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A Product of a Templated Solid-State Photodimerization Acts as a Template: Single-Crystal Reactivity in a Single Polymorph of a Cocrystal

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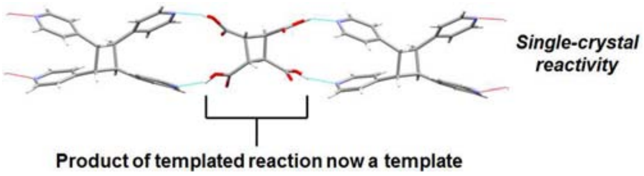
ABSTRACT



The concept of using a product of a template-directed solid-state reaction as a template is demonstrated. A cyclobutane lined with four carboxylic acid groups is employed as the template in photoreactive cocrystals. The resulting material is shown to exhibit polymorphism.

Products of template-directed reactions that act as templates themselves occupy a unique position in chemistry and biology. In Nature, such molecules function as reciprocal templates (e.g., nucleic acids), providing a high-order means to control and direct reactivity in processes such as replication.[1] Templates that function in a reciprocal sense pass on complementary molecular information in a sequential, independent reaction directed by noncovalent bonds. In this context, the field of supramolecular chemistry aims to mimic a means to direct chemical reactivity encountered in biology.[2] Small molecules that function akin to reciprocal templates, however, remain rare, which can be attributed to difficulties in controlling subtleties of intermolecular forces encountered in solution.[3] To our knowledge, there exist only two examples of small molecules formed *via* template-directed reactions that have been used in a subsequent reaction as a template.[4] More specifically, Rebek has described a system of receptors based on Kemp's triacid that support rate enhancements of bimolecular reactions[4a,b] while Philp has, more recently, reported two mutually complementary templates that catalyze the formation of each other.[4c] Both examples have been reactions performed in solution (*i.e.*, liquid phase).

The past decade has witnessed the organic solid state emerge as an attractive medium to perform template-directed reactions using small-molecule templates. The constrained yet flexible environment enables molecules to be assembled into well-defined spatial arrangements that can accommodate movements of atoms in covalent-bond-forming reactions.[5] The [2 + 2] photodimerization is the most well-studied reaction to occur in organic solids. The cycloaddition generally requires carbon−carbon double

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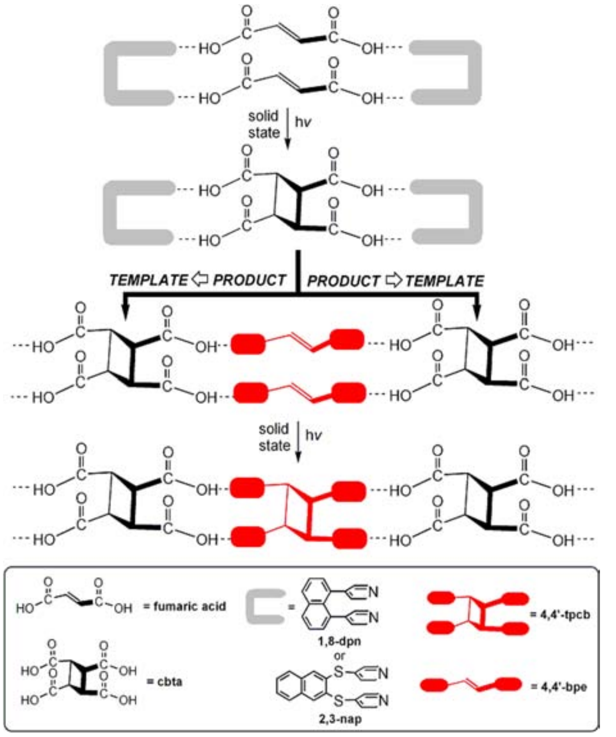
(C=C) bonds to lie parallel and separated less than 4.2 Å to react.[6] Small-molecule bifunctional templates equipped with hydrogen-bond-donor or -acceptor groups have been employed to preorganize C=C bonds in the appropriate position for the cycloaddition to enable the synthesis of molecules difficult to achieve in solution.[7] Despite advances, however, questions regarding whether the resulting photoproducts, which *de facto* are lined with functional groups complementary to the templates, can function as small-molecule templates themselves have been unexplored.

