Multi-Mechanophore Polymers for Mechanically Triggered Small Molecule Release with Ultrahigh Payload Capacity

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ABSTRACT: Polymers that release small molecules in response to mechanical force are promising for a variety of applications including drug delivery, catalysis, and sensing. While a number of mechanophores have been developed for the release of covalently bound payloads, existing strategies are either limited in cargo scope, or in the case of more general mechanophore designs, are restricted to the release of one or two cargo molecules per polymer chain. Herein, we introduce a non-scissile mechanophore based on a masked 2-furylcarbinol derivative that enables the preparation of multi-mechanophore polymers with ultrahigh payload capacity. We demonstrate that polymers prepared via ring-opening metathesis polymerization are capable of releasing hundreds of small molecule payloads per polymer chain upon ultrasound-induced mechanochemical activation. This non-scissile masked 2-furylcarbinol mechanophore overcomes a major challenge in cargo loading capacity associated with previous 2-furylcarbinol mechanophore designs, enabling applications that benefit from much higher concentrations of delivered cargo.

Stimuli-responsive polymers that release small molecule payloads in response to an external trigger are enabling materials for applications including drug delivery, catalysis, and sensing.[1] In particular, mechanical force is an appealing stimulus because of its ubiquity in materials systems as well as the broad range of available methods for applying mechanical force,[2] which include tension and compression in bulk polymeric materials and techniques using ultrasound that afford remote control.[3] In the emergent field of polymer mechanochemistry, mechanical force is transduced to force-sensitive moieties termed mechanophores that are covalently incorporated into polymers to achieve specific chemical transformations.[4] The development of mechanophores enabling the mechanically triggered release of covalently bound payloads has recently attracted significant attention.[5] Mechanophores have been judiciously designed for the liberation of a wide range of small molecules including CO,[6] HCl,[7] furans,[8] *N*-heterocyclic carbenes,[9] ammonium compounds,[10] 9-fluorenone,[11] and others.

In contrast to the examples above, systems that leverage mechanically gated cascade reactions have been developed to decouple the mechanochemical activation step from cargo release resulting in more general and modular mechanophore platforms.[5a] For example, Göstl and Herrmann introduced a disulfide mechanophore that undergoes a mechanically facilitated disulfide reduction triggering the efficient release of various alcohols.[12] Our group has developed a system based on furan–maleimide Diels–Alder mechanophores in which a mechanically triggered formal retro-[4+2] cycloaddition reaction unveils a reactive 2-furylcarbinol derivative that spontaneously fragments to release a covalently bound cargo molecule.[13] The cargo scope and release kinetics are systematically modulated through substitution of the masked 2-furylcarbinol derivative enabling the mechanically triggered release of

