerocyanine ($NDP_{O\text{–}C}{\cdot}nBF_3$) wherein one pyran ring has opened and the other remains closed (Figure 1b). The absorption maximum is bathochromically shifted by 65 nm in comparison to the spectrum acquired after photoirradiation of **PMA-1** in the absence of $BF_3{\cdot}Et_2O$ (Figure S5), in excellent agreement with similar experiments performed on a simple 3*H*-naphthopyran.[19]

In contrast to the photochemical reaction, ultrasound-induced mechanochemical activation of **PMA-1** with $BF_3{\cdot}Et_2O$ produces a unique absorption spectrum with longer wavelength features that extend into the near-infrared region, consistent with generation of the dimerocyanine product in which both pyran rings have opened ($NDP_{O\text{–}O}{\cdot}nBF_3$) (Figure 2a). Again, the mechanochemical reaction product is thermally persistent (Figure S6). This unique absorption is not observed without $BF_3{\cdot}Et_2O$, consistent with the anticipated transience of the untrapped dimerocyanine (Figure S7). Intriguingly, the kinetics of mechanochemical activation observed for the naphthodipyran mechanophore report colorimetrically on temporal exposure to ultrasound-induced mechanical force (Figure 2b). At early reaction times, only monomerocyanine product $NDP_{O\text{–}C}{\cdot}nBF_3$ is observed; the longer wavelength absorption features associated with dimerocyanine $NDP_{O\text{–}O}{\cdot}nBF_3$ emerge later in the reaction and increase with extended sonication time. This apparent sequential ring-opening behavior juxtaposes the mechanochemical reactivity of our previously studied bis-naphthopyran mechanophore.[13] In that system, bis-naphthopyran is converted directly to the bis-merocyanine species, consistent with recently discovered dynamic effects whereby the momenta derived from extrinsic force drive reaction trajectories that completely bypass reactive intermediates.[22] While the observed kinetic behavior of naphthodipyran is effectively indistinguishable from a sequential ring-opening mechanism, we speculate that both pyran

