Disentangling the effect of pressure on a mechanochemical bromination reaction by solid-state NMR spectroscopy

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The mechanochemical bromination of a heterocyclic sulfoximine is studied by ex- and in-situ solid-state NMR spectroscopy. A clean and fast reaction is observed in a mixer mill, which can alternatively be induced either using the centrifugal pressure of magic-angle spinning or by solely magnetic stirring the solid entities.
Abstract

Mechanical forces, including compressive stresses as one of the most important consequences, have a significant impact on chemical reactions. Besides the preparative opportunities, mechanochemical conditions benefit from the absence of any organic solvent, the possibility of a significant synthetic acceleration and unique reaction pathways. Together with an accurate characterization of ball-milling products, the development of a deeper mechanistic understanding of the occurring transformations at a molecular level is critical for fully grasping the potential of organic mechanosynthesis. In this vein, we studied a bromination of a cyclic sulfoximine in a mixer mill and used solid-state nuclear magnetic resonance (NMR) spectroscopy for structural characterization of the reaction products. Magic-angle spinning (MAS) NMR was applied for elucidating the product mixtures taken from the milling jar without introducing any further post-processing on the sample-of-interest. Ex-situ $^{13}$C-detected NMR spectra of ball-milling products showed the formation of a rather crystalline solid phase with the regioselective bromination of the $S$-aryl group of the heterocycle in position 4. Completion is reached in less than 30 minutes as deduced from the NMR spectra. The bromination can also be achieved by magnetic stirring, but then, a longer reaction time is required. Mixing the solid educts in the NMR rotor allows to get in-situ insights into the reaction and enables the detection of a reaction intermediate. The pressure alone induced in the rotor by MAS is not sufficient to lead to full conversion and the reaction occurs on slower time scales than in the ball mill, which is crucial for analysing mixtures taken from the milling jar by solid-state NMR. Our data suggest that on top of centrifugal forces, an efficient mixing of the starting materials is required for reaching a complete reaction.
Introduction

The influence of mechanical forces on chemical reactions has attracted chemists for many decades, for instance, due to the possibility of opening alternative synthetic pathways otherwise unachievable using different means of energetic input, such as light and temperature. The field of mechanochemistry has experienced enormous advances in the past years, reflected in versatile chemical and biological applications (for selected reviews see 6-23), ranging from the solid-state synthesis of inorganic materials, metal-organic and organic compounds, covalent organic frameworks, and polymers to enzymatic reactions and release of drug molecules from nucleic acids. The field employing mechanical energy input induced by grinding or milling is called trituration mechanochemistry and the approach has been used to develop synthetic protocols with superior results for a variety of organic reactions. On a laboratory scale, trituration mechanochemical reactions are generally performed in ball-milling devices, such as a mixer or planetary mills. Exemplary advantages of this technique are the environmentally friendly protocols, the often short reaction times, and product selectivity enhancement, which work together with an alternative and often unexpected reactivity, pointing to different reaction mechanisms under mechanochemical conditions than in solution.

Although mechanically-induced reactions have been studied for a long time in organic chemistry, a deeper understanding of the solid-state chemical changes and the underlying complex molecular-level mechanisms induced by mechanical forces is still in its infancy, mainly due to the physical limitations the common mechanical devices (e.g. fast oscillating and rotating parts in ball mills) impose on the accessibility of the analytical instruments. To tackle this problem and to gain control over mechanochemical reactions, time-resolved in-situ X-ray diffraction and X-ray absorption spectroscopy methods have been developed to monitor changes occurring inside the milling jar during mechanochemical transformations. Also, Raman spectroscopy has allowed unprecedented insights into the real-time kinetics of mechanochemical reactions during ball-milling events. Along these lines, nuclear magnetic resonance (NMR) spectroscopy, as a non-destructive and atom-specific technique, could enable molecular-level insights into the proceeding of mechanochemical reactions. However, the characterization of milled solid-state products by solution-state NMR raises the question of whether the reaction has occurred in the ball-milling device or, eventually, during the aftermath of work-up procedures or at the analysis stage.
To circumvent these issues, solid-state NMR is a convenient tool to investigate the ball milling reaction products while avoiding further manipulation of the obtained solid materials. For instance, this has been explored to follow the ball-milling reaction ex situ, e.g. by recording NMR spectra of the reaction products or of the solid mixture from a ball mill in discrete time steps. Additionally, van Wüllen and co-workers described an in-situ solid-state NMR setup based on integrating a ball-milling device into a static solid-state NMR probe, which has allowed them to access the kinetics of the mechanochemical formation of zinc phenylphosphonate from zinc acetate and phenylphosphonic acid in a ball mill. Very recently, also magnetic-resonance relaxation-time correlation experiments were proposed to investigate metal-organic framework formation upon ball milling.

