Mechanochromic cyclodextrins

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Mechanochromic cyclodextrins

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Mechanochromic cyclodextrins (MCDs) that can generate blue radical species, which are exceptionally stable toward atmospheric oxygen and can thus be quantitatively characterized via electron paramagnetic resonance (EPR) spectroscopy, were synthesized. MCDs have a defined structure that consists of a diarylbibenzofuranone skeleton mechanophore sandwiched between two CDs. Grinding tests and EPR measurements of the MCDs revealed their high mechanoresponsiveness, reflecting the inherent rigidity of the CDs and the formation of a supramolecular structure in the bulk.

Mechanochromic functionality,[1-9] i.e., colour change in response to mechanical stimuli, can be used to visualize stress and damage in materials and to predict their lifetimes. The introduction of mechanophores, which are skeletons that change their chemical structure in response to mechanical stimuli, into polymer matrices, especially into the polymer mid-chain, is an effective method to endow materials with mechanochromism. Many mechanophores, based on e.g., spiropyrans,[10] cinnamate dimers,[11] dioxetanes,[12] hexaarylbiimidazoles (HABIs),[13] 2-arylindane-l,3-dione dimers,[14] and diarylbibenzofuranones (DABBFs)[15] have been reported in recent years. Radical-type mechanophores such as DABBF have the special feature of generating stable radicals upon mechanical stimulation, and these can be quantitatively examined using electron paramagnetic resonance (EPR) spectroscopy (**Fig. 1a**). For example, the central carbon–carbon bond of DABBF is cleaved by mechanical stimulation to produce blue radicals that are highly stable toward atmospheric oxygen and can be measured quantitatively using EPR; these are great advantages for the investigation of mechanoresponsiveness not only in solution, but also in the bulk.[15-19]

In recent years, mechanophores have been widely used to fabricate stimulus-responsive materials that enable the visualization of macroscopic forces on materials, and to evaluate microscopic forces that accumulate on the molecular chains. In our group, we have introduced DABBF into polymer chains with various structures and compared the dissociation ratios of

DABBF upon mechanical stimulation in the bulk to clarify the relationship between the primary structure and the mechanoresponsiveness; we have found that their mechanoresponsiveness improves with increasing molecular weight and number of branches.[16] We have also discovered that supramolecular interactions play an important role in the activation of mechanophores, which is consistent with other reports. [20-24]

Although mechanophore-containing polymers have the advantage of easy fabrication, it should be noted that polymers are considered to have relatively indefinite structures due to the molecular weight distribution. To further describe the relationship between structure and mechanoresponsiveness, we have introduced DABBF into dendrimers as structurally well-defined polymers without a molecular weight distribution, but this approach has practical limitations associated with the complexity of their synthesis (**Fig. 1b**). [25,22]
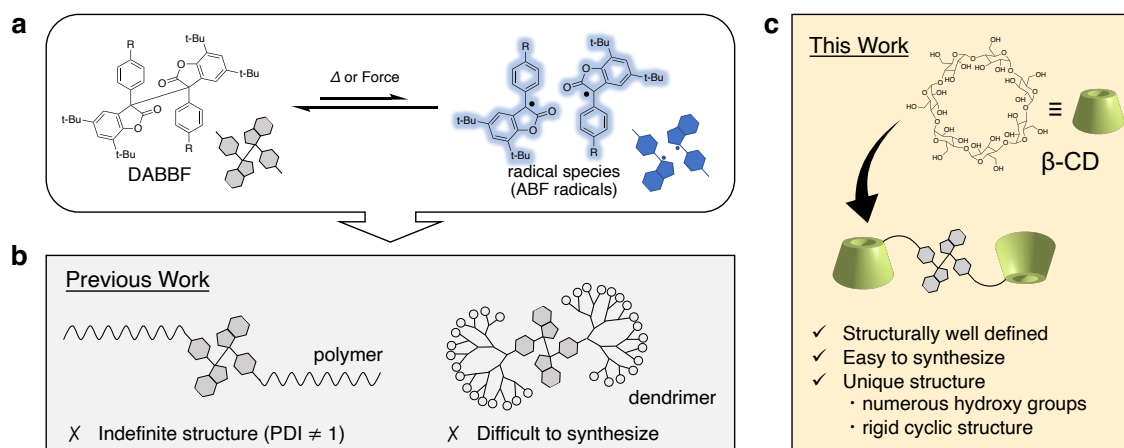
To investigate the relationship between structure and mechanoresponsiveness using an easy-to-fabricate system, we focus herein on cyclodextrins (CDs) as structurally well-defined molecules.[26-28] CDs are cyclic oligosaccharides that can be synthesized on an industrial scale and are widely used in the pharmaceutical industry.[29-34] As CDs have a unique structure that consists of cyclic oligomers and numerous hydroxy groups on their surface, it is expected that the inherent rigidity of CDs and their assembly into structures in the bulk through supramolecular interactions would have a synergetic effect on the mechanochromism.[35] Two CDs were attached to a DABBF-derivative as an alternative to polymer chains, and the mechanochromic properties of the resulting compounds were investigated via grinding tests and EPR measurements (**Fig. 1c**).