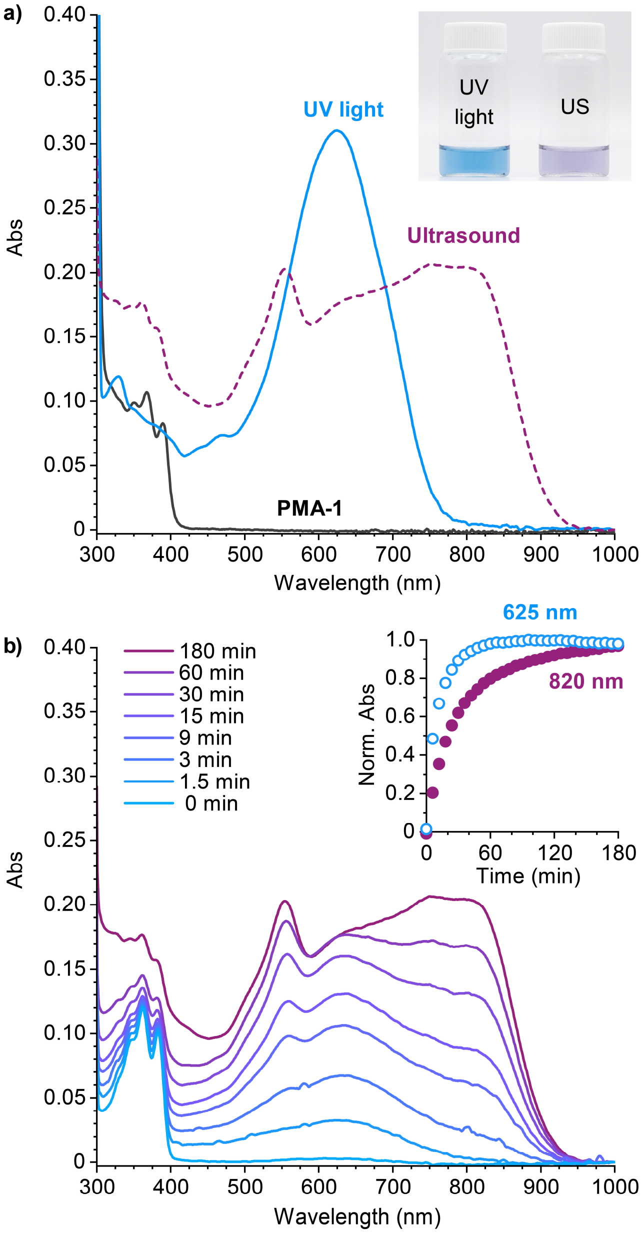

Figure 2. a) UV–vis–near-infrared absorption spectra of **PMA-1** (5.8 μM in CH_3CN, 30 mM BHT, 1.5 mM $BF_3{\cdot}Et_2O$) before and after photoirradiation with 365 nm UV light (15 min, −30 °C) or ultrasonication (180 min, −15 °C). The photograph shows the two solutions after activation with UV light or ultrasound (US). b) Spectral evolution during sonication of **PMA-1** and time-dependent absorption profiles at 625 nm and 820 nm characteristic of monomerocyanine $NDP_{O\text{-}C}{\cdot}nBF_3$ and dimerocyanine $NDP_{O\text{-}O}{\cdot}nBF_3$, respectively.

rings open during a single chain extension event;[23] however, the lifetime of the free dimerocyanine may be too transient for efficient trapping. Instead, rapid reversion of the dimerocyanine species to the more stable monomerocyanine upon chain relaxation would permit BF_3 coordination. A second chain extension is then primed for a relatively facile intramolecular trapping process to form dimerocyanine $NDP_{O\text{-}O}{\cdot}n BF_3$ (Scheme S1). Although we cannot rule out that BF_3 coordination is necessary for the second ring-opening reaction, this hypothesis is inconsistent with the observed photochemical reactivity of monomerocyanine $NDP_{O\text{-}C}{\cdot}n BF_3$ as well as DFT calculations employing an explicit BF_3-binding model (Figure S8).

Control experiments confirmed that the spectral changes ascribed to the dual ring-opening reactions of naphthodipyran are uniquely enabled by mechanical activation. First, negligible changes in absorption were observed upon ultrasonication of control polymer **PMA-Control** (M_n = 173 kDa, $Đ$ = 1.20) incorporating the naphthodipyran moiety at the chain-end, which is not subjected to mechanical force (Figure S9). Given the unprecedented nature of the second ring-opening reaction, we sought additional evidence to support that the transformation attributed to the conversion of $NDP_{O\text{-}C}{\cdot}n BF_3$ to $NDP_{O\text{-}O}{\cdot}n BF_3$ observed for **PMA-1** was indeed mechanochemically mediated (Figures 3a and S10). A solution of **PMA-1** in the presence of $BF_3{\cdot}Et_2O$ was irradiated with 365 nm UV light to generate the trapped monomerocyanine species, $NDP_{O\text{-}C}{\cdot}n BF_3$, near the center of the polymer chains (Figure 3b). After 10 min, UV light was turned off and ultrasonication was applied to the solution, causing the attenuation of the absorption peak at 625 nm and the concurrent appearance of longer wavelength absorption features, consistent with the conversion of $NDP_{O\text{-}C}{\cdot}n BF_3$ to dimerocyanine $NDP_{O\text{-}O}{\cdot}n BF_3$. In direct contrast, the same experiment performed on **PMA-Control**, in which $NDP_{O\text{-}C}{\cdot}n BF_3$ is photochemically generated at the polymer chain-end, resulted in no changes to the absorption spectrum after initiation of ultrasound (Figure 3c). The time-dependent changes in absorbance at characteristic wavelengths of 625 nm ($NDP_{O\text{-}C}{\cdot}nBF_3$) and 820 nm ($NDP_{O\text{-}O}{\cdot}n BF_3$) clearly illustrate the divergent reactivity of **PMA-1** and **PMA-Control** upon ultrasonication and the critical role of mechanical force in the activation of the putative second ring-opening reaction (Figure 3d).