Highly-resolved solid-state NMR spectra, however, typically require magic-angle spinning (MAS). The spinning induced pressure during MAS has been used, for instance, to study the kinetics of the mechanochemical halogen bond formation involving triphenylphosphine oxide and para-diodotetrafluorobenzene, to induce polymorphic forms of sodium acetate obtained by solid-state dehydration of sodium acetate trihydrate, and to observe the phase transitions (amorphous-to-crystalline and crystalline-to-crystalline) of active pharmaceutical ingredients (APIs), such as atorvastatin calcium, ezetimibe, and efavirenz. Nonetheless, the mechanistic insights uniquely offered by the NMR analysis of mechanochemically-induced reactions, are required to shed light on the often unprecedented reactivity in ball-milling devices. This study thus aims at systematically investigating the potential of MAS solid-state NMR in characterizing an organic reaction performed in a ball mill by ex- and in-situ methods.

While studying halogen bonding of sulfoximines, we also investigated co-crystallizations of cyclic scaffolds with brominating agents and found a fast bromination reaction when a cyclic sulfoximine (specifically, 2-methyl-3H-2λ4-benzo[c]isothiazole 2-oxide, in the following denoted as sulfoximine) was treated with NBS. This result motivated us to investigate this halogenation in more detail. We herein describe a bromination of 2-methyl-3H-2λ4-benzo[c]isothiazole 2-oxide with N-bromosuccinimide (NBS) performed in a mixer mill and its detailed solid-state NMR spectroscopic investigation (for previous halogenation reactions of arenes, see ). 13C-detected solid-state MAS NMR has been used to study the reaction products ex situ. Both, the brominated product and the formed succinimide, are unambiguously identified from their characteristic spectral fingerprints in 13C solid-state NMR spectra, which also allowed us to determine the optimum reaction time in the ball mill. Our first attempts to follow the reaction inside the NMR rotor (in situ), exploring the effects of centrifugal pressure...
during MAS, led to a partial product generation. The mixture of the two components was also dry stirred, which led as well to product formation, although in a significantly slower manner than in the ball mill. The data pinpoint to the importance of mixing to increase the reaction effective contact surface between the two solid starting materials at which the molecules can possibly undergo significant conformational rearrangements and solid-state molecular-recognition processes, all in all favoured by the ball milling processing. The solid-state NMR in-situ analyses even revealed the formation of an unexpected intermediate, both illustrating the potential of solid-state NMR characterization and highlighting the necessity of this approach for the mechanistic studies of solid-solid organic reactions. MAS solid-state NMR will contribute to a better mechanistic understanding of chemical reactions occurring in ball mills, which is crucial for the desired upscaling of mechanochemical reactions for industrial applications, but also to explore the potential of mechanochemistry further in many research fields ranging from catalysis, polymer sciences to biological applications.
Results and Discussion

The bromination of a sulfoximine in a mixer mill.

Scheme 1 shows the studied reaction of sulfoximine 1 with 1 equiv. of NBS 2 to give 4-bromo-sulfoximine 3 and succinimide 4. The reaction was performed on a 0.2 mmol scale in a mixer mill using a poly(methyl methacrylate) (PMMA) jar ($V = 15$ ml) with 10 zirconia balls ($\Theta = 5$ mm) at a mixing frequency of 25 Hz for a certain time (for images of the ball milling setup, see Figure S1).

Scheme 1: Mechanochemical bromination of the cyclic sulfoximine 1 with NBS 2 in a mixer mill, under various conditions. For details, see the Methods Section.

Ex-situ solid-state NMR enables characterizing the reaction products from a mechanochemically-induced bromination reaction.

