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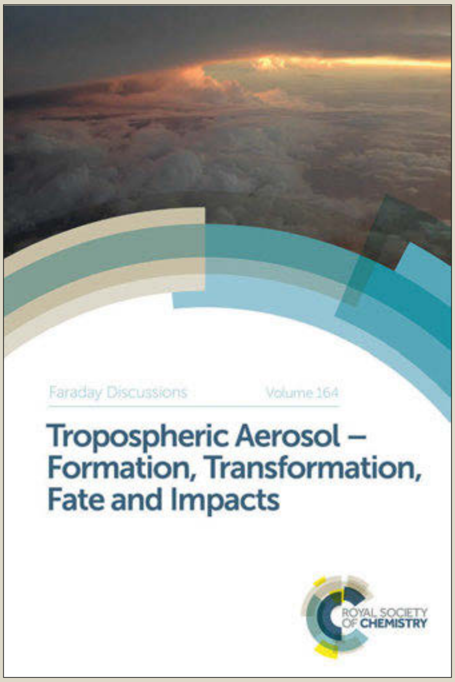

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Liquid-assisted vortex grinding supports the single-step solid-state construction of a [2.2]paracyclophane

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We employ vortex grinding to generate a [2.2]paracyclophane in the organic solid state. The vortex grinding is aided with the addition of a small amount of liquid phase to facilitate topochemical [2+2] photodimerizations that generate the cyclophane stereoselectively and in up to quantitative yield. The use of the liquid phase increases the scope of the vortex method.

1 Introduction

Mechanochemistry can be defined as chemical synthesis induced by external mechanical energy, such as grinding two solids using a mortar-and-pestle.[1] Historically, mechanochemistry has been more of a secondary approach to organic synthetic chemistry as compared to mainstream liquid-phase synthesis.[2] However, recent years have witnessed a rapid development in the use of mechanochemistry to generate organic molecules,[3] as well as supramolecular assemblies and frameworks.[4] A reason behind such increased development is related to the fact that mechanochemistry can facilitate reactions that result in covalent and/or noncovalent bonds that afford products difficult or even impossible to achieve via the liquid or solution phase.[5] Mechanochemistry can also offer more efficient, practical, and inherently safer approaches to synthesis.[6] To fully employ mechanochemistry to generate molecular and supramolecular products of increasing complexity, as well as products connected to more mainstream chemistry, however, it will be necessary to develop deeper understandings of underlying mechanisms, principles, and scopes of the approach. With this in mind, we present here an application of a recently reported form of mechanochemistry known as vortex grinding[7] to facilitate the formation of the [2.2]paracyclophane **1** (Scheme 1). Specifically, we show that while dry vortex grinding alone fails to generate **1** in substantial amounts, the use of a small amount of liquid phase enables vortex grinding to generate the [2.2]paracyclophane stereoselectively and in up to quantitative yield. We expect the integration of the liquid constituent to allow vortex grinding to be applied more generally to synthesize molecules of increasing complexity in organic solids.

Vortex grinding

Automated techniques to perform mechanochemical reactions and transformations (e.g. ball mills) as replacements to mortar-and-pestle grinding are attractive not only to alleviate manual work but to achieve reproducibility and minimize cross-contamination.[8] In this context, we have reported a method to facilitate topochemical [2+2] photodimerizations in the solid state that is based on vortex grinding.[7] In our research, we employ small ditopic molecules as templates (e.g. resorcinol, 1,8-naphthalenedicarboxylic acid, Rebek's imide) to assemble olefins into prerequisite geometries for photodimerizations in organic solids.[9,10] The templates assemble the

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olefins via hydrogen bonds within two-component solids in the form of co-crystals. Moreover, we have recently demonstrated that the vigorous shaking and vibrations provided by a simple and inexpensive vortex mixer can be used akin to mortar-and-pestle grinding to generate photoreactive co-crystals involving templates. The co-crystals are generated in small, transparent sample vials that are loaded with two metal balls or BBs (Fig. 1). The relatively small size of the vortex apparatus allows the hydrogen-bonded co-crystals to be generated within standard laboratory-sized photochemical reactors such that the grinding and application of ultraviolet (UV) light are applied simultaneously. To date, the method has only been applied for a photodimerization of the monoolefin *trans*-4,4'-bis(4-pyridyl)ethylene) that reacted to form *rctt*-tetrakis(4-pyridyl)cyclobutane. The monocyclobutane formed under completely dry, or neat, conditions stereoselectively and in quantitative yield.