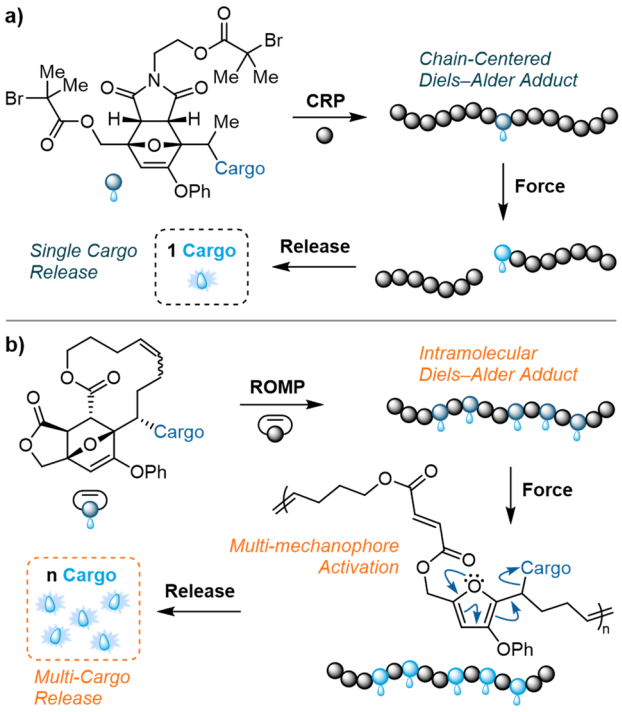
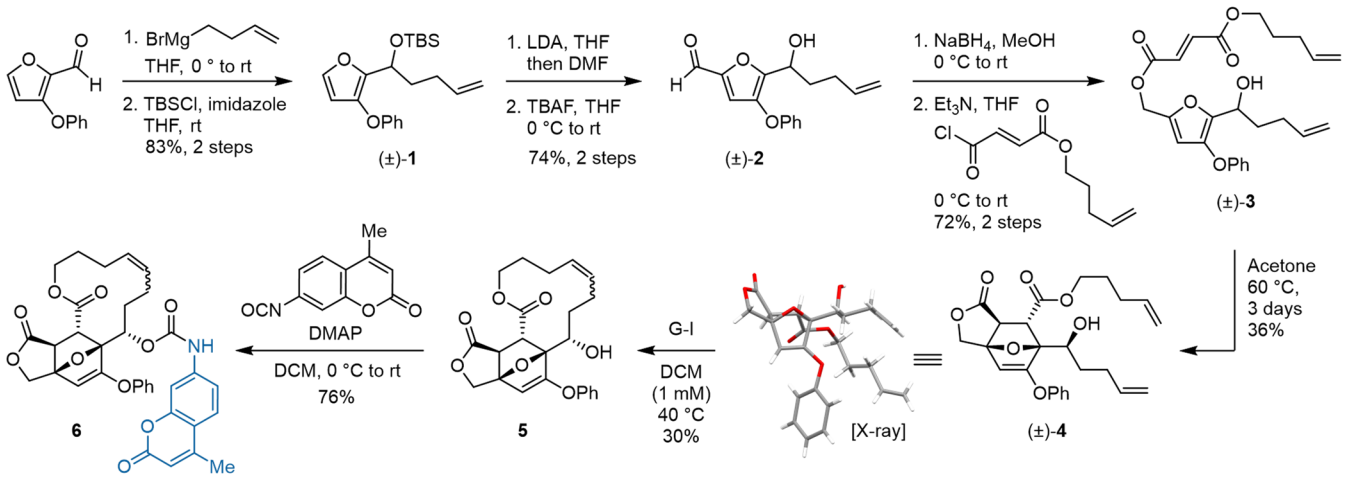


Figure 1. Mechanically triggered small molecule release from polymers containing a masked 2-furylcarbinol mechanophore via a retro-Diels–Alder/fragmentation cascade. (a) Mechanochemical activation of a typical chain-centered mechanophore releases up to one cargo per polymer chain. (b) A multi-mechanophore polymer design incorporating a non-scissile mechanophore capable of releasing hundreds of cargo molecules per chain.

Scheme 1. Synthesis of the Non-Scissile Masked 2-Furylcarbinol Mechanophore Macrocycle Loaded with an Amino-coumarin Payload.



functionally diverse payloads including phenols, alcohols, arylamines, alkylamines, sulfonic acids, and carboxylic acids.[13b] Polymers are synthesized via a typical controlled radical polymerization (CRP) strategy that positions the mechanophore near the chain midpoint where mechanical force is greatest during ultrasonication (Figure 1a).[14] Critically, however, the scissile nature of this Diels–Alder mechanophore generally precludes the mechanochemical activation of more than one unit per polymer chain, which significantly restricts the amount of deliverable payload and represents a limitation of this design.

Non-scissile mechanophores can be incorporated into multi-mechanophore polymers (MMPs) containing many repeats that are activated mechanochemically along a substantial portion of the polymer chain.[15] Craig has pioneered a strategy for the synthesis of MMPs that leverages the ring-opening metathesis polymerization (ROMP) of mechanophores containing macrocyclic olefins.[16] This methodology has been employed extensively, including in the two examples mentioned above enabling the mechanically triggered release of hundreds of equivalents of HCl and CO.[6a,7b] Inspired by these reports, here we introduce a novel non-scissile masked 2-furylcarbinol mechanophore that capitalizes on the modularity of the 2-furylcarbinol system and enables the preparation of MMPs with significantly higher deliverable payload capacity for mechanically triggered small molecule release (Figure 1b). The mechanophore design is based on the intramolecular Diels–Alder reaction of a furfuryl fumarate ester, which upon macrocyclization can be copolymerized via ROMP to afford MMPs capable of multi-mechanophore activation and efficient payload release. In addition to facilitating small molecule release,[13b] the phenoxy substituent renders the Diels–Alder adduct more thermally stable and protects the alkene against undesired olefin metathesis. The mechanochemical reactivity of the Diels–Alder adduct was validated by density functional theory (DFT) calculations using the constrained geometries simulate external force (CoGEF) method,[17] which predict that the retro-Diels–Alder reaction occurs with a relatively low rupture force of 3.4 nN (Figure S1).

