Mechanophore activation enhanced by hydrogen bonding of diarylurea motifs: An efficient supramolecular force-transducing system

Jumpei Kida | Daisuke Aoki | Hideyuki Otsuka

Department of Chemical Science and Engineering, Tokyo Institute of Technology, Meguro-ku, Tokyo, Japan

Correspondence
Hideyuki Otsuka, Department of Chemical Science and Engineering, Tokyo Institute of Technology, 2-10-1 Ookayama, Meguro-ku, Tokyo 152-8550, Japan.
Email: otsuka@mac.titech.ac.jp

Funding information
Japan Society for the Promotion of Science, Grant/Award Number: 17H01205; Core Research for Evolutional Science and Technology, Grant/Award Number: JPMJCR1991

Abstract
Macromolecules are efficient as mechanical transducers for mechanically induced chemical bond cleavage reactions. Although various classes of polymers have been studied as effective mechanical-force transducers for mechanophores, alternatives to polymer chains, that is, small molecules, have rarely been studied. In this paper, the role of hydrogen bonding as small-molecule mechanical-force transducers for the activation of mechano-responsive molecular units (mechanophores) in the bulk is investigated. The introduction of diarylurea linkage motifs, which are known as strong hydrogen bonding groups, enhances the mecanochemical activation of the fluorescent mechanophore tetraarylsuccinonitrile (TASN) as effectively as the attachment of a typical macromolecular transducer. Electron paramagnetic resonance measurements of mechanically activated TASN with diphenyl urea motifs demonstrate its higher carbon–carbon bond dissociation ratio compared to that of TASN without diphenyl urea motifs. This efficient supramolecular-force-transducing system represents a new concept in the field of mecanochemistry, namely, the enhancement of mecanochemical bond scission by simply changing the substituents of a mechanophore, even in small molecules.

KEYWORDS
hydrogen bonding, mechanophore, radical

Mechanical force has been used as a basic technology for changing the properties of materials since prehistoric times. In the field of the chemical synthesis, the mechanical force has been recognized as an effective tool.[1–4] In the past decade, many reactions have been reported that induce the scission of chemical bonds by mechanical stimuli using macromolecules as mechanical transducers.[5] Macromolecules have been reported to be efficient transducers for a variety of mechanically induced chemical reactions, including reactions that involve chromism,[6–8] luminescence,[9–11] strengthening by cross-linking,[12] activation of latent metal catalysts,[13,14] polymer degradation,[15,16] and the generation of reactive species.[17–18] The effect of macromolecular structure on the mechanical activation of mechanophores has been widely studied.[19–22] Moore and co-workers have reported that the degree of polymerization, that is, the length of the polymer chains, is a good descriptor of ultrasound-induced mecanochemical transduction in solution.[23] Our group has reported that increased molecular weight,[24] number of branches,[24] and dendrimer generation[25] positively affect the ability of a polymer to mecanochemically activate mechanophores in solid systems.

Although various classes of polymers have been found to be effective mechanical-force transducers for mechanophores, alternatives to polymer chains have rarely been studied. The use of small molecules as mechanical-force transducers could overcome the complications associated with reaction systems involving high-molecular-weight macromolecules and mechanical side reactions on the polymer chains, which prevent the transmission of the force to the mechanophore. Although some alternative non-polymeric mechanical-force transducers have been reported to be effective,[26,27] their versatility is limited by their complicated molecular designs. In the present study, we have focused on a general and simple supramolecular hydrogen-bonding system as an alternative mechanical-force transducer. Polymeric systems that combine macromolecules and hydrogen bonding have been studied previously, and
The strength of the hydrogen bonding has been found to affect the activation of the mechanophores. However, systems in which the mechanophore is simply combined with a hydrogen-bonding moiety have not been studied in detail. Here, diarylurea, which strongly self-assembles through hydrogen bonding, was used as a supramolecular mechanical-force transducer and directly introduced to tetraarylsuccinonitrile (TASN), a mechanophore that generates diarylacetonitrile (DAAN) radicals via the cleavage of its central carbon–carbon bond under mechanical force (Figure 1A). In this paper, we report an effective mechanical-stimulus-transduction system in which mechanophore activation is enhanced by the hydrogen bonding of diarylurea motifs (Figure 1B). The enhancement was quantitatively characterized by electron paramagnetic resonance (EPR) measurements in the bulk.

The synthesis of TASN with two diarylurea motifs, which were expected to exhibit supramolecular self-assembly through hydrogen bonding (TASN-urea), was accomplished in four steps from commercially available precursors (Scheme 1). In the first step, 1 was prepared by the coupling of 4-methoxyphenylacetonitrile with 4-fluoronitrobenzene. A Bechamp reduction converted 1 into the corresponding amine (2), and a subsequent reaction with phenyl isocyanate afforded 3. Finally, the oxidative dimerization of 3 yielded TASN-urea as a colorless powder. The chemical structure of TASN-urea was confirmed using $^1$H NMR, $^{13}$C NMR, and Fourier transform-infrared (FT-IR) spectroscopy (Figures S1–S9) as well as electrospray ionization time-of-flight mass spectrometry.

