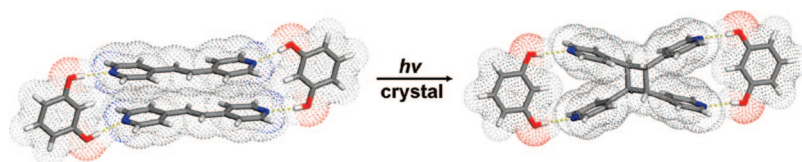# Organic Synthesis in the Solid State via Hydrogen-Bond-Driven Self-Assembly

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This Perspective describes how chemists can control intermolecular [2 + 2] photodimerizations in the solid state using small molecules as linear templates. The templates assemble olefins into positions for the reaction via hydrogen-bond-driven self-assembly. We attach functional groups to the olefins that complement hydrogen bond donor and acceptor groups of the templates. The resulting cyclobutane-based products form stereospecifically, quantitatively, and in gram amounts. The templates are used to direct the formation of a [2.2]paracyclophane and ladderanes. The organic solid state is an exciting medium within which to control chemical reactivity since it is possible to synthesize, or construct, molecules that may be, otherwise, unobtainable from solution. The products form with a high degree of stereocontrol provided by a crystal lattice. The critical covalent-bond-forming process also occurs in a solvent-free environment. That molecules are virtually frozen in position in a solid also means that this methodology enables chemists to employ principles of molecular recognition and self-assembly to direct and conduct organic synthesis.

I. Introduction

Covalent bond-forming reactions (e.g., carbon–carbon bond) lie at the heart of organic synthetic chemistry.[1] Such reactions are used to construct molecules of remarkable complexities. It is highly desired to form covalent bonds in the most efficient manner possible—high yields, limited byproducts, and minimal waste.[2] Organic chemists continue to search and develop improved ways to control the formation of covalent bonds.

In this context, the organic solid state is an intriguing medium in which to control the formation of covalent bonds.[3] The environment is flexible to allow atoms to move and react yet rigid to enable reactions to proceed with remarkable stereocontrol. The homogeneous nature (i.e., 3D regularity) of a crystal lattice means that covalent-bond-forming reactions can proceed

in quantitative yield. There is also a clear environmental benefit to control the formation of covalent bonds in such a solvent-free medium.[4] The solid state also enables molecules to adopt geometries impossible to achieve in the liquid phase. This means that opportunities exist to synthesize molecules in solids that may be, otherwise, inaccessible in solution.

Although covalent bonds have been known to form in organic solids for more than a century,[3] it is only within the past decade that chemists have developed concepts and tools that are enabling the solid state to be used as medium to synthesize molecules by design.[5] Rapid advances in the field of X-ray crystallography (e.g., CCD X-ray diffraction technology) have permitted structural data to be collected and analyzed on timescales of hours-to-minutes as opposed to days-to-months using more traditional instruments (e.g., single-point detectors). Moreover, conceptual advances in the field of crystal engineer-

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SCHEME 1

α-cinnamic acid

α-truxillic acid

β-cinnamic acid

β-truxinic acid
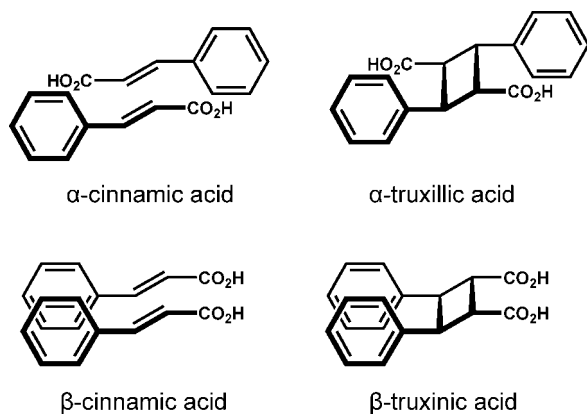
ing,[6] and the related field of supramolecular chemistry,[7] have resulted in marked improvements of our understanding of how intermolecular forces influence the organization of molecules such that the design and construction of solids with predetermined physical properties (e.g., reactivity, optical) is becoming a reality.