Encouraged by the computationally predicted mechanochemical reactivity, we targeted the synthesis of a Diels–Alder macrocycle loaded with aminocoumarin (**CoumNH$_2$**) as a model fluorogenic cargo (Scheme 1, see the SI for details). Starting from 3-phenoxyfurfural, a two-step sequence involving Grignard addition and TBS protection afforded furfuryl silyl ether (±)-**1** in 83% yield. Next, a formylation reaction with LDA/DMF followed by removal of the TBS group with TBAF provided furfuryl alcohol (±)-**2** in 74% yield. Subsequent reduction of the aldehyde with $NaBH_4$ followed by selective esterification of the primary alcohol with a fumaric acid monoester chloride derivative gave furfuryl alcohol (±)-**3** in 72% yield. An intramolecular Diels–Alder reaction was then carried out at 60 °C in acetone and the major diastereomer (±)-**4** was isolated in 36% yield and characterized by X-ray crystallography. Formation of the 12-membered ring was accomplished by a ring-closing metathesis reaction using Grubbs' 1st generation catalyst in DCM (1 mM) to afford macrocycle **5** in 30% isolated yield. Finally, the aminocoumarin payload was installed by reaction of the secondary alcohol with 4-methylcoumarin-7-isocyanate[13b] to afford macrocyclic monomer **6** in 76% yield.

Polymers were synthesized via ROMP of macrocycle **6** with 5-acetoxycyclooctene (**COE$_{OAc}$**) as a comonomer in $CHCl_3$ (2 M) using Grubbs' 2nd generation catalyst (Figure 2a). Three different MMPs were prepared with varying molar mass and comonomer composition, which were characterized using gel permeation chromatography coupled with multi-angle light scattering (GPC-MALS) and ^{1}H NMR spectroscopy, respectively (Table 1 and Figures S2 and S3). We also prepared small molecule model compound (±)-**7**, which closely resembles the expected mechanophore-containing repeat unit structure in the MMPs (Figure 2b). Comparison of the ^{1}H NMR spectra of **MMP$_{80}$** (M_n = 80.3 kDa, $Đ$ = 2.40) and (±)-**7** confirms that the characteristic features of the Diels–Alder motif and the aminocoumarin payload were retained upon polymerization. Importantly, the signal corresponding to the alkenyl proton of the Diels–Alder adduct is also clearly observed in the ^{1}H NMR spectrum of **MMP$_{80}$**, confirming that ROMP was selective towards the macrocyclic alkene. The phenoxy substituent also enhances the thermal stability of the Diels–Alder adduct,[13b] which was stable at room temperature for more than two weeks (Figure S4). The composition of each MMP was determined by