To investigate whether TASN-urea is able to act as a mechanophore, it was ground in a ball mill (30 Hz, 10 min) at room temperature; the colorless solid became red after grinding and exhibited an absorption peak at 575 nm in its solid-state UV-vis spectrum (Figure S16). Moreover, the ground powder showed orange fluorescence under irradiation at 365 nm (Figure 2A) with a fluorescence peak at 590 nm (Figure S17). To confirm the generation of radical species during the grinding process, EPR measurements were conducted before and after grinding. After grinding,
FIGURE 2 (A) Photographs of TASN-urea before and after grinding under UV light (365 nm) irradiation. (B) Structure of the TASN derivatives. (C) Dissociation ratio of the TASN derivatives (TASN-NO2, TASN-tetraOMe, TASN-OH, and TASN-urea) under mechanical force, which was calculated from the integral value of EPR spectra after grinding. The error bars represent a standard deviation of the values of three times of measurements.

A radical peak was clearly observed (Figure S10). The g value (2.002) of the peak is indicative of a carbon-centred radical, suggesting that TASN-urea generates radicals via the homolytic cleavage of the central carbon–carbon bond in response to mechanical stimuli, as has been previously reported for TASN.\(^{[33]}\)

To obtain further insight into the effect of the intermolecular hydrogen bonding of urea on the mechanochemical reactivity, we compared the dissociation ratio under mechan-

ical force of TASN-urea with those of TASN-tetraOMe and TASN-NO2, which do not contain strongly hydrogen-bonding substituents, and TASN-OH, which contains hydrogen-bonding hydroxy groups. As shown in Figure 2C, the dissociation ratio calculated from the integral values of the EPR spectra of TASN-urea was 28 times higher than that of TASN-NO2 (Figure S11) and 21 times higher than that of TASN-tetraOMe (Figure S12). These results indicate that the introduction of a urea linkage enhances the intermolecular interaction among TASN moieties, and that the linkage acts as a transducer of mechanical force to the mechanophore. Importantly, such great enhancement of the dissociation ratio of TASN was not observed for TASN-OH, which had more weakly hydrogen-bonding hydroxy groups (1.6 times greater than TASN-NO2) (Figures 2 and S13). The aggregation of TASN-urea was observed by the results of dynamic light scattering measurements, suggesting the aggregation of TASNs (Figure S34). These results show that the stronger hydrogen bonding of urea groups, which act like supramolecular polymers, is necessary to effectively transduce mechanical force.

To obtain further support for the proposed mechanism, we synthesized ToNU with a nitro group at the ortho position of the urea bond, which is known to weaken its intermolecular hydrogen bonding, and TmNU with a nitro group at the meta position of urea bond, which strengthens intermolecular hydrogen bonding.\(^{[37]}\) A solid-state FT-IR spectroscopy analysis revealed the effect of the nitro-group substitution pattern. In ToNU, the splitting of the peak assigned to N–H in-plane bending deformation at approximately 1595 cm\(^{-1}\) into two indicates that ortho substitution leads to the formation ofintramolecular hydrogen bonds between the nitro group and the N–H group of urea (Figure S21). Moreover, the peak assigned to non-hydrogen-bonded C = O stretching at 1719 cm\(^{-1}\) indicates that the C = O group of ToNU is not as involved in intramolecular hydrogen bonding as that of TASN-urea (Figure S21).\(^{[38]}\) In the case of TmNU, no non-hydrogen-bonded C = O peak was detected, and the nonhydrogen bonded N–H peak at approximately 3500 cm\(^{-1}\) was weaker than that of TASN-urea (Figure S22). These results show that the intensity of intermolecular hydrogen bonding follows the order TmNU > TASN-urea > ToNU. The dissociation ratio of ToNU (Figure S14) was approximately half that of TASN-urea, and that of TmNU (Figure S15) was 1.36 times higher than that of TASN-urea (Figure 3), reflecting the difference in the intensity of the intermolecular interactions.

Subsequently, we confirmed the electronic effects of TASN substitution based on the experimental thermal bond dissociation energy (BDE) and simulated mechanical C–C bond scission force and examined whether the inherent differences in bond strength affect the mechano-reactivity. The BDEs of the central C–C bonds of the various TASN derivatives were estimated using variable-temperature EPR measurements. The peak intensity of the TASN solution in 1,4-dioxane gradually increased with increasing temperature, demonstrating the generation of radical species from TASN upon heating (Figure S18). The relationship between the dissociation enthalpy, which was calculated from the van’t Hoff plots (Figure S19), and the mechanical dissociation ratio is summarized in Figure S20. No correlation was observed, which indicates that the differences in the mechanical dissociation ratios of the TASNs are not related to their thermal dissociation enthalpy.
but instead to their hydrogen bonding strength. The strength of the C = O—H–N hydrogen bonds of urea groups is generally several kcal mol⁻¹, which is much lower than that of the central C–C bond of TASNs calculated here (16–23 kcal mol⁻¹). When a TASN powder experiences the force, bond scission occurs preferentially at the weakest bond. In the present system, it might be expected that the supramolecular hydrogen bonds would preferentially dissociate during grinding and that the weak hydrogen bonding interaction would not drastically affect the degree of mechanochemical reaction. However, our results indicate that the hydrogen bonding acts as an effective transducer of mechanical force to chemical reaction. It can be interpreted that the introduction of intermolecular hydrogen bonds has the effect of improving the relative cleavage probability of C–C bonds.