Herein, we report the ability of a product of a template-directed [2 + 2] photodimerization performed in the organic solid state to act as a template. We reveal the ability of *rctt*-cyclobutanetetracarboxylic acid (**cbta**) to assemble *trans*-1,2-bis(4-pyridyl)ethylene (**4,4′-bpe**) into one-dimensional (1D) hydrogen-bonded chains in cocrystals of composition (**cbta**)•2(**4,4′-bpe**). We show the olefin **4,4′-bpe** to react to form *rctt*-tetrakis(4-pyridyl)cyclobutane (**4,4′-tpcb**) stereoselectively and in up to 100% yield. In the course of our studies to employ **cbta** as a template, we have also isolated a polymorph of (**cbta**)•2(**4,4′-bpe**) that undergoes a rare single-crystal-to-single-crystal (SCSC) reaction that generates **4,4′-tpcb** in near-quantitative yield. The fact that the reaction occurs in an SCSC manner allows us to unambiguously establish the ability of the cyclobutane ring of **cbta** to act as a scaffold that directs and accommodates the photoreaction and product, respectively. To our knowledge, **cbta** is the first example of a product of a templated solid-state reaction shown to act as a template.

In previous work, bipyridines 2,3-bis(4-methylenethiopyridyl)naphthalene (**2,3-nap**)[8] and 1,8-bis(4-pyridyl)-naphthalene (**1,8-dpn**)[9] have been used to assemble fumaric acid into geometries suitable for photodimerizations in the solid state to form **cbta** stereoselectively and in up to 100% yield. In an effort to determine if the resulting cyclobutane **cbta** can act as a template, we focused on cocrystallizing **cbta** with **4,4′-bpe** (Scheme 1).

In our initial experiments, slow cooling of a solution of **cbta** and **4,4′-bpe** (ratio 1:2) in DMSO−MeOH (v/v 1:1) afforded block-shaped crystals of (**cbta**)•2(**4,4′-bpe**), hereafter referred to as *Form I*, after a period of 1 h. The composition of (**cbta**)•2(**4,4′-bpe**) (*Form I*) was confirmed using ^{1}H NMR spectroscopy, as well as powder and single-crystal X-ray diffraction.

Scheme 1



The components of *Form I* crystallize in the monoclinic space group $P2_1/c$ with a half molecule of **cbta** and one molecule of **4,4′-bpe** in the asymmetric unit. The components assemble *via* COOH···N(pyridyl) hydrogen bonds (d(O1···N1) = 2.609(2) Å and d(O4···N2) = 2.652(2) Å) to give parallel 1D chains that run along the crystallographic *c*-axis. In the arrangement, **cbta** assembles **4,4′-bpe** as face-to-face stacked pairs with adjacent C=C bonds parallel and separated by 4.05 Å (Figure 1). The stacked geometry of the olefins conforms to the geometry criteria of Schmidt for a photodimerization in a solid.[6] The 1D chains interact laterally *via* (pyridyl)C—H···O=C(carboxylic acid) forces. Adjacent chains are tilted at an angle of 44.5° while olefins of neighboring chains lie at separation distances of > 4.20 Å. A photodimerization would, thus, be expected to occur within a 1D chain structure.

To test the photoreactivity of *Form I*, a powdered crystalline sample (10 mg) was spread between two glass plates and exposed to broad-band UV irradiation (450 W medium-pressure Hg lamp). **4,4′-bpe** was completely converted to **4,4′-tpcb** in a period of 2 h, as confirmed by the emergence of a cyclobutane peak (4.62 ppm) in the ^{1}H NMR spectrum. When single crystals of *Form I* were exposed to the UV-light the samples experienced

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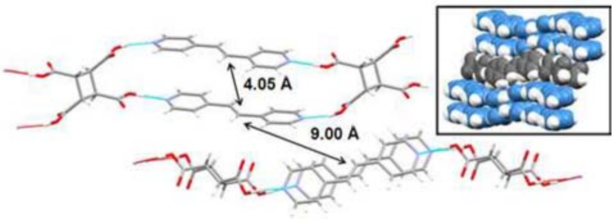

Figure 1. X-ray structure of (cbta)·2(4,4′-bpe) (*Form I*). Inset: space-filling view of packed chains highlighting tilts.

widespread cracking and disintegrated to a powder during the cycloaddition reaction. Moreover, these experiments establish the ability of the cyclobutane of **cbta**, which forms in a templated photodimerization, to function as a small-molecule hydrogen-bond-donor template.

In the course of our work to study **cbta** as a template, we discovered an ability of **cbta** and **4,4′-bpe** to assemble to generate a second polymorph of (**cbta**)•2(**4,4′-bpe**), hereafter, referred to as *Form II*. Slow cooling of a solution of **cbta** and **4,4′-bpe** (ratio 1:2) in DMSO alone afforded single plate-like crystals. The composition of (**cbta**)•2(**4,4′-bpe**) (*Form II*) was confirmed using ^{1}H NMR spectroscopy, as well as powder and single-crystal X-ray diffraction.