Ex-situ solid-state NMR was employed to structurally elucidate the bromination reaction mixture taken directly from the ball mill without any further manipulation. Figure 1 shows the $^{13}$C cross-polarization (CP) spectra of the initial starting materials 1 and 2 (Figures 1a and b) and the product mixture of 3 and 4 after 90 minutes of ball milling (Figure 1c). While NBS 2 gives rather broad $^{13}$C resonances, probably because of the influences of the fast quadrupolar relaxation of the bromine and/or structural heterogeneity (low crystallinity), sulfoximine 1 provides highly resolved NMR signals. Narrow resonances were detected for the product mixture of 3 and 4 from the ball mill as well, indicating the presence of well-defined crystalline phases. The tendency to amorphization, which is sometimes induced under milling conditions, would have led to broadened NMR resonances. The assignment of the individual $^{13}$C resonances to the mixture of the two product species was carried out by comparing the spectrum of the ball-milled sample with the spectra of the starting materials 1 and 2 (Figures 1a and b) and of the two products 3 and 4 obtained by separate synthesis (4-bromo-sulfoximine) or purchased (succinimide), respectively. For the corresponding $^{13}$C spectra see also Figures 1d and e. And indeed, the $^{13}$C chemical-shift values of the isolated products agree well with the ones of the ball-milled products. While the succinimide resonances are virtually similar, the spectrum of the isolated product 3 reveals an additional set of smaller resonances assigned to an unknown

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**Scheme 1**

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\[ \begin{array}{c}
\text{1}  \\
\text{2 (NBS)}  \\
\text{ball milling}  \\
\text{3}  \\
\text{4}
\end{array} \]

\text{N-S=O} + \text{N-Br} \rightarrow \text{N-S=O} + \text{N-H}
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isomeric product which is absent in the ball-milled product. The brominated aromatic carbon resonance is directly identified from the spectra by a rather broad peak, caused by quadrupolar relaxation of the spin-$\frac{3}{2}$ $^{79}$Br/$^{81}$Br nuclei, as well as incompletely resolved $^{13}$C-$^{79}$Br/$^{81}$Br $J$-couplings influenced by the residual dipolar coupling which lead to an asymmetric quartet. The resonance assignments were further validated by $^{13}$C-detected dipolar-dephasing experiments, $^{15}$N CP-MAS spectra as well as $^1$H-detected $^1$H,$^1$H,$^1$C heteronuclear correlation spectra (see Supporting Information, Figures S2 and S3).

The $^{13}$C CH$_2$ and CO resonances of succinimide are rather sharp, both in the purchased succinimide (full-width at half maximum, FWHM, around 80 Hz for the CO resonances and 60 Hz for the CH$_2$ resonances) and in the succinimide formed in the ball mill (FWHM around 100 Hz for the CO resonances and 80 Hz for the CH$_2$ resonances), although there is some extent of broadening present in the succinimide obtained in the ball mill. The two methylene and carbonyl peaks have different chemical-shift values, the latter experiencing a chemical-shift separation of $\approx$4 ppm. This observation agrees with their crystallographic inequivalence revealed in the crystal packing of succinimide, in which only one carbonyl group is engaged in intermolecular hydrogen bonding with the amide proton (see Figure S4). We note that although the $^{13}$C chemical-shift values of purchased and mechanochemically synthetized succinimides are identical, the $^1$H longitudinal relaxation times ($T_1$) differ significantly by several orders of magnitude ($\approx$3500 s for the purchased succinimide without ball milling vs. $\approx$12 s for the succinimide in the reaction mixture taken after 2 h in the ball mill, see Figures S5a and b). The origin of this discrepancy might be related, among others, to different degrees of crystallinity affecting $T_1$ relaxation times (as also reflected in the slightly broader $^{13}$C resonances for the succinimide obtained upon ball milling, see above) or the formation of different succinimide phases, which we currently investigate further. We note that already 1 h of ball milling of purchased succinimide reduces the $^1$H $T_1$-values by one order of magnitude, although the $^{13}$C spectra reveal no chemical-shift changes (Figures S5c S6 and Table S1).
Figure 1: Ex-situ solid-state NMR reveals product formation during ball milling. Comparison of $^1$H→$^{13}$C CP-MAS spectra recorded at 16.4 T static magnetic-field strength of a sulfoximine 1, b NBS 2, c the mixture from the ball mill employing a milling time of 90 minutes 3+4, d synthesized brominated sulfoximine 3,74 and e purchased succinimide 4. The black arrows indicate chemical-shift changes between the sulfoximine 1 and the brominated sulfoximine 3 product. * indicate spinning sidebands. + resonances are attributed to an unknown isomeric product. The MAS frequency for the experiments was set to 17 kHz for a, b and e, 14 kHz for b and 20 kHz for d. Black dashed lines are guidance for the eye to highlight identical shifts.
between the products 3 and 4 separately synthesized or purchased and the ball-milled product mixture.