To confirm the identity of the photochemical and mechanochemical reaction products, a series of characterization experiments were performed on the small molecule naphthodipyran bis-initiator used to prepare **PMA-1**. Photoirradiation of the naphthodipyran (0.5 mM in CD_3CN) with 365 nm UV light in the presence of $BF_3{\cdot}Et_2O$ (1.5 mM) produces an absorption spectrum with a peak at 625 nm that matches the spectrum obtained upon similar treatment of **PMA-1** (Figure 4a). Analysis of the same sample by ^1H NMR spectroscopy supports the photochemical generation of monomerocyanine $NDP_{O\text{-}C}{\cdot}n BF_3$. The ^1H NMR spectrum of the naphthodipyran starting material contains two diagnostic doublets at 6.52 (J = 10.0 Hz) and 6.55 ppm (J = 9.9 Hz) corresponding to one pyran alkene proton on each of two diastereomers (Figure 4b). After UV irradiation, two new doublets appear concurrently at 8.70 ppm (J = 15.2 Hz) and 6.55 ppm (J = 10.0 Hz) characteristic of an olefin proton on the merocyanine and a unique pyran resonance, respectively

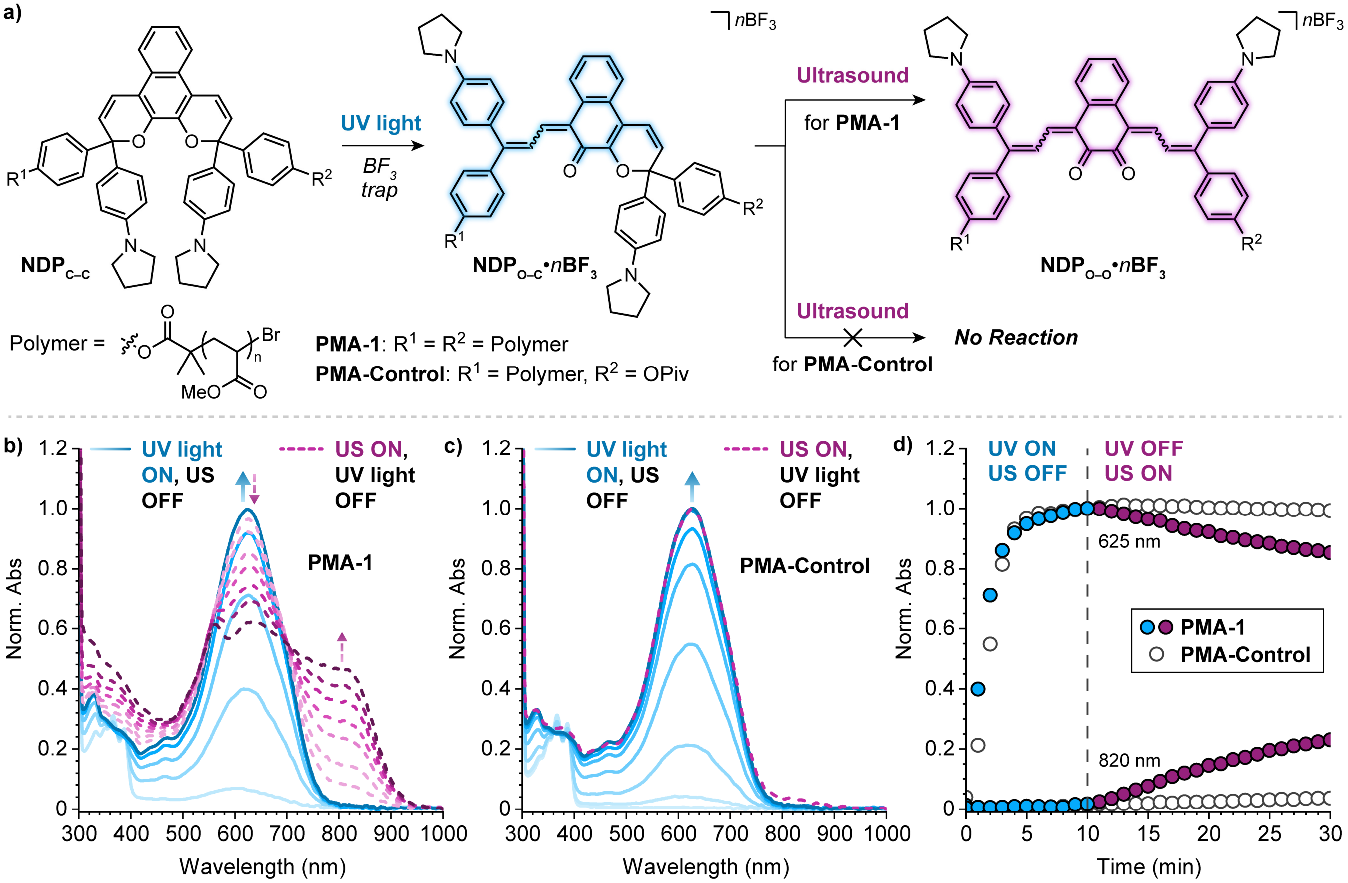

Figure 3. a) Reaction scheme for the photochemical conversion of naphthodipyran to monomerocyanine $NDP_{O-C}\cdot nBF_3$ in chain-centered polymer **PMA-1** and chain-end functional control polymer **PMA-control** followed by ultrasonication. UV–vis–near-infrared absorption spectra of b) **PMA-1**, and c) **PMA-Control** during photoirradiation and subsequent ultrasonication. d) Time-dependent changes in absorbance at characteristic wavelengths of 625 nm ($NDP_{O-C}\cdot nBF_3$) and 820 nm ($NDP_{O-O}\cdot nBF_3$) for **PMA-1** and **PMA-Control**.

(Figure 4c). We found that at sufficiently high concentrations of $BF_3\cdot Et_2O$, photochemically-generated monomerocyanine $NDP_{O-C}\cdot nBF_3$ is thermally converted to trapped dimerocyanine $NDP_{O-O}\cdot nBF_3$ (Figure S11). This behavior is not unexpected[24] and is similar to the strong thermodynamic driving force responsible for acidochromic and metallochromic phenomena commonly observed for spiropyrans.