The synthesis of DABBF with two CD units (CD-DABBF) was accomplished using commercially available CD precursors and DABBF-dialkyne (**Fig. 2**). CD-DABBF was synthesized via the Cu-catalyzed azide alkyne cycloaddition (CuAAC)[36] of DABBF-dialkyne[16] and mono-(6-azide-6-deoxy)-β-CD (CD-N$_3$).[37] β-CD was chosen in this study based on the easy access to mono-substituted β-CD.[37] The crude product was purified by reprecipitations into acetone, followed by washing with water, to give CD-DABBF as a white powder in 92% yield. The solubility of the obtained CD-DABBF was good in DMSO, but low in water. The chemical structure of CD-DABBF was confirmed using ^{1}H NMR, ^{13}C NMR, Fourier transform-infrared (FT-IR)

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Fig. 1 (a) Equilibrium of DABBF. (b) Previous work investigating the relationship between the structure and mechanoresponsiveness of DABBF-containing polymers. (c) Structure of β-cyclodextrin (β-CD) and the concept of this work.

spectroscopy and electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) (Figs. S1–S2).

In order to investigate the mechanoresponsiveness of CD-DABBF, a grinding test was carried out. After being ground using a ball mill (30 Hz, 10 min) at room temperature, the initially white CD-DABBF powder turned deep blue (**Fig. 3a**). Its solid-state UV-vis spectrum showed absorption peaks similar to those previously reported for the ABF radical (**Fig. 3b**).[15] In order to confirm the generation of radical species during the grinding process, EPR measurements were conducted (**Fig. 3c**). The g value (2.003) of the peak indicated the generation of carbon-centered radicals, confirming that CD-DABBF produces carbon radicals via the homogeneous cleavage of the central carbon–carbon bond upon mechanical stimulation. The dissociation ratio of the DABBF skeleton calculated from the integral intensities in the EPR measurement (4.1%) is 32 times higher than that of DABBF-diol (**Fig. 4a**) and also higher than that of DABBF-bridged polystyrene (PS-DABBF; 3.1%, over 14 kDa) and benzyl-terminated 4th generation dendrimers (1.5%, over 14 kDa)[25] (Fig. S7). It is well known that longer polymer chains induce mechanochemical activation more effectively.[38,16] Considering the molecular weight of CD-DABBF, which is slightly less than 3 kDa in total, the inherent rigidity of the CD structure and the structure assembled in the bulk through the numerous hydroxy groups on the CD surface, actually play a key role in the high mechano-responsiveness of the DABBF skeleton.

When alcoholic solvents, such as methanol, ethanol and even water, were added to the ground CD-DABBF, the blue color faded immediately, while it did not fade in common organic solvents for polymers such as ethyl acetate, tetrahydrofuran (THF), dichloromethane (DCM), as well as benzyl alcohol which is protic but less hydrophilic solvent (Fig. S9). Based on these results, CD-DABBF can be regarded as a mechanochromic molecule that exhibits an affinity with polar solvents, which is a special feature of CD-based mechanophores.[35] This special characteristic of CD-DABBF also indicates that the motility of the whole molecule, rather than the specific motility of the mechanophore skeleton, affects the recombination behavior of the generated radicals, i.e., the mechanophore skeleton DABBF is hydrophobic and CD is hydrophilic. Namely, the combination

of a mechanophore and CD, which has the special features of rigid structure and hydrophilicity, endows radical-type mechanophores with not only high mechano-responsiveness, but also hydrophilicity, which allows their dynamic behavior to be controlled using water, i.e., the most convenient solvent in the world.