Next, we sought to determine the minimal reaction time required for a complete conversion of the starting material by bromination in the ball mill. To this end, several $^{13}$C CP-MAS spectra on samples from the ball mill with different milling times were measured (Figure 2). The spectra recorded on the samples exposed for 5 and 15 minutes of ball milling still showed an incomplete conversion of the starting material, especially evident from the signals of the unreacted sulfoximine 1 (highlighted by grey transparent rectangles in Figure 2). These signals disappeared from the spectra after 30 minutes of ball milling, which clearly indicates that the reaction under ball-milling conditions proceeded in a selective and fast way without significant amorphization, as deduced from the solid-state MAS NMR data.

**Figure 2:** The reaction in the ball mill is complete within 15 to 30 min. Comparison of $^1$H→$^{13}$C CP-MAS recorded at 16.4 T static magnetic-field strength for the solid material taken from the milling jar employing different ball milling times ranging from 5 min to 120 min. Resonances assigned to the sulfoximine (starting material 1) leftovers are highlighted by grey transparent rectangles. All spectra were recorded with 17 kHz MAS, except for the spectrum for 15 minutes ball-milling time, which was recorded at 14 kHz MAS. * denote spinning sidebands.
In-situ product formation using the spinning-induced pressures during MAS.

In light of the previous discussion, the repetitive dynamic mechanical stress that the ball milling action delivers in the forms of repeated pulsed impact pressure and shearing, together with the continuous stochastic mixing, causes an efficient bromination reaction. As a matter of fact, the MAS technique (see Figure 3a, for schematics) induces rather high centrifugal pressures, which increase quadratically with the MAS frequency and reach their maximum on the rotor walls (for the radial dependence see Figure S7 and for the mathematical treatment see Supplementary information). We have estimated the resulting centrifugal pressure on the inner rotor wall as a function of the MAS frequency applied for different rotor diameters (Figure 3b, for more details, see the SI, Table S2). Since our NMR experiments have been performed in 3.2 mm rotors (thin-walled, $V = 46.7 \, \mu\text{L}$) at a MAS frequency of 20 kHz, we expect pressure on the inner rotor wall of approximately 150 bar (Figure 3b, filled line). For the calculation, we assumed the density of the material inside the rotor to be the average of the crystallographic densities of the individual educts $1$ and $2$, which is around 1760 kg/m$^3$ and an homogeneously filled rotor, the latter being only a reasonable estimation at the beginning of the experiment, since upon MAS the material distributes non-uniformly (i.e. is compressed) along the rotor volume (see also Figure 3a). Previous studies have shown that such pressure value is only achieved directly on the rotor walls, not causing any pressure-induced conformational changes in biomacromolecules, for instance. Nonetheless, we tried to determine whether the centrifugal pressure throughout the whole effective volume of the MAS rotor is sufficient to already initiate our bromination reaction. In doing so, we filled a 1:1 molar ratio obtained by careful mixing (using a spatula) of starting materials $1$ and $2$ in the NMR rotor and recorded time-dependent $^{13}\text{C}$ solid-state MAS NMR spectra. Spectra for five representative time-points are shown in Figure 3d and indeed indicate product formation over a time course of several hours (see red transparent backgrounds for spectral regions characteristic for $^{13}\text{C}$ NMR resonances of products $3$ and $4$). In Figure 3c we further demonstrate that it is possible to follow and quantify the real-time kinetics of in-situ product formation, by evaluating the time-dependent changes in the signal intensities of some representative product peaks over the course of the experiments. Indeed, an initial consistent increase in the integrated intensities of the two peaks can be observed, indicating the gradual progression of the mechanochemical reaction in-situ in the rotor. After approximately 40 h of continuous spinning, the peak intensities reach a plateau, at which point no further product formation is detected. Similar to the real-time kinetic data obtained by van Wüllen et al. with their static in-situ solid-state NMR setup, we assumed that the in-situ reaction proceeded following – to a first approximation – a first-order kinetic reaction.
model and, thus, we performed mono-exponential fits of the integrated intensities of two peaks for products formation (Figure 3c) to determine the rate constants of the reaction (for more details, see the Supporting Information). For the peaks considered in the data progression (the C(1) and CH₃(8) resonances, see Figure 1 for the nomenclature), rate constant values of $0.10 \pm 0.02\ h^{-1}$ and $0.11 \pm 0.02\ h^{-1}$, respectively, were obtained for the conversion to products. Note that these values should be interpreted only qualitatively due to the rather large scattering of the data points caused by the low signal-to-noise ratios and possible probe instabilities over the course of the experiment (resulting in $R^2$-values of 0.61 and 0.51, respectively). We can further infer that an eventual induction period, which has been hypothesized and described for mechanochemically-induced reactions, must be very short as it remained unobservable in our in-situ NMR approach.