[25] After increasing the concentration of $BF_3\cdot Et_2O$ to 3 mM, additional photoirradiation replenished the monomerocyanine, which is thermally transient without a sufficient stoichiometric excess of trapping agent. The ^1H NMR spectrum slowly transformed in the dark at room temperature with loss of the resonances associated with monomerocyanine $NDP_{O-C}\cdot nBF_3$ and the concomitant appearance of a new doublet at 9.19 ppm (J = 14.8 Hz) consistent with the formation of dimerocyanine $NDP_{O-O}\cdot nBF_3$ (Figure 4d and Figure S12). As illustrated in Figure 4a, the absorption spectrum of this chemically-generated small molecule closely matches the spectrum acquired after extended ultrasonication of **PMA-1**, providing further support that the mechanochemical reaction product is the same dimerocyanine species.

High resolution mass spectrometry provided additional insight into the structure of trapped dimerocyanine $NDP_{O-O}\cdot nBF_3$. Analysis of a solution containing a mixture of small molecule naphthodipyran bis-initiator and chemically-generated $NDP_{O-O}\cdot nBF_3$ analogous to the sample that produced the ^1H NMR spectrum in Figure 4d provided the expected $[M+H]^+$ peaks of the naphthodipyran as well as new signals corresponding to $[M+BF_2]^+$ (Figure 4e). In addition, synchronous visible–near-infrared absorption measurements demonstrated the concomitant increase of the long-wavelength spectral features characteristic of the trapped dimerocyanine product (Figure S13). We hypothesize that the 1,2-diketone subunit of the dimerocyanine species forms a thermally and hydrolytically stable 5-membered difluoroborocyclic motif upon reaction with BF_3, which is presumably charge-balanced by a BF_4^- counterion (Figure 4e). Taken together, these results provide compelling support for the mechanochemical generation of an unprecedented dimerocyanine species from naphthodipyran.