Moreover, constrained geometry simulates external force (CoGEF) calculations were conducted at the B3LYP/6-31G* level of theory to predict the maximum force ($F_{\text{max}}$) along the CoGEF curve, which represents the force associated with the mechanochemical transformation. $F_{\text{max}}$ is known to be affected by substituents, and the values of $F_{\text{max}}$ calculated using CoGEF have a positive correlation with the forces measured experimentally using single molecule force spectroscopy. The relationship between the calculated $F_{\text{max}}$ values of the TASN and their experimental dissociation ratio in response to mechanical force is summarized in Figure S23. No correlation was observed between the calculated $F_{\text{max}}$ and experimental dissociation ratio of the TASN moieties under mechanical force, indicating that the change in the dissociation ratio does not originate from a difference in the force required to cleave bonds.

Mechanically generated DAAN radicals slowly recombine into TASN at room temperature. Figure 4 shows the recombination of the generated radical species. The number of radicals in TASN-urea, TASN-OH, TASN-NO₂, TASN-OH, TASN-tetraOMe, and TASN-NO₂ gradually decreased with time after grinding. The activation ratios of the TASN moiety 30 min after grinding were 99%, 98%, 96%, and 89% (TASN-urea, TASN-OH, TASN-tetraOMe, and TASN-NO₂, respectively), indicating that the recombination rate of the generated radicals also influences the improvement in the mechano-responsiveness, but recombination is minor on the grinding and measurement time-scale (≈15 min). Surprisingly, TASN-urea and TASN-OH showed slow decay curves, with 94% of the generated DAAN radicals still present even 15 h after grinding, unlike TASN-tetraOMe (72%) and TASN-NO₂ (32%). The radical lifetime of the TASN derivatives with hydrogen bond units, that is, TASN-urea, TASN-OH, TASN-tetraOMe, and TASN-NO₂ gradually decreased with time after grinding. The activation ratios of the TASN moiety 30 min after grinding were 99%, 98%, 96%, and 89% (TASN-urea, TASN-OH, TASN-tetraOMe, and TASN-NO₂, respectively), indicating that the recombination rate of the generated radicals also influences the improvement in the mechano-responsiveness, but recombination is minor on the grinding and measurement time-scale (≈15 min). Surprisingly, TASN-urea and TASN-OH showed slow decay curves, with 94% of the generated DAAN radicals still present even 15 h after grinding, unlike TASN-tetraOMe (72%) and TASN-NO₂ (32%). The radical lifetime of the TASN derivatives with hydrogen bond units, that is, TASN-urea, TASN-OH, TASN-tetraOMe, and TASN-NO₂ gradually decreased with time after grinding. 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![Figure 3](image1.png) Dissociation ratios of TASN-urea, ToNU, and TmNU after ball-milling (30 Hz, 10 min), which were calculated from the integral value of EPR spectra after grinding. The error bars represent a standard deviation of the values of three times of measurements.

![Figure 4](image2.png) Time-dependent dissociation ratios of TASN-urea, TASN-NO₂, TASN-OH, and TASN-tetraOMe calculated from EPR measurements, showing the recombination of the dissociated TASN moieties.
In summary, we have successfully synthesized TASN moieties with directly connected hydrogen-bonding urea linkages and evaluated the role of the hydrogen bonding in mechanical-force transduction to the mechanophores. The introduction of a diarylurea linkage into the mechanophores clearly enhances their activation ratio upon grinding, despite the low molecular weight of the mechanophores. However, we revealed that the hydrogen bonding acts as a supporting unit to maintain the activated mechanophores, despite its low molecular weight (TASN-urea: 712.81). In contrast, the hydrogen bonding of the hydroxy groups in TASN-OH enables them to act as a supporting unit to maintain the mechanophores in the activated state, but does not provide good mechanical-force transduction.

Acknowledgements

This work was supported by KAKENHI grant 17H01205 (Hideyuki Otsuka) from the Japan Society for the Promotion of Science (JSPS), as well as by JST CREST grant JPMJCR1991 (Japan). Junpei Kida acknowledges financial support from a JSPS Research Fellowship for Young Scientists with directly connected hydrogen-bonding urea linkages.

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