After more than four days of continuous spinning, approximately 20% of the product was formed in situ, under the effect of MAS-induced centrifugal pressure (Figure S8). It is thus evident that the reaction occurs much slower inside the NMR 3.2 mm rotor compared to the reaction in the ball mill (see also the rate constants mentioned above) and by far not to completion. Hence, at this point, we can conclude that the centrifugal pressure during MAS alone is insufficient for the reaction to proceed and that particularly the missing mixing process – which is present in the ball mill – is relevant for the differences in the kinetics and the incomplete product formation. Efficient mixing of the starting materials within the NMR rotor typically occurs only at the beginning of the MAS experiment, whereas after some time the powdered sample is pressed against the rotor wall due to spinning. At this point, the in-situ product formation gradually stops, since only solid-state diffusion might lead to further mixing at the molecular level. This process, however, is rather slow (possibly in the order of weeks, vide infra), since no significant product increase is observed after the plateau is reached (Figure 3c). The slower product formation kinetics however is essential for analysing the mixtures taken from the ball milling jar by solid-state NMR.

Figure 3a shows a picture of a broken 3.2 mm rotor (which happened during external handling) for the 1:1 mixture of the two starting materials. The material is entirely adhering to the rotor wall caused by the strong centrifugal pressures (Figure 3b). We further noticed that in-situ reactions performed without actively cooling the rotor (causing the sample to heat up due to frictional heating of the rotor and the bearing gas used for MAS by around 25 °C 91, 92) led to a colour change of the material inside the rotor (a brownish material was observed) and rather broad $^{13}$C NMR resonances, pointing towards a radical-induced polymerization reaction (see Figure S9 for the colour change of the material and resulting broad spectrum and Figure S10
for time-dependent spectra). This finding further supports the strength of ball milling in shortening the reaction times, thereby suppressing unwanted side reactions.

*Detecting an intermediate phase in the in-situ solid-state NMR experiments.*

An additional interesting observation was made with respect to the carbonyl resonances of the formed succinimide 4. In the first hours of the in-situ investigation, two sharp resonances at 181.1 and 183.7 ppm were formed, one of them shifted by around 2 ppm to lower frequencies compared to the spectra of succinimide formed upon ball-milling or the purchased succinimide (Figures 1c and e, resonances at 181.1 ppm and 185.7 ppm, denoted with CO). Upon longer reaction times, however, the CO resonance at 183.7 ppm experienced a shift to higher frequencies, to the ppm-value previously measured for succinimide (Figures 1c and e, ~185.7 ppm). We assume that the formed succinimide molecules in the NMR rotor were initially embedded in a sulfoximine phase (both being starting material 1 and brominated product 3) and only over time, they began to form the pure succinimide phase with the presence of dimeric succinimide molecules (Figure S4). This conclusion is further supported by the solid-state NMR spectra obtained on a 1:2 mixture (molar ratios) of NBS 2 and sulfoximine 1 exposed to 60 min ball milling. Here, indeed, the succinimide carbonyl resonances are shifted with respect to succinimide formed after ball milling of a 1:1 molar ratio mixture of the starting materials (Figure S11) possibly pointing to a phase in which succinimide molecules are embedded in a sulfoximine phase. The mixing of only NBS 2 and succinimide 1 in the ball mill does not induce chemical-shift changes with respect to “pure” succinimide (for the spectra with different molar ratios see Figure S12).
Figure 3: The centrifugal pressure in the MAS rotor can be used to induce in-situ product formation. a Schematic representation of a MAS rotor highlighting the centrifugal pressure acting on a rotor wall, as well as an image of a broken 3.2 mm rotor after spinning a 1:1 mixture of starting materials, b estimated centrifugal pressure acting on the inner rotor wall as a function of the MAS frequency for several rotor sizes,\textsuperscript{86,93} c time-dependent integrated intensities for two representative product peaks together with their relative mono-exponential fits, to follow the (first-order) kinetics of reaction conversion with real-time solid-state NMR, d overlay of $^1\text{H}\rightarrow^{13}\text{C}$ CP-MAS spectra recorded at 11.7 T of static magnetic-field strength of the bromination reaction occurring in the MAS rotor taken at different time points (the resonance numbering follows the one in Figure 1). The red transparent rectangles indicate spectral regions characteristic of products 3 and 4. All spectra were recorded at 20 kHz MAS frequency.