It is with these ideas in mind that work in our laboratory during the past 6 years that is aimed to achieve control of a carbon–carbon bond-forming reaction in the solid state, namely, the [2 + 2] photodimerization, will be described.[8] It will be shown that control of this cycloaddition reaction can be achieved by using small organic molecules, termed linear templates,[9] that assemble and preorganize alkenes in geometries suitable for the photoreaction. The templates assemble the alkenes via hydrogen bonds. It will be demonstrated that this supramolecular approach to control the formation of covalent bonds can be employed to code the construction of carbon–carbon bonds with virtually perfect control of regiochemistry. Whereas our initial focus was to expand the nature of the templates, we are beginning to learn how this method can be employed to synthesize, or construct, molecules with architecturally rich frameworks.

II. The Problem of Crystal Packing

The field of crystal engineering finds its origins in the work of Gerhardt Schmidt who, through a number of crystallographic investigations, determined geometry criteria for a [2 + 2] photodimerization to occur in an organic solid.[8] By studying series of cinnamic acids, Schmidt determined that two carbon–carbon double (C=C) bonds should be aligned parallel and separated by less than 4.2 Å to react to form a cyclobutane product. Thus, UV irradiation of α-*trans*-cinnamic acid, a polymorph of cinnamic acid with olefins arranged head-to-tail, produces α-truxillic acid, while irradiation of β-*trans*-cinnamic acid, with olefins arranged head-to-head, produces β-truxinic acid (Scheme 1). Cinnamic acids mainly undergo geometric isomerizations in the liquid phase;[10] thus, the fact that the acid dimerizes in the solid state represented an intriguing departure from solution-phase chemistry. Schmidt showed that the solid state enables the dimerization to occur stereospecifically such that the geometry of the product is consistent with the geometric relation of the olefins in the crystal lattice. Topologically, the photodimerization provides a simple way to cross-link, or couple, two molecules.

Whereas Schmidt provided criteria for a [2 + 2] photodimerization to occur, Schmidt also showed how the extreme sensitivity of solid-state organization to subtle changes to

molecular structure hampers synthetic value of the reaction.[11] In particular, Schmidt showed that members of homologous series' of cinnamic acids did not exhibit homologous reactivities in solids. Such differences in reactivity are a result of both steric and electronic influences of organic functional groups on packing in a crystal. Thus, whereas *p*-methylcinnamic acid formed a crystal structure that was photoactive, *o*-methylcinnamic acid formed a structure that was photostable.[11] These observations contrast the liquid phase where subtle changes to structures of reactants typically do not have such adverse effects on reactivity.

## III. Template-Controlled Solid-State Reactivity using Resorcinol

In 2000, our group embarked to determine whether it is possible to separate, or decouple, the [2 + 2] photodimerization from effects of crystal packing. We hypothesized that by decoupling reactivity from packing we could broaden the synthetic scope of the reaction.

In particular, we expected that the photoreaction could be decoupled from packing using small, ditopic molecules that function as linear templates.[9] Such a template could be used to assemble and preorganize, via relatively strong directional forces such as hydrogen bonds, two suitably functionalized olefins in a geometry that is both appropriate for the photoreaction and independent of crystal packing (Scheme 2). In the minimalist case, a single template could assemble two monofunctionalized olefins. Additional copies of the template could also be integrated into the reactivity so as to integrate the process of self-assembly. Since the template would assemble along the exterior of the olefins, the approach could be used to couple a variety of olefins (e.g., addition of functional group) so that the templates could be used to synthesize a variety of products.

Prior to our work, there were two studies that suggested that the [2 + 2] photodimerization could be separated from crystal packing. First, a "J"-shaped dicarboxylic acid was shown to self-assemble in the solid state to form a dimer held together by four O–H···O hydrogen bonds (Scheme 3).[12] The C=C bonds of the monomers conformed to Schmidt's geometry criteria for a photoreaction in the dimer. That the diacid formed a 0D assembly (i.e., where the strongest intermolecular forces are within the dimer) meant that the arrangement of the olefins, and any reactivity, would be largely independent of packing. The solid reacted to produce the expected cyclobutane in quantitative yield. Second, a number of photoactive crystalline diammonium cinnamate salts wherein the ammonium groups participated in N⁻–H···O⁻ hydrogen bonds with cinnamates were reported (Scheme 4).[13] The reactivity was attributed to the ammonium ions adopting gauche conformations (e.g., ethylenediammonium) that forced the cinnamates to stack to react. The cations also adopted anti conformations that placed the cinnamates into unreactive geometries. In some cases, the ammonium ions participated in N⁺–H···O⁻ hydrogen bonds with other components of the lattice to give hydrogen-bonded polymers that were photostable. Nevertheless, the solids demonstrated that olefins could be forced into reactive geometries using a ditopic system.