Mechanical force has been demonstrated to bias reaction pathways, promoting chemical transformations that are not attainable using light or heat alone. Our results complement previous work revealing that mechanochemical activation can formally override orbital symmetry rules conventionally governing the electrocyclic ring-opening reactions of benzocyclobutene and *gem*-dihalocyclopropranes to yield products with unexpected stereochemistry.[1,26] Here, we show that mechanical force promotes a previously elusive and photochemically inaccessible dual ring-opening

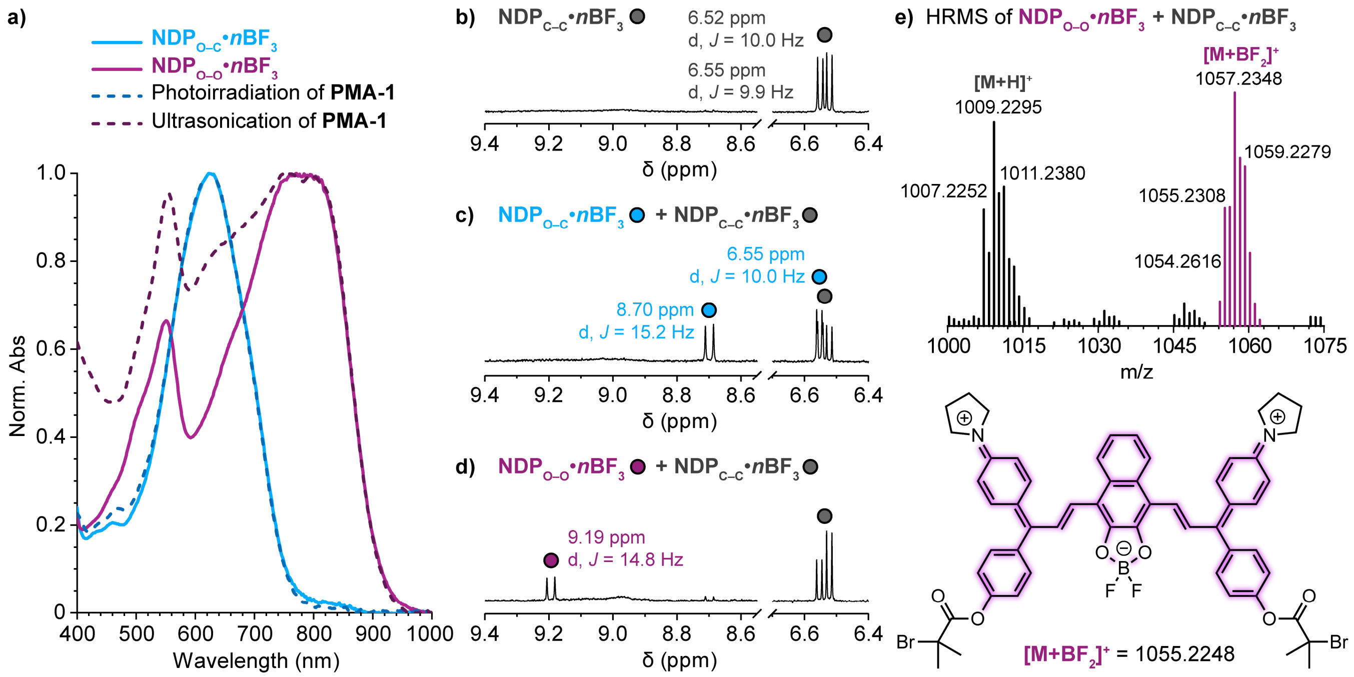

Figure 4. a) UV–vis–near-infrared absorption spectra of small molecule merocyanine species $\text{NDP}_{\text{O-C}}\cdot n\text{BF}_3$ and $\text{NDP}_{\text{O-O}}\cdot n\text{BF}_3$ obtained from the naphthodipyran bis-initiator compared to spectra of **PMA-1** after photochemical and mechanochemical activation. ^{1}H NMR spectra (CD_3CN, 600 MHz) of naphthodipyran bis-initiator b) in the presence of $BF_3\cdot Et_2O$ (1.5 mM), and c) the same solution after irradiation with 365 nm UV light (2 min, rt). d) Similar experiment as (c) using 3.0 mM $BF_3\cdot Et_2O$ illustrating the thermal conversion of $\text{NDP}_{\text{O-C}}\cdot n\text{BF}_3$ to $\text{NDP}_{\text{O-O}}\cdot n\text{BF}_3$. e) High resolution mass spectrometry data from a similar experiment as (d) using 7.8 mM $BF_3\cdot Et_2O$ and the proposed structure of the trapped dimerocyanine cation.