Increasing the contact surface by stirring also induces product formation – but slower.

To further disentangle the influences of pressure and mixing on the studied bromination reaction, the two starting materials were dry stirred in the absence of light for 14 h on a magnetic-stirring device and solid-state NMR spectra of the obtained material were recorded. A comparison of the spectrum of the stirred sample (Figure 4b) with the one obtained after 30 minutes of ball milling (Figure 4a), reveals clearly visible product resonances (highlighted by grey rectangles in Figure 4). Even though the bromination was not quantitative, ~60% of product was formed solely by stirring. Although the time scale of the reaction was still orders of magnitude longer than in the ball mill, the clean product formation pinpoints to the importance of the mixing process. Such stochastic mixing is certainly more efficient in the ball mill and rather inefficient in the NMR rotor when correlated with the amount of observed product formation. A similar effectiveness of a simple mixing, without the actual action of grinding, for mechanochemical reactions has also been reported for acoustic resonant mixing.\textsuperscript{94} However, we note that frictional forces and grinding might also be present during stirring on a magnetic-stirring device. Interestingly, a quite small amount of product was also observed by only mixing a 1:1 molar ratio of the starting materials and storing it at R.T. for 56 days (Figure S13) highlighting a slowly occurring “contact reaction” based on solid-state diffusion, which is further slowed down at lower temperature (see Figure S13a for an identical sample stored at –18 °C for 46 days). Note that the sample stored at R.T. showed also broader spectral features, eventually revealing similarities with the results obtained without temperature control (\textit{vide infra}) (Figure S13).
Figure 4: Stirring leads to around 60% of product formation in 14 h. Overlay of $^1$H→$^{13}$C CP-MAS spectra of a 30 min ball-milled product mixture, b starting materials exposed to 14 h stirring in the dark at ambient conditions, c starting materials after 16 h of IR press and d ball milled starting materials without zirconia balls. In all cases, a 1:1 molar ratio of educts 1 and 2 was used. Grey transparent rectangles highlight the resonances indicating product formation. Spectra in a, b and d were recorded at 16.4 T of static magnetic-field strength, while the spectrum in c was recorded at 11.7 T. The MAS frequency was set to 17 kHz for a and 20 kHz for b, c and d.

Pressure in the absence of mixing is not sufficient to induce the reaction.

In order to further disentangle the effects of constant pressure from the mixing action on the reaction, the system was subjected to compression by an infrared (IR) press. Figure 4c shows the $^{13}$C CP-MAS spectrum recorded on a 1:1 molar ratio mixture of 1 and 2 exposed to an IR
press for 16 h. Assuming a pellet diameter of 13 mm inside the anvil, the induced pressure was calculated in the order of 7500 bar. Despite the elevated uniaxial pressure, higher than the one developed in the spinning rotor, the spectrum shows nearly no product formation. Thus, constant pressure alone did not lead to product formation, being in agreement with the aforementioned solid-state NMR experiments.