Subsequently, in order to investigate the effect of the hydroxy groups of the CDs on the mechanochromic properties, the hydroxy groups of the CDs in CD-DABBF were fully substituted. We chose acetylation as the substitution reaction[39] because it allowed all the hydroxy groups to be substituted without adverse reactions in the presence of DABBF. AcCD-DABBF, in which all the hydroxy groups of CD-DABBF are acetylated, was obtained via the reaction of CD-DABBF with acetic anhydride (**Fig. 2**). The chemical structure of CD-DABBF was confirmed using ^{1}H NMR, ^{13}C NMR, and FT-IR spectroscopy as well as ESI-TOF-MS (Figs. S3-4). After the acetylation of the hydroxy groups of CD, the affinity of AcCD-DABBF toward water was lost, while its affinity toward organic solvents such as ethyl acetate, THF, and DCM increased; these observations are
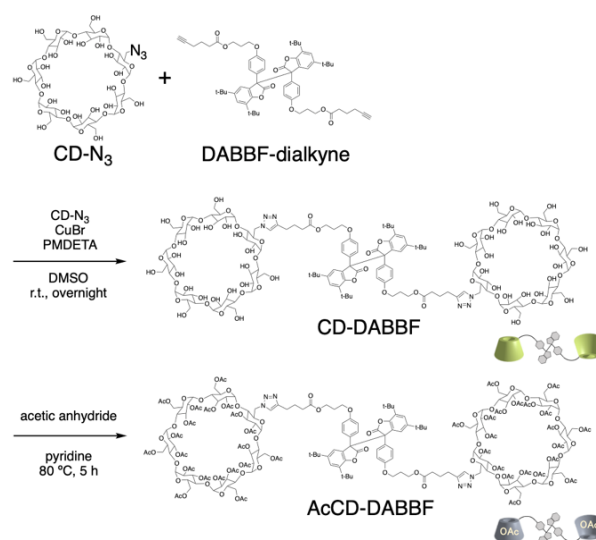
Fig. 2 Synthesis of CD-DABBF and AcCD-DABBF.

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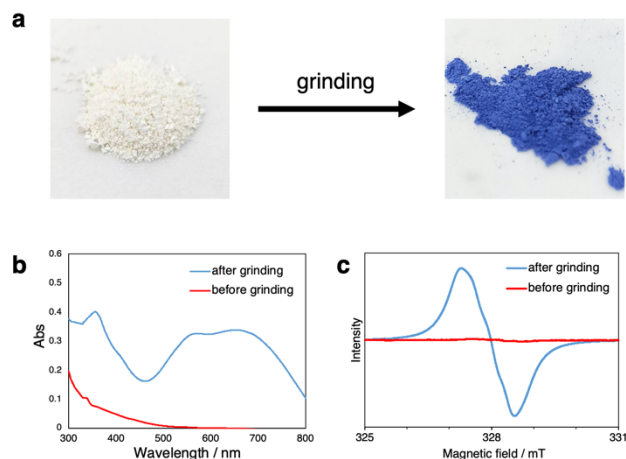
Fig. 3 (a) Photographs of CD-DABBF before and after grinding using a ball mill (30 Hz, 10 min) at room temperature. (b) Solid-state UV-vis spectra of CD-DABBF before (red) and after (blue) grinding. (c) EPR spectra of CD-DABBF before (red) and after (blue) grinding.

consistent with the recombination behavior of the generated radicals (Fig. S10).

AcCD-DABBF was subjected to the same grinding test as CD-DABBF, and the dissociation ratio of the DABBF skeleton was calculated from the radical intensity in the EPR measurements. The results show that the dissociation ratio of the DABBF skeleton in AcCD-DABBF (2.9%) is 0.7 times lower than that of CD-DABBF and 23 times higher than that of DABBF-diol (**Fig. 4a**). This result indicates that the acetylation of CD weakens the aforementioned interactions between the CDs, i.e., the hydrogen bonding between the CD units enhances the mechanoresponsiveness of CD-DABBF. In order to obtain further insight into the enhancement of the mechanoresponsiveness via the hydrogen bonding of CD, especially higher-order structures based on the rigid structure of CD and its hydroxy groups, wide-angle X-ray diffraction (WAXD) measurements were carried out. The diffraction pattern of CD-DABBF exhibits a strong peak (ca. 4.4 nm), whereas those of AcCD-DABBF and the original β-CD do not (**Fig. 4b**). The value of 4.4 nm is almost equal to the distance between the two CDs in CD-DABBF when DABBF adopts the *trans*

conformation, suggesting that CD-DABBF exhibits a highly ordered structure due to the strong hydrogen bonding of the CD units. The high dissociation ratio of CD-DABBF could be indicative for the formation of supramolecular structures in the bulk. Although the enhancement of mechanoresponsiveness by hydrogen bonding has already been reported,[22,20] this is the first report in which hydrogen bonding among hydroxy groups is the main reason for such a substantial enhancement via higher-order structures.