reaction of naphthodipyran to generate a unique dimerocyanine species with near-infrared absorption. More broadly, we envision that the newly unveiled multimodal reactivity of naphthodipyran coupled with unusual mechanochemical activation kinetics will enable the design and study of additional mechanophores and force-responsive polymers with multicolor mechanochromic function.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website: Experimental details, synthetic procedures, DFT calculations, GPC chromatograms, UV-vis absorption and mass spectrometry data, and NMR spectra.

AUTHOR INFORMATION

Corresponding Author

mrobb@caltech.edu

Authors

Molly E. McFadden:0000-0003-3174-6385
Skylar K. Osler: 0000-0003-1021-7011
Yan Sun: 0000-0002-3882-131X
Maxwell J. Robb: 0000-0002-0528-9857

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

Financial support from Caltech and an NSF CAREER award (CHE-2145791) is gratefully acknowledged. M.E.M. was supported by an NSF Graduate Research Fellowship (DGE-1745301) and a Barbara J. Burger Fellowship. S.K.O. was supported by an Institute Fellowship from Caltech. We thank Dr. Scott Virgil and the Center for Catalysis and Chemical Synthesis of the Beckman institute at Caltech for access to equipment and Dr. David VanderVelde for technical assistance with NMR spectroscopy. We thank the Fu laboratory at Caltech for use of their mass spectrometer.

REFERENCES

(1) Hickenboth, C. R.; Moore, J. S.; White, S. R.; Sottos, N. R.; Baudry, J.; Wilson, S. R. Biasing reaction pathways with mechanical force. *Nature* **2007**, *446*, 423–427.

(2) Lenhardt, J. M.; Ong, M. T.; Choe, R.; Evenhuis, C. R.; Martinez, T. J.; Craig, S. L. Trapping a Diradical Transition State by Mechanochemical Polymer Extension. *Science* **2010**, *329*, 1057–1060.

(3) McFadden, M. E.; Robb, M. J. Generation of an Elusive Permanent Merocyanine via a Unique Mechanochemical Reaction Pathway. *J. Am. Chem. Soc.* **2021**, *143*, 7925–7929.

(4) Li, J.; Nagamani, C.; Moore, J. S. Polymer Mechanochemistry: From Destructive to Productive. *Acc. Chem. Res.* **2015**, *48*, 2181–2190.

(5) Hepworth, J. D.; Heron, B. M. Photochromic naphthopyrans. In *Functional Dyes*; Elsevier Science, 2006; pp 85–135.

(6) Corns, S. N.; Partington, S. M.; Towns, A. D. Industrial organic photochromic dyes: Industrial organic photochromic dyes. *Color Technol* **2009**, *125*, 249–261.

(7) Robb, M. J.; Kim, T. A.; Halmes, A. J.; White, S. R.; Sottos, N. R.; Moore, J. S. Regioisomer-Specific Mechanochromism of Naphthopyran in Polymeric Materials. *J. Am. Chem. Soc.* **2016**, *138*, 12328–12331.

(8) Versaw, B. A.; McFadden, M. E.; Husic, C. C.; Robb, M. J. Designing naphthopyran mechanophores with tunable mechanochromic behavior. *Chem. Sci.* **2020**, *11*, 4525–4530.

(9) Osler, S. K.; McFadden, M. E.; Robb, M. J. Comparison of the reactivity of isomeric 2H- and 3H-naphthopyran mechanophores. *J. Polym. Sci.* **2021**, *59*, 2537–2544.

(10) Gossweiler, G. R.; Hewage, G. B.; Soriano, G.; Wang, Q.; Welshofer, G. W.; Zhao, X.; Craig, S. L. Mechanochemical activation of covalent bonds in polymers with full and repeatable macroscopic shape recovery. *ACS Macro Lett.* **2014**, *3*, 216–219.

