General application of mechanochemistry to templated solid-state reactivity: rapid and solvent-free access to crystalline supermolecules†‡

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Received (in Austin, TX, USA) 24th July 2008, Accepted 27th August 2008
First published as an Advance Article on the web 30th September 2008
DOI: 10.1039/b812728j

Supermolecules with olefins organized by hydrogen-bond donor and acceptor templates and that react in the solid state rapidly form co-crystals *via* solvent-free and liquid-assisted grinding.

Solvent-free and liquid-assisted preparations of molecular co-crystals are rapidly expanding areas in solid state, supramolecular, and green chemistry.[1] Both mechanochemical methods have been used to synthesize co-crystals of both fundamental (*e.g.* synthon formation) and technological relevance (*e.g.* pharmaceuticals). Co-crystals with molecules that react to form covalent bonds are attractive for the synthesis of molecules that may otherwise be difficult to obtain from the liquid phase. In this context, ditopic molecules, in the form of templates, have emerged as reliable tools to direct covalent-bond-forming reactions in crystalline solids.[2] The templates assemble and preorganise reactants within discrete (*i.e.* 0D) assemblies of molecules, or supermolecules, for single and multiple reactions. Importantly, the localised structure of a supermolecule decouples undesired effects of long-range packing from stringent geometry criteria[3] that dictate whether a reaction will proceed in a solid. This is particularly true in the case of a bimolecular reaction where the positioning of two reactants, in the absence of a template, will be under strict control of a crystal lattice.[4] The utility of directing the formation of covalent bonds within supermolecules has also recently been demonstrated by evidence that suggests that templates can direct reactions within polycrystalline and/or amorphous solids.[5] Indeed, by combining mechanochemistry with methods that reliably direct the formation of covalent bonds in solids, stereocontrolled and solvent-reduced routes to a variety of molecular products can be developed.[6]

With this in mind, we report here the ability of a series of reactive hydrogen-bonded crystalline supermolecules to form *via* solvent-free and liquid-assisted mortar-and-pestle grinding.[7] We reveal supermolecules in co-crystals based on resorcinol (**res**) of general composition 2(**res**)·2(**4,4′-bpe**)[2] (where: **4,4′-bpe** = *trans*-1,2-bis(4-pyridyl)ethylene) to form *via* solvent-free grinding within periods of minutes. In these solids, **res** acts as a hydrogen-bond donor template that assembles **4,4′-bpe** for a stereocontrolled [2 + 2] photodimerisation that generates *rctt*-tetrakis(4-pyridyl)cyclobutane (**4,4′-tpcb**) in 100% yield (Scheme 1). To generalize the approach, we describe two recently reported crystalline supermolecules 2(**2,3-nap**)·2(**fum**)[2] and 2(**1,8-dpn**)·2(**fum**)[8] (where: **2,3-nap** = 2,3-bis(4-methylenethiopyridyl)naphthalene; **1,8-dpn** = 1,8-bis(4-pyridyl)naphthalene; **fum** = fumaric acid) to form *via* mortar-and-pestle co-grinding. In these solids, **2,3-nap** and **1,8-dpn**, in contrast to **res**, act as hydrogen-bond acceptor templates, assembling **fum** for a photodimerisation that generates *rctt*-cyclobutanetetracarboxylic acid (**cbta**) stereospecifically in up to 100% yield. In contrast to 2(**res**)·2(**4,4′-bpe**), however, we have determined that liquid-assisted grinding[7] is required to generate both supermolecules.

The [2 + 2] photodimerisation of olefins can be considered the most widely-studied organic solid-state reaction. Despite being widely studied, applications of mechanochemical solvent-free and liquid-assisted methods to prepare solids that undergo the photodimerisation have been relatively rare. The lack of applicability of mechanochemistry to this reaction can be attributed to frustrating effects of crystal packing,[4] which have largely prohibited the development of reliable and systematic methods to direct the photoreaction in solids. Pioneering work of Toda demonstrated that mortar-and-pestle grinding can generate host–guest materials with channels that accommodate ketones that undergo the reaction.[9] Similarly, solvent-free grinding has been used to prepare reactive host–guest materials based on β-cyclodextrin and cucurbit[8]uril.[10] More recently, Shan and Jones used liquid-assisted grinding to prepare co-crystals of 1,2,4,5-benzenetetracarboxylic acid (**bta**) and **4,4′-bpe**.[11] In contrast to a discrete supermolecule, the components formed the infinite 1D hydrogen-bonded polymer (**bta**)·2(**4,4′-bpe**), which reacted to give **4,4′-tpcb** in up to 100% yield. Given the recent successes of templates based on **res** to direct the photodimerisation in crystalline supermolecules so as to generate synthetically appealing molecules such as ladderanes and a [2.2]paracyclophane,[2] we sought to apply mechanochemistry to the **res** system.