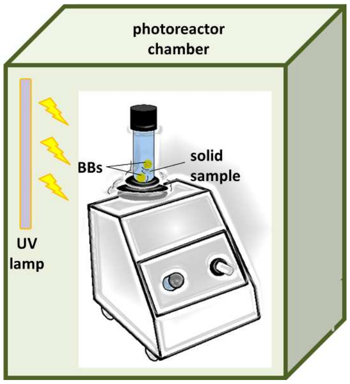

Fig. 1 Schematic vortex grinding apparatus with application of UV radiation**.**

Given that ditopic templates can assemble higher olefins (e.g. dienes) that react to form higher cyclobutanes as photoproducts (e.g. cyclophanes, ladderanes),[11],[12] we were led to consider whether vortex grinding can be applied to generate **1**. Our selection was guided by the ready availability of both the template (4-benzyl-resorcinol or **4-benz-res**) and precursor diene (*p*-di[2-(4-pyridyl)ethenyl]benzene or **1,4-bpeb**), as well as a mechanistic knowledge of the photoreaction producing an intermediate monocyclobutane[13] when 2(**4-benz-res**)·2(**1,4-bpeb**) reacts to give **1**. From our studies, we demonstrate here a critical role of the use of a small amount of liquid phase to support the formation of **1** using the vortex method. It is well known that small amounts of liquid can be used to generate hydrogen-bonded co-crystals using mortar-and-pestle grinding.[14] Compared to dry grinding, such liquid-assisted grinding (LAG) can be faster, offer better yields, and generate solids of relatively high crystallinities. It has been suggested that the use of the liquid phase in LAG serves to enhance molecular diffusion without a dependence on solvent effects so as to essentially provide an ideal environment to explore molecular recognition and self-assembly.[15] Here, we employ liquid-assisted vortex grinding (LAVG) to generate **1** in a single step with outcomes that parallel the more conventional two-step solution growth approach (Fig 2).

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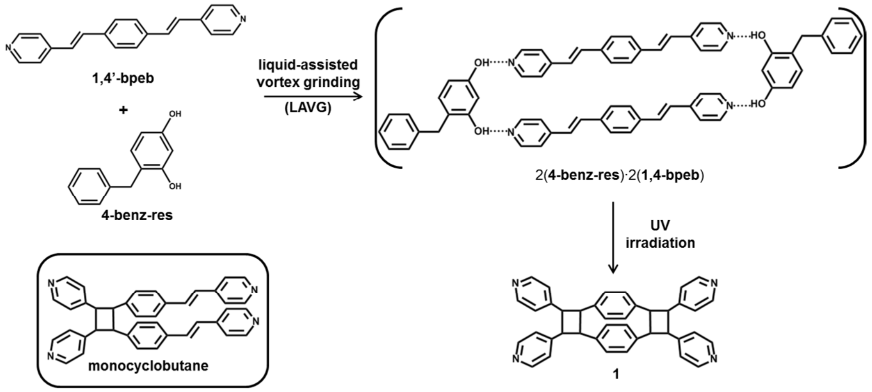