(11) Wang, T.; Zhang, N.; Dai, J.; Li, Z.; Bai, W.; Bai, R. Novel Reversible Mechanochromic Elastomer with High Sensitivity: Bond Scission and Bending-Induced Multicolor Switching. *ACS Appl. Mater. Interfaces* **2017**, *9*, 11874–11881.

(12) Raisch, M.; Maftuhin, W.; Walter, M.; Sommer, M. A mechanochromic donor-acceptor torsional spring. *Nat. Commun.* **2021**, *12*, 4243.

(13) McFadden, M. E.; Robb, M. J. Force-Dependent Multicolor Mechanochromism from a Single Mechanophore. *J. Am. Chem. Soc.* **2019**, *141*, 11388–11392.

(14) Van Gemert, B. Benzo and Naphthopyrans (Chromenes). In *Organic Photochromic and Thermochromic Compounds*; Springer: Boston, MA, 2002; pp 111–140.

(15) Hepworth, J. D.; Heron, B. M. Synthesis and photochromic properties of naphthopyrans. In *Progress in Heterocyclic Chemistry*; Elsevier Ltd, 2005; Vol. 17, pp 33–62.

(16) Hepworth, J. D.; Heron, B. M. Photochromic naphthopyrans. In *Functional Dyes*; Elsevier Science, 2006; pp 85–135.

(17) Beyer, M. K. The mechanical strength of a covalent bond calculated by density functional theory. *J. Chem. Phys.* **2000**, *112*, 7307–7312.

(18) Klein, I. M.; Husic, C. C.; Kovács, D. P.; Choquette, N. J.; Robb, M. J. Validation of the CoGEF Method as a Predictive Tool for Polymer Mechanochemistry. *J. Am. Chem. Soc.* **2020**, *142*, 16364–16381.

(19) Guo, K.; Chen, Y. 'Locking and unlocking control' of photochromism of naphthopyran derivative. *J. Phys. Org. Chem.* **2010**, *23*, 207–210.

(20) Berkowski, K. L.; Potisek, S. L.; Hickenboth, C. R.; Moore, J. S. Ultrasound-Induced Site-Specific Cleavage of Azo-Functionalized Poly(ethylene glycol). *Macromolecules* **2005**, *38*, 8975–8978.

(21) May, P. A.; Munaretto, N. F.; Hamoy, M. B.; Robb, M. J.; Moore, J. S. Is Molecular Weight or Degree of Polymerization a Better Descriptor of Ultrasound-Induced Mechanochemical Transduction? *ACS Macro Lett.* **2016**, *5*, 177–180.

(22) Liu, Y.; Holm, S.; Meisner, J.; Jia, Y.; Wu, Q.; Woods, T. J.; Martinez, T. J.; Moore, J. S. Flyby reaction trajectories: Chemical dynamics under extrinsic force. *Science* **2021**, *373*, 208–212.

(23) Lin, Y.; Zhang, Y.; Wang, Z.; Craig, S. L. Dynamic Memory Effects in the Mechanochemistry of Cyclic Polymers. *J. Am. Chem. Soc.* **2019**, *141*, 10943–10947.

(24) Harié, G.; Samat, A.; Guglielmetti, R.; van Parys, I.; Saeyens, W.; de Keukeleire, D.; Lorenz, K.; Mannschreck, A. Chiral 2-Aryl-2-methyl-2 H -1-benzopyrans: Synthesis, characterization of enantiomers, and barriers to thermal racemization. *Helv. Chim. Acta* **1997**, *80*, 1122–1132.

(25) Kortekaas, L.; R. Browne, W. The evolution of spiropyran: fundamentals and progress of an extraordinarily versatile photochrome. *Chem. Soc. Rev.* **2019**, *48*, 3406–3424.

(26) Wang, J.; Kouznetsova, T. B.; Niu, Z.; Ong, M. T.; Klukovich, H. M.; Rheingold, A. L.; Martinez, T. J.; Craig, S. L. Inducing and quantifying forbidden reactivity with single-molecule polymer mechanochemistry. *Nat. Chem.* **2015**, *7*, 323–327.