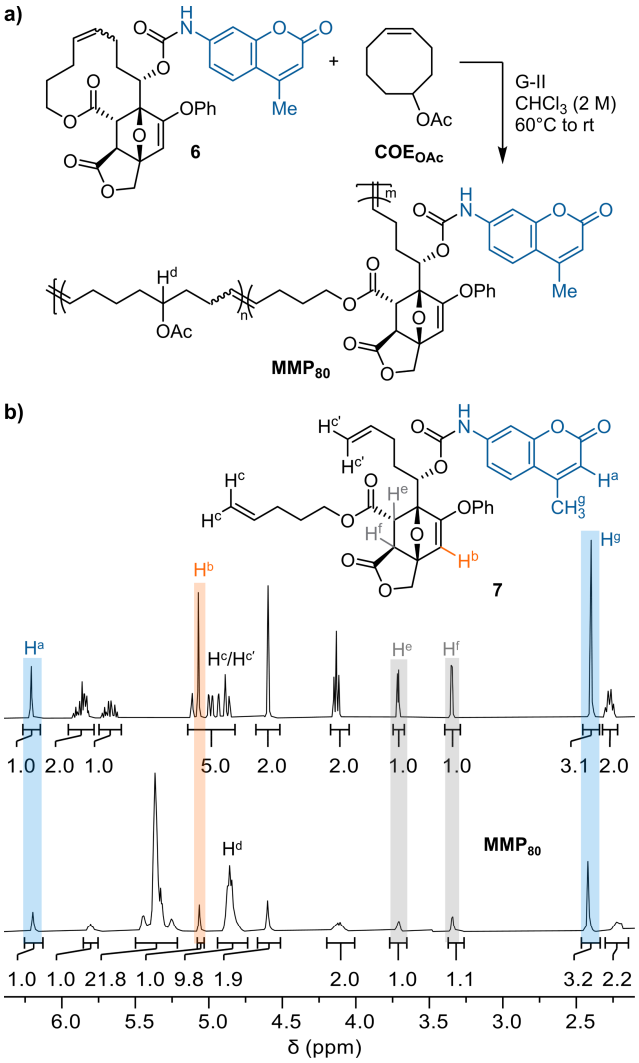
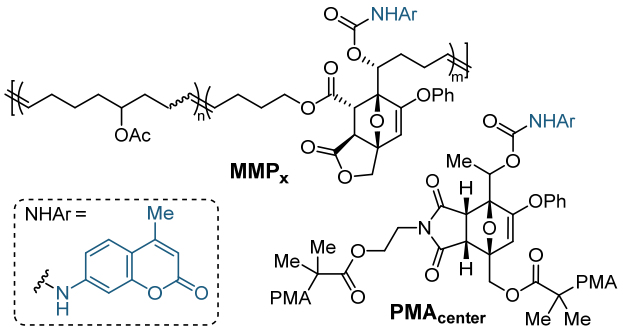


Figure 2. (a) Synthesis of multimechanophore polymer **MMP$_{80}$** (M_n = 80.3 kDa, $Đ$ = 2.40) via ROMP of macrocycle **6** and a cyclooctene comonomer. (b) ^{1}H NMR spectra (400 MHz, $CDCl_3$) comparing small molecule model compound **7** (*top*) and **MMP$_{80}$** (*bottom*) with diagnostic protons labeled for the polymer backbone, mechanophores, and cargo.

integrating the tertiary proton resonance at ~4.9 ppm on the **COE$_{OAc}$** repeat unit relative to the signals corresponding to the Diels–Alder adduct (see Table 1 and Figure S2). For **MMP$_{80}$**, approximately 9% of the total repeat units comprise the Diels–Alder motif, which translates to an average of 34 aminocoumarin payloads per chain (see the SI for additional details).

To evaluate the mechanochemical reactivity of the MMPs, we first subjected **MMP$_{80}$** (0.1 mg/mL in 3:1 THF/MeOH) to pulsed ultrasonication (1s on/1s off, 9–13 °C, 20 kHz, 13.9 W/cm^2) and aliquots were removed periodically for analysis by photoluminescence (PL) spectroscopy to quantify the release of aminocoumarin (Figure 3a, see the SI for details). THF was used as the cosolvent in these experiments due to improved solubility of the polymers compared to acetonitrile mixtures employed previously,[13a,b] despite slower fragmentation kinetics of the 2-furylcarbinol derivatives. Samples were allowed to incubate at room temperature for ~5 days after sonication to ensure complete fragmentation of the furfuryl carbamate intermediate prior to characterization

Table 1. Characterization of Multi-Mechanophore Polymers (**MMP$_x$**) and a Poly(Methyl Acrylate) Polymer Containing a Chain-Centered Mechanophore (**PMA$_{center}$**).



	M_n (kDa)[a]	$Đ$[a]	DP[b]	m : n[c]	cargo/chain[c]
MMP$_{80}$	80.3	2.40	383	9 : 91	34
MMP$_{295}$	295	2.25	851	40 : 60	340
MMP$_{23}$	22.5	1.36	103	12 : 88	12
PMA$_{center}$	83.9	1.17	976	–	1

[a]Determined by GPC-MALS. [b]Average total number of repeat units per chain (n + m). [c]Determined by ^{1}H NMR spectroscopy.