Fig. 2 Solid-state synthesis of **1** via LAVG combined with UV irradiation**.**

2 Experimental

Materials

1,4-bpeb was prepared as reported.[16] **4-benz-res** was purchased from TCI Tokyo Chemical Industry Co., LTD. and was used as received. Methanol was purchased from Sigma-Aldrich and used as received. ^{1}H NMR spectra were collected using a Bruker 300 MHz spectrometer and DMSO-d_6 as solvent. Powder X-ray diffraction (XRD) data were collected on a Bruker D-5000 diffractometer equipped with a Bruker SOL-X energy-sensitive detector using Cu K_α radiation (λ=1.54056 Å). Vortex grinding was performed using a VWR vortex mixer type Vortex Genie 2. All photoreactions were carried out in a photoreactor chamber equipped with a broadband, low-pressure UV lamp with a quartz Hg arc, Hanovia lamp, model number PC451.050 and ACE Glass Inc. Power supply: 230 V, 50 Hz, 450 W. Borosilicate glass vial of dimensions 21 x 70 mm were used as sample vials along with premium grade steel BBs (5 mm diameter) washed with soap, water, and acetone.

Manual grinding

In a typical grinding experiment, 50 mg of **1,4-bpeb** and 35 mg of **4-benz-res** (1:1 molar ratio) were placed in a mortar-and-pestle and ground for up to 1 h. The solid was analyzed using XRPD. LAG experiments were conducted in the same manner save for a single drop of methanol (50 µl) being added to the solid mixture. The resulting solid samples were then spread between glass plates and exposed to UV irradiation for a period of up to 120 h.

Vortex grinding

In a typical experiment, 50 mg of **1,4-bpeb** and 35 mg of **4-benz-res** (1:1 molar ratio) were placed in a capped sample vial with two metal BBs. The vial was mounted onto the vortex mixer and secured to a ring stand with a test tube holder. The samples were ground up to 1 h. The LAV vortex grinding was conducted in the same manner except for a single drop of methanol or nitromethane (50 µl) being added to the sample vial. To simultaneously conduct LAVG and UV irradiation, the vortex assembly was placed in the photochemical reactor, being approximately 15 cm from the UV lamp. Upon initiation of the vortex mixer, the photochamber was

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closed and sample was exposed to UV radiation for a period of 10 h.

3 Results and discussion

Initially, we subjected a mixture of **4-benz-res** and **1,4-bpeb** (1:1 molar ratio) to dry mortar-and-pestle grinding for a period of 1 h. A powder XRD analysis demonstrated partial formation of the co-crystal 2(**4-benz-res**)·2(**1,4-bpeb**) along with crystalline phases consistent with **4-benz-res** and **1,4-bpeb** (Fig. 3). Moreover, when the ground solid sample was exposed to broadband UV-radiation for a period of 60 h, the [2.2]paracyclophane **1** formed, along with intermediate monocycle (yield: 5 %), in relatively low yield (yield: 35 %). Neither **1** nor the monocyclized product formed in significantly greater amounts beyond 60 h of irradiation time. For comparison, **1** forms stereoselectively and in up to quantitative yield when the co-crystal 2(**4-benz-res**)·2(**1,4-bpeb**) that is grown from solution is subjected to UV light for a period of 20 h. An application of LAG using methanol was also unsuccessful in affording **1** in appreciable amounts. Specifically, a powder XRD diffractogram with peaks similar to the solid obtained via dry mortar-and-pestle grinding was obtained when **4-benz-res** and **1,4-bpeb** were ground for a period of 1 h in the presence of methanol (50 μL). UV-irradiation of the solid for 60 h also generated a mixture of **1** (yield: 38 %) and the monocyclized photoproduct (yield: 8 %) in comparatively low yields.

Table 1. Mechanochemistry involving **4-benz-res** to generate **1** from **1,4-bpeb**.

grinding conditions	**grinding time (h)**	**UV-irradiation time (h)**	**yield monocycle (%)**	**yield 1 (%)**
dry mortar-and-pestle	1	60	5	35
LAG-methanol	1	60	8	38
dry vortex then UV	1	60	9	38
LAVG-methanol then UV	1	20	2	97

We next turned to vortex grinding. In particular, when 50 mg of **4-benz-res** and 35 mg of **1,4-bpeb** (1:1 molar ratio) were placed in a transparent sample vial along with two metal BBs and subjected to vortex grinding for a period of 1 h, a powder XRD pattern similar to the pattern from the manual grinding experiments was obtained. Moreover, exposure of the solid to broadband UV-radiation for a period of 60 h also generated **1** (yield: 38 %) and the monocyclized product (yield: 9 %) in relatively low yields.