*Increasing the amount of NBS allows for a double bromination reaction.*

In light of the observed clean and fast bromination of the sulfoximine in the 4-position of the S-aryl group, a double bromination of 1 was attempted in analogy to previously reported mechanochemical halogenations with NBS 2. Thus, milling 2 equiv. of NBS with respect to the sulfoximine 1 (molar ratios) was tested. Figure 5a shows the $^{13}$C CP-MAS spectrum of the ball-milled material (2:1 ratio NBS:sulfoximine). For comparison, in Figure 5b the spectrum of the 4-brominated sulfoximine 3 obtained by ball milling is depicted. From those data, we conclude that the intended double bromination had indeed taken place and that the aryl group of the sulfoximine had been halogenated at positions 2 and 4 to give product 5. Solution-state NMR and the solid-state NMR spectrum on 2-brominated sulfoximine 6 support this analysis (see Figures S14-S15 and S16).

![Figure 5: Doubly brominated sulfoximine obtained in the ball mill. Comparison of $^1$H→$^{13}$C CP-MAS spectra of a the solid material [consisting of 2,4-brominated sulfoximine 5 and succinimide 4] taken from the ball mill employing a 1:2 molar ratio of starting materials 1 and 2, b the mixture from the ball mill employing a milling time of 90 minutes [consisting of 4-brominated sulfoximine 3 and succinimide 4]. The spectrum in a was recorded at 11.7 T static magnetic-field strength, while the spectrum in b was recorded at 16.4 T. The MAS frequency was set to 20 kHz for a, and 17 kHz for b. The spectrum in panel a shows significant FID](image)
truncation effects for the succinimide resonances, which originate from the too short acquisition time employed for the measurement.

**Conclusions**

We investigated the mechanochemical bromination of a cyclic sulfoximine with NBS in a mixer mill by solid-state NMR. The products obtained from the mill feature sharp $^{13}$C resonances pointing to rather crystalline phases. They can be clearly assigned to the product with a bromo substituent located at position 4 of the aryl group. Appealing synthetic aspects of the mechanochemically conducted reaction are the high regioselectivity of the bromination, the short reaction time (less than 30 minutes for a full conversion to the desired products), and a strict stoichiometric dependence with respect to the amount of NBS.

We analyzed the effect of constant pressure on the solid-solid reaction and distinguished it from the effect of a pulsed or time-variated compression present inside of a milling jar. For doing so, advantage was taken of the MAS-induced centrifugal pressure on the MAS rotor walls (of the order of 150 bar) in combination with constant NMR readings of the mixture. The pressure exerted inside the rotor, in combination with the induced partial mixing of the reactants in the initial time of the experiment, was sufficient to generate small product amounts (< 20%) on a time scale of several hours. The kinetics of the product formation in the NMR rotor was analyzed, and an intermediate phase was detected by in-situ NMR measurements. The finding points to the unique characteristics that ball milling procedures have in generating tight molecular packings for effective reactions. The fact that the centrifugal pressure induces the reaction on slower time scales than in the ball mill is an important requirement for analyzing mixtures taken from the milling jar by solid-state NMR.

The importance of efficient mixing was illustrated by stirring the starting materials with a magnetic stirrer, which led to significant product formation (~60%) as well. Compared to ball milling, however, that time scale is about an order of magnitude longer. The constant pressure applied in an IR press was not sufficient to induce the reaction. This clearly shows the need for efficient mixing for the bromination reaction to occur, which, more generally, demonstrates how rates of solid-solid reactions dramatically depend on the contact surface between the reagents. Individual molecules must possess a certain degree of conformational freedom being essential for solid-state molecular recognition through specific non-covalent bonds such as $\pi$-$\pi$ and hydrogen bonding. Similar conclusions were drawn, for instance, in solid-state hydrogenation reactions of frustrated Lewis pairs from molecular dynamics simulations.
short reaction time in the ball mill also avoids unwanted side-reactions, such as the one observed at higher temperatures in the NMR rotor. Our study is only a first step towards the application of solid-state NMR to unravel the mechanism of mechanochemically-induced organic reactions, which is crucial for further expanding the chemistry of this strongly emerging field.

**Author contributions**

C.S., F.P. and R.P. prepared the samples. E.B., L.H., R.D. and T.W. recorded solid-state NMR spectra. E.B., C.S., F.P. and L.H. analyzed data with the support of all co-authors. All authors contributed to the writing of the article. C.B. and T.W. designed and supervised the research.