Initally, we subjected a mixture of **res** and **4,4′-bpe** (1 : 1 molar ratio) to dry mortar-and-pestle co-grinding for a period of 1 h. Our selection of the 1 h time period was based on the study of Shan and Jones[11] where co-crystallization of

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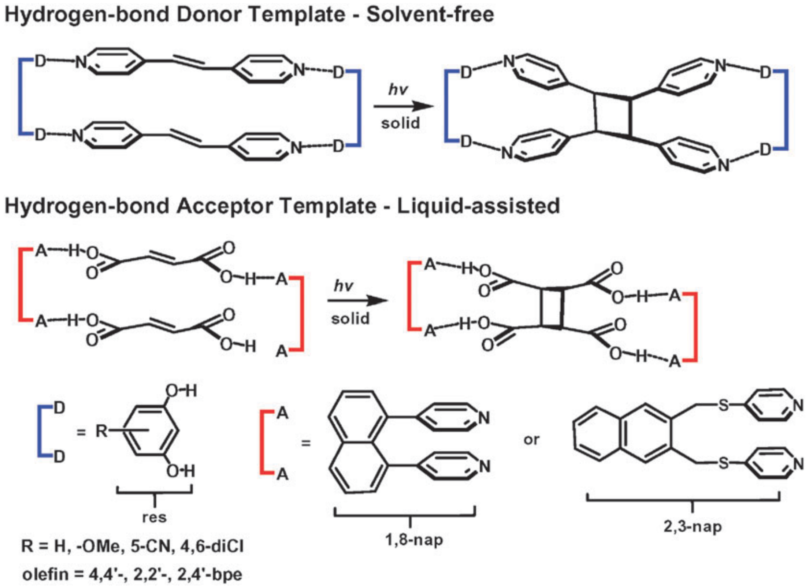
† Dedicated to Professor J. Rebek and Professor J. de Mendoza on the occasions of their 65th birthdays.

‡ Electronic supplementary information (ESI) available: Single structure powder X-ray diffraction patterns, NMR and cell constant data. See 10.1039/b812728j



Scheme 1

4,4′-bpe with **bta** by dry grinding was extremely slow, requiring periods greater than 2 h. As shown in Fig. 1a–b, a powder X-ray diffraction (PXRD) analysis of the ground solid revealed that crystalline 2(**res**)·2(**4,4′-bpe**) formed in 1 h. UV-irradiation produced, consistent with the structure of 2(**res**)·2(**4,4′-bpe**), **4,4′-tpcb** in 100% yield.

Having achieved the formation of 2(**res**)·2(**4,4′-bpe**) *via* dry grinding in 1 h, we turned to determine whether the co-crystal forms in shorter time periods. We, thus, monitored the grinding process using PXRD at intervals of 15, 30, and 45 min. The co-crystal was determined to form in 15 min (Fig. 1c). Photoirradiation of the solid generated **4,4′-tpcb** in 100% yield. Evidence was also obtained for the solid forming in as little as 3 min (Fig. 1d). The diffractogram exhibited peaks at $2\theta = 10.0^\circ$, 11.9°, and 25.9°, which are consistent with the reactive structure 2(**res**)·2(**4,4′-bpe**). UV-irradiation of the solid ground for 3 min generated **4,4′-tpcb** stereospecifically in up to 55% yield.