The dissociation ratio of AcCD-DABBF (2.9%) is by a factor of 29 higher than that of DABBF-diol (0.1%) but and furthermore, it is similar to that of PS-DABBF (3.1%) (Fig. S7, ESI), even though its molecular weight is four times lower. This suggests that the molecular rigidity derived from the cyclic structure of CD also has a significant impact on the mechanoresponsiveness. It is inferred that this high dissociation ratio is achieved due to the low relaxation in response to mechanical stimuli due to the rigid and coherent structure of CD. The achievement of a high dissociation ratio despite the use of low-molecular-weight pendants (CDs) is a promising feature for the design of mechano-responsive functional materials, because a high density of the activated mechanophore can be obtained, i.e., the mechanophore accounts for a large fraction of the volume of the overall molecules. The introduction of mechanophores into polymer chains increases the mechanoresponsiveness of the mechanophores but decreases the number of activated states per volume of material due to the high molecular weight of the polymer chains. On the other hand, small-molecule mechanophores like DABBF-diol produce very few activated mechanophores (low dissociation ratio) despite the high volume of the mechanophore part relative to that of the whole molecule due to its low mechanoresponsiveness. Consequently, there is a trade-off between mechanoresponsiveness and the ratio of activated states per volume in polymer-based systems. 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. Mechanophores with CD can easily produce more activated states per volume of material due
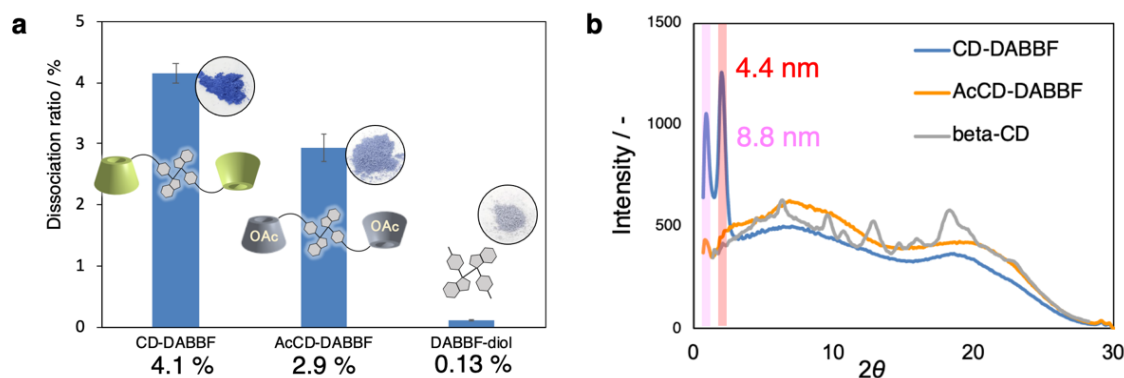
Fig. 4 (a) Dissociation ratios (%) of the DABBF skeletons of CD-DABBF, AcCD-DABBF, and DABBF-diol after grinding using a ball mill (30 Hz, 10 min) at room temperature. (b) X-ray diffraction patterns of CD-DABBF (blue), AcCD-DABBF (orange), and β-CD (grey) powder.

to their high mechanoresponsiveness and low molecular weight, which is particularly important for the molecular design of mechanophore materials, which could be applicable not only for color change, but also for small-molecule release or useful reactions.[40]

In summary, we have successfully synthesized CD-DABBF, which consists of two CDs sandwiching a DABBF skeleton, and evaluated its mechanical response. The mechanophores with CD units show a very high mechanical response due to the inherent rigidity of CD and the formation of a supramolecular structure through the hydroxy groups on CD in the bulk. We also discovered that the introduction of CD into DABBF endows mechanoresponsive materials with affinity toward polar solvents. The findings obtained in this study provide a novel, structurally well-defined mechanical-force transducer unit (CD) to activate mechanophores simply in small molecules. As it is well known that CDs provide unique chemistry based on their cavity, CD-DABBF can be expected to find further applications. We are currently studying such further applications of CD-DABBF, especially with respect to supramolecular chemistry involving the cavity of CD in the bulk.

Conflicts of interest

There are no conflicts to declare.

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