(Figure S5). Fluorescence intensity increased systematically with increasing sonication time indicating the successful release of **CoumNH$_2$** upon mechanochemical activation. The PL intensity reached a maximum after ~35 min of sonication corresponding to 65% release, or ~22 cargo molecules per chain (Figure 3b). To compare these results directly with our previous mechanophore design,[13b] we prepared poly(methyl acrylate) **PMA$_{center}$** equipped with a single chain-centered furan–maleimide mechanophore (M_n = 83.9 kDa, $Đ$ = 1.17, see Table 1). Ultrasonication of **PMA$_{center}$** under identical conditions and with the same initial polymer concentration resulted in 96% release, or ~1 unit of **CoumNH$_2$** per chain (Figure 3b, see the SI for details). We note that despite having a similar average molar mass, **PMA$_{center}$** required ~170 min of sonication to reach maximum conversion, corresponding to a nearly 5-fold slower rate compared to **MMP$_{80}$** (Figure S6). As evident from this comparison, the concentration of **CoumNH$_2$** released from **MMP$_{80}$** is ~24 times greater than that from **PMA$_{center}$** for the same initial concentration of polymer on a mass basis. We note that a small amount of background fluorescence was observed from **MMP$_{80}$** in the absence of mechanical activation (0 min sonication) after 5 days of incubation in 3:1 THF/MeOH that is tentatively ascribed to hydrolysis of the carbamate linkers. Nevertheless, this only corresponds to the release of ~1.4 **CoumNH$_2$** units, or ~4% release per polymer chain (Figure S7). Additional control experiments performed on small molecule model (±)-**7** demonstrated no observable changes in the ^{1}H NMR spectrum after 10 days in 3:1 THF-d_8/MeOH solution (Figure S8).

Having demonstrated the substantially increased payload capacity and successful cargo release from **MMP$_{80}$** compared to our previous mechanophore, we next sought to leverage the multi-mechanophore design to control the amount of cargo release and also confirm its

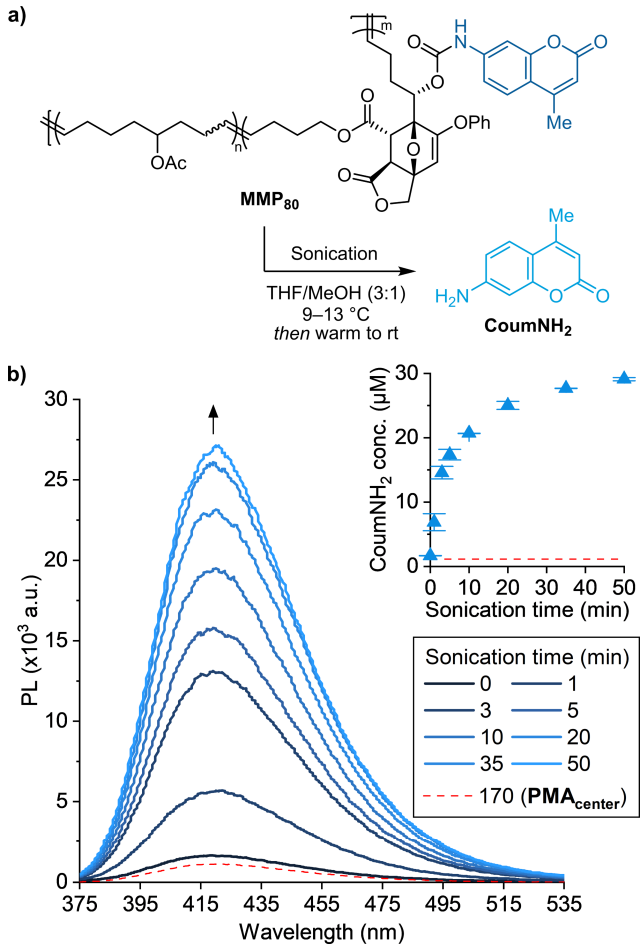


Figure 3. (a) Ultrasound-induced mechanochemical activation of **MMP$_{80}$** (0.1 mg/mL in 3:1 THF/MeOH), and (b) release of aminocoumarin (**CoumNH$_2$**) characterized by PL spectroscopy (λ_{ex} = 365 nm). Inset shows concentration of released **CoumNH$_2$** as a function of sonication time. Data are compared directly to the mechanochemical activation of **PMA$_{center}$** (M_n = 83.9 kDa, $Đ$ = 1.17) under identical conditions. The red dashed line in the inset represents the maximum release of **CoumNH$_2$** from **PMA$_{center}$** after sonication for 170 min. Error bars denote the range from two replicate experiments.