Resorcinol as a Template. Our first study involved 1,3-dihydroxybenzene, or resorcinol, as a linear template.[14] We expected that cocrystallization of resorcinol with *trans*-1,2-bis(4-pyridyl)ethylene (4,4′-bpe) would produce the four-component complex 2(resorcinol)·2(4,4′-bpe) held together by four O–H···N
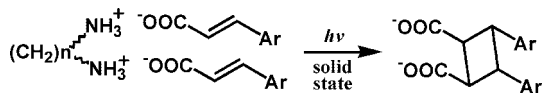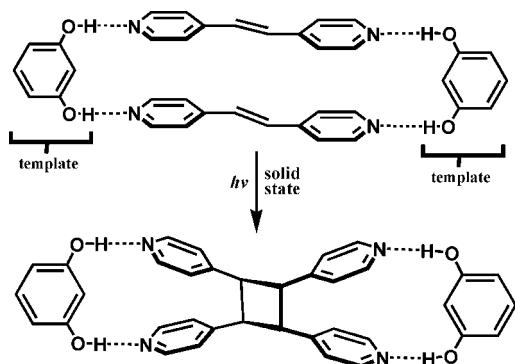
SCHEME 2

$\boxed{}$ = linear template, R—R = reactant
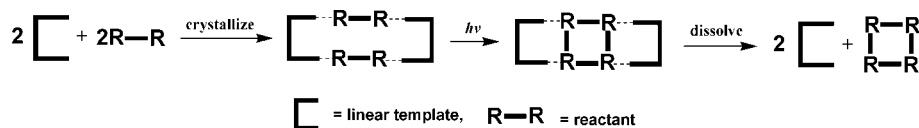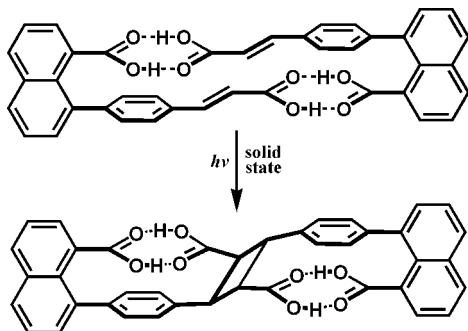
SCHEME 3

SCHEME 4

SCHEME 5

hydrogen bonds wherein two molecules of 4,4′-bpe are positioned for a [2 + 2] photodimerization (Scheme 5). In line with our strategy, cocrystallization of resorcinol with 4,4′-bpe produced the 0D complex 2(resorcinol)·2(4,4′-bpe). The two C=C bonds were oriented parallel and separated by 3.65 Å. This was an ideal position for a photodimerization. UV irradiation produced the anticipated photoproduct, *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb), in 100% yield. The structure of the product was determined using single-crystal X-ray analysis wherein 4,4′-tpcb assembled with resorcinol in the three-component complex 2(resorcinol)·(4,4′-tpcb) (Figure 1).
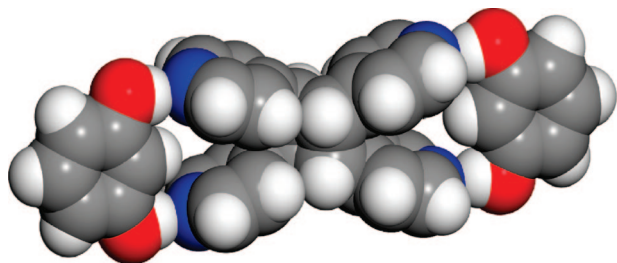