In contrast to *Form I*, the components of *Form II* crystallize in the triclinic space group $P\bar{1}$. The asymmetric unit consists of two half molecules of **cbta** and two full molecules of **4,4′-bpe**. The C=C bond of one olefin lies disordered over two sites (occupancies: 0.81/0.19).[10] As with *Form I*, the components are sustained by COOH···N(pyridyl) hydrogen bonds (*d*(O2···N3) = 2.650(3) Å, *d*(O4···N4) = 2.567(4) Å, *d*(O6···N2) = 2.677(5) Å, and *d*(O7···N1) = 2.833(5) Å) that define 1D chains with stacked **4,4′-bpe** molecules aligned parallel. Adjacent chains in *Form II* are crystallographically distinct, with the olefins stacked at 3.65 and 3.74 Å (Figure 2). Whereas neighboring 1D chains run parallel similar to *Form I*, adjacent chains are tilted by only 2.3°. The lack of a significant tilt angle between chains accounts for the major structural difference between the two polymorphs. Olefins of neighboring tapes are separated at a distance >4.20 Å, meaning that a photoreaction is also to be expected to occur within a 1D chain structure.

To test the photoreactivity of *Form II*, a powdered crystalline sample (10 mg) was placed between two glass plates and exposed to broad-band UV irradiation. **4,4′-bpe** was completely converted to **4,4′-tpcb** in a period of only 40 min, as confirmed by ^{1}H NMR spectroscopy. The time required to convert **4,4′-bpe** to **4,4′-tpcb** in *Form II* was, thus, shorter than in *Form I*.

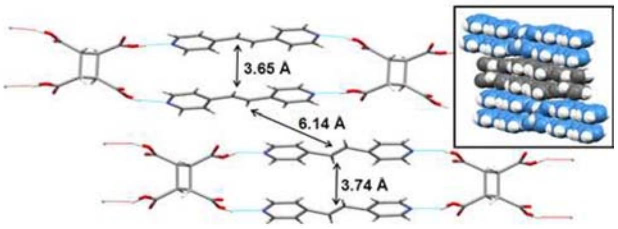

Figure 2. X-ray structure of cbta·2(4,4′-bpe) (*Form II*). Inset: space-filling view of packed chains highlighting lack of a tilt.

Single crystals of *Form II*, in contrast to *Form I*, were determined to maintain crystal integrity during the course of the photodimerization, which suggested the reaction to proceed *via* an SCSC transformation.[11] A single-crystal X-ray diffraction study confirmed the reaction to occur in an SCSC manner. The asymmetric unit contains one molecule of **cbta** and one molecule of **4,4′-tpcb**, with the components being sustained by COOH···N(pyridyl) hydrogen bonds (*d*(O1···N2) = 2.655(7) Å, *d*(O3···N1) = 2.669(6)Å, *d*(O6···N4) = 2.723(7)Å, and *d*(O7···N3) = 2.604(6) Å) (Figure 3). Moreover, the generation of the cyclobutane ring was not accompanied by significant changes to the structure, with adjacent chains parallel and without a tilt. The SCSC reaction unambiguously establishes the ability of the cyclobutane ring of **cbta** to enable the tetraacid to act as a template.

The polymorphism of cocrystals in the context of photoreactivity is not well documented. To our knowledge, the only reported examples are polymorphs of 2(resorcinol)·2(**4,4′-bpe**) wherein one polymorph is photoactive and the other is photostable.[12] For (**cbta**)•2(**4,4′-bpe**), the differences in both C=C stacking and tilts of adjacent chains likely contribute to the resulting SCSC behavior, as well as the generally shorter time of the photodimerization of *Form II* versus *Form I*.

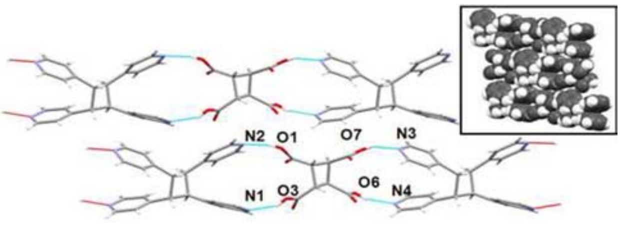

Figure 3. X-ray structure of (**cbta**)·(**4,4′-tpcb**) (SCSC). Inset: space-filling view demonstrating the generation of **4,4′-tpcb**.

In conclusion, we have demonstrated that a product of a templated solid-state [2 + 2] photodimerization can function as a template. The acid groups of the cyclobutane ring of **cbta** are in a geometry suitable to facilitate a photocycloaddition reaction of **4,4′-bpe** within two polymorphs, with the reaction in one polymorph proceeding in an SCSC

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(10) Disorder resolved using low-temperature data.

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reaction. We are now beginning to determine whether other cyclobutane products generated in the solid state can act as templates. Applications of such templates to higher-level processes of chemical reactivity are also under investigation.[4]

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Supporting Information Available. Experimental procedures, spectroscopic data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.