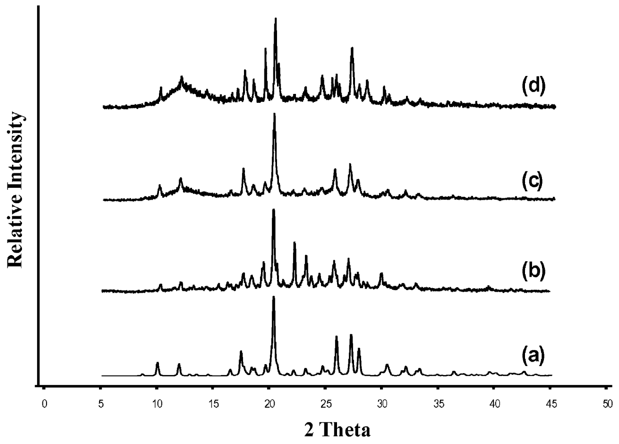


Fig. 1 PXRD analysis of reactive 2(**res**)·2(**4,4′-bpe**): (a) simulated, (b) 1 h, (c) 15 min and (d) 3 min of dry grinding.

The solvent-free grinding of supermolecules and rapid assembly of the components is general in terms of both the **res** template and olefinic reactant. In particular, dry co-grinding of *R*-**res** (where: *R* = 5-methoxy; 5-cyano; 4,6-dichloro) with **4,4′-bpe** afforded the supermolecules 2(*R*-**res**)·2(**4,4′-bpe**) in approximately 15 min. Likewise, 2(**res**)·2(**2,2′-bpe**) and 2(4-Cl-**res**)·(**2,4′-bpe**), with symmetrical and unsymmetrical olefins, respectively, formed *via* dry grinding in 15 min. The solids reacted to give either **4,4′-tpcb**, **2,2′-tpcb**, or **2,4′-tpcb**, where appropriate, in near 100% yield.

In contrast to the supermolecules based on **res**, the reactive assemblies 2(**2,3-nap**)·2(**fum**)[2] and 2(**1,8-dpn**)·2(**fum**),[8] which are based on hydrogen-bond acceptor templates, do not form under dry conditions. In particular, dry co-grinding of either **2,3-nap** or **1,8-dpn** and **fum** for up to 1 h yielded only mixtures of the pure components. Liquid-assisted grinding,[7] however, generated the assemblies. Thus, when **2,3-nap** and **fum** were co-ground with a small aliquot (100 μL) of ethyl acetate for a period of approximately 10 min, crystalline 2(**2,3-nap**)·2(**fum**) cleanly formed, as determined by PXRD. UV-irradiation of the solid produced **cbta**, as reported. Likewise, 2(**1,8-dpn**)·2(**fum**) was generated when **1,8-dpn** and **fum** were ground in the presence of ethyl acetate (0.1 mL) for a period of approximately 10 min.

That the reactive assemblies based on **res** form rapidly and under dry conditions is remarkable, particularly given that the mechanochemistry is general in both template and reactant.[12] A reason for the **res**-based supermolecules forming rapidly and without solvent, in contrast to (**bta**)·2(**4,4′-bpe**),[11] may be attributed to intermolecular forces of the pure solid components.[13] For **res**, and derivatives, single O–H(phenol)···O(phenol) hydrogen bonds predominate.[14] This contrasts the double O–H(acid)···O(carbonyl) hydrogen bonds of acid dimers of a molecule such as **bta**. Moreover, that **bta** is a tetraacid means that a dry grinding process will also be required to break apart a network of hydrogen bonds to afford crystalline (**bta**)·2(**4,4′-bpe**), which is likely facilitated by the addition of the liquid phase.[7] Our experiments involving 2(**2,3-nap**)·2(**fum**) and 2(**1,8-dpn**)·2(**fum**) support this assertion since **fum** forms a hydrogen-bonded network in the solid state sustained by acid dimers.[15] This contrasts the structures of the pure bipyridines **2,3-nap** and **1,8-dpn**, as well as **4,4′-**, **2,2′-** and **2,4′-**, which are sustained by weaker van der Waals and $\pi\cdots\pi$ forces.

In summary, we have demonstrated that mechanochemistry is generally applicable to templated solid-state reactivity. The **res**-based assemblies form both rapidly and solvent-free, which increases the practical value of the **res** system. Our results also suggest that the structures of the individual components should be considered when planning such co-crystal syntheses.[16] We now aim to determine how mechanochemistry can be employed to construct more complex molecules in organic solids. We are also planning to determine how interactions between functional groups involving templates and reactants further impact mechanochemistry and covalent-bond-forming reactions.

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