mechanochemical origin. To this end, we prepared two additional MMPs following a similar procedure as above with varying molar mass and/or mechanophore incorporation (see Table 1). Synthesis of **MMP$_{295}$** (M_n = 295 kDa, $Đ$ = 2.25) was accomplished using a higher feeding ratio of macrocycle **6** to **COE$_{OAc}$**, resulting in 40% mechanophore incorporation and ~340 cargo molecules per chain. On the other hand, **MMP$_{23}$** (M_n = 22.3 kDa, $Đ$ = 1.36) has a similar mechanophore incorporation of ~12% compared to **MMP$_{80}$**, but is significantly smaller (see the SI for details). While faster and greater overall payload release is expected from **MMP$_{295}$**, the molar mass of **MMP$_{23}$** is likely near or below the threshold for mechanophore activation, therefore leading to an insignificant amount of payload release.[18] Following the same experimental conditions as above, all three MMPs were sonicated at the same mass concentration (0.1 mg/mL in 3:1 THF/MeOH) and the release of **CoumNH$_2$** was quantified using PL spectroscopy as a function of sonication time (Figure 4). Remarkably, ultrasound-induced mechanochemical activation of **MMP$_{295}$** resulted

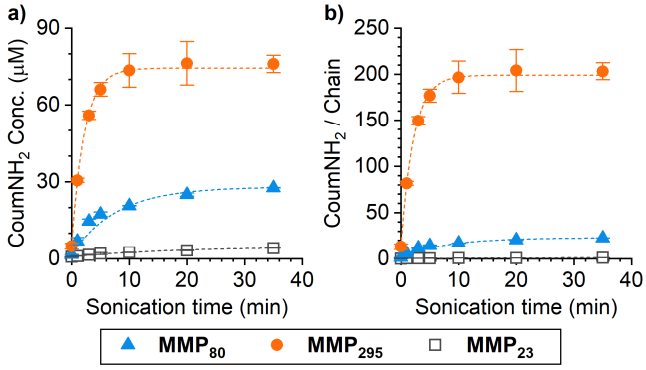


Figure 4. (a) Mechanically triggered release of **CoumNH$_2$** from multimechanophore polymers of varying molar mass and composition as a function of sonication time (0.1 mg/mL polymer in 3:1 THF/MeOH). Theoretical cargo concentrations assuming 100% release: [**CoumNH$_2$**]$_{theo}$ = 127 μM (**MMP$_{295}$**), 44 μM (**MMP$_{80}$**), 53 μM (**MMP$_{23}$**). (b) Number of **CoumNH$_2$** units released per chain as a function of sonication time. Error bars denote the range from two replicate experiments.

in 60% release of **CoumNH$_2$**, corresponding to ~203 cargo molecules per chain. As expected, cargo release also occurs significantly faster from **MMP$_{295}$**, achieving maximum release after only ~10 min of sonication. In contrast, only 8% release of **CoumNH$_2$** was achieved upon ultrasonication of **MMP$_{23}$**, corresponding to the release of ~1 payload unit per chain. Taken together, these results are fully consistent with the expected molar mass dependence on ultrasound-induced mechanochemical activation and provide evidence for the mechanical origin of cargo release.[4]

In summary, we report a non-scissile masked 2-furylcarbinol mechanophore that enables the preparation of multi-mechanophore polymers via ROMP for mechanically triggered small molecule release. Compared to typical chain-centered mechanophore designs that are limited to the release of one or two cargo molecules per polymer chain, we demonstrate that the release of hundreds of small molecule payloads can be triggered from a multi-mechanophore polymer upon ultrasound-induced mechanochemical activation. The substantial increase in deliverable payload capacity on a polymer mass basis overcomes a major existing limitation in mechanophore design and opens the door to applications that require greater concentrations of delivered small molecule cargo.

ASSOCIATED CONTENT

Experimental details, synthetic procedures, DFT calculations, GPC chromatograms, fluorescence data, NMR spectra, and crystallographic data (PDF).

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Notes
The authors declare no competing financial interests.

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