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Methods and Materials

Synthesis.

Samples of (brominated) sulfoximines were prepared according to a reported literature method. The used samples were obtained from that particular project.⁷⁴

Mechanochemical bromination: A 15 mL PMMA jar equipped with 10 ZrO₂-Y balls (Ø = 5 mm) was charged with sulfoximine 1 (33.4 mg, 0.200 mmol) and NBS (2, 1.00 equiv. or 2.00 equiv. in the case the double bromination was performed) in the given order. The jar was closed and placed in a MM400 mixer mill. The reaction mixture was milled at a frequency of 25 Hz for the indicated time (5 min–120 min). Then, the resulting solid reaction mixture was analyzed.

Control experiments – stirring: A 4 mL screw cap vial equipped with a magnetic stirring bar was charged with sulfoximine 1 (33.4 mg, 0.200 mmol) and NBS (2, 35.6 mg, 0.200 mmol, 1.00 equiv.) in the given order. The vial was closed with a cap, packed in aluminium foil, and the reaction mixture was stirred at room temperature for 14 h. Then, the solid reaction mixture was analyzed.

Control experiments – IR pellet press: A 4 mL screw cap vial was charged with sulfoximine 1 (83.6 mg, 0.500 mmol) and NBS (2, 89.0 mg, 0.500 mmol, 1.00 equiv.) in the given order. The vial was closed and shaken manually to ensure a mixing of the two powders. With the help of a spatula, 50.0 mg of this mixture was loaded into the anvil of an IR manual hydraulic press. The powders were compressed for 1–16 hours at a developed force of 10 tons. Then, the solid pellet was gently crushed with the tip of a spatula, and the solid reaction mixture was analyzed.

Note: The NBS used for all transformation was freshly recrystallized from water and stored under light exclusion at –18 °C.

Solid-state NMR.

A complete overview of the experimental parameters for all NMR spectra is reported in the SI in Table S3. ¹³C detected solid-state NMR experiments were acquired at 11.7 and 16.4 T static magnetic-field strengths in Bruker 3.2 mm probes (a prototype triple-resonance probe as a loan of Bruker Biospin and a standard triple-resonance probe, respectively). ¹H detected solid-state NMR spectra were acquired at 16.4 T static magnetic field strength in a Bruker 1.3 mm double-resonance probe. The MAS frequency for ¹³C-detected ¹³C CP spectra was set to 14 kHz, 17 kHz and 20 kHz (see Table S3), while the MAS frequency for ¹H detected spectra was set to 60 kHz. All spectra were processed with the software topspin (versions 3.6.4 and 4.1.3, Bruker
Biospin). 2D $^1$H-$^1$H spin-diffusion spectra were processed with a shifted (2.0) squared cosine apodization function, while 2D $^1$H-$^{13}$C hCH spectra were processed with a shifted (2.0) squared cosine apodization function and automated baseline correction in direct and indirect dimensions. 2D spectra were analyzed with the software CcpNmr$^{102, 103}$ (version 2.4.2). For the target sample temperatures during acquisition, we refer to Table S3. These temperatures were determined from a temperature calibration using KBr. All spectra were referenced to adamantane based on the tetramethyl silane (TMS) scale, for which the methylene resonance is set to 38.56 ppm.$^{104}$

In-situ real-time solid-state NMR: The in-situ reaction was conducted by carefully mixing a 1:1 molar ratio of starting materials 1 and 2 using a spatula. The mixture was packed in the solid-state NMR rotor, and a piece of Teflon was put on top before closing the rotor.

Kinetic model: The peak intensities of $^{13}$C product resonances for the in-situ mechanochemical bromination reaction were determined by manually extracting individual signal-to-noise values ([a.u.]) from the 1D spectra via the build-in TOPSPIN module SiNo (signal-to-noise calculator, intensity of a peak divided by the square of the noise intensity). From the time-dependent series, data points were normalized to account for the plateau in product formation and also to consider the sole presence of starting materials at the beginning of the series of measurements. The last data point in the in-situ product formation was normalized to one for the plateau. Data visualization and processing of the peak intensities of interest were performed in Origin 2020b. Fitting of the data was carried out assuming a first-order kinetics, for which product formation follows a mono-exponential law. For more details we refer to the SI.
References