While the dry and LAG conditions involving mortar-and-pestle grinding, as well as dry vortex grinding, to form **1** quantitatively were unsuccessful, an application of vortex grinding in the presence of a small amount of methanol was successful.

In the experiment, a single drop of methanol (50 μL) was added to a solid mixture of **1,4-bpeb** and **4-benz-res** (1:1 molar ratio) in a capped sample vial containing the two BBs. The vial was then subjected to vortex grinding for a period of 1 h. Remarkably, in contrast to dry vortex grinding, the resulting powder XRD pattern matched the simulated pattern of the single-crystal X-ray structure of 2(**4-benz-res**)·2(**1,4-bpeb**) (Fig 3).[12] Exposure of the solid sample to UV-radiation for 20 h resulted in the stereoselective and near quantitative conversion of **1,4-bpeb** to **1**. The addition of the liquid phase, or application of liquid-assisted vortex grinding

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(LAVG), thus, served as a suitable mechanochemical method to generate **1** as compared to solution-grown 2(**4-benz-res**)·2(**1,4-bpeb**).

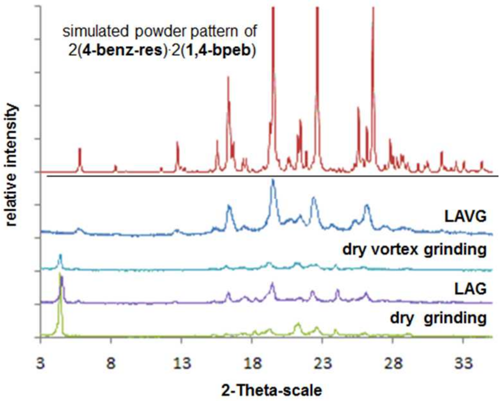

Fig. 3. X-ray powder patterns of solid mixture of **4-benz-res** and **1,4-bpeb** after being subjected to different mechanochemical methods.

A successful application of LAVG was also achieved when the vortex grinding and application of UV light were performed simultaneously or in a single step. A mixture of **1,4-bpeb** and **4-benz-res** along with one drop of methanol were placed in a sample vial that was mounted on the vortex mixer. The assembly was then placed in the photochemical reaction chamber and the vial was exposed to UV-radiation under continuous vortex grinding. A ^{1}H NMR spectrum of the solid collected after a period of 4 h displayed peaks that correspond to the intermediate monocycle (yield: 16 %) and **1** (yield: 60 %). Moreover, a photoreaction to generate **1** stereoselectively and in near quantitative yield (yield: 97%) was complete in a period of approximately 10 h. The LAVG experiments were also successfully conducted using nitromethane as the liquid component. Thus, in addition to generating **1** in a single step, the photoreaction involving LAVG proceeded two times faster than the irradiated solution-grown co-crystals. We ascribe success of LAVG compared to LAG to form **1** to external stress exerted by the BBs in the vortex mixer, which may be comparable to a vibrating ball mill (i.e. 'shakers'). There may also be appreciable liquid vapour present in the vial during the grinding[17,18] that contributes to the formation of **1**. We note that exact reasons behind dramatic effects of liquid on grinding, however, remain to be fully studied and understood.[19]

4 Conclusion

In this report, we have employed methods of mechanochemistry to generate the [2.2]paracyclophane **1** via topochemical [2+2] photodimerization in the organic solid state. We have demonstrated the ability of LAVG to afford access to **1** stereoselectively and in near quantitative yield. The results demonstrate viability of LAVG as a practical approach to a complex organic molecule. We are now exploring applications of vortex grinding as a means to generate additional architecturally-rich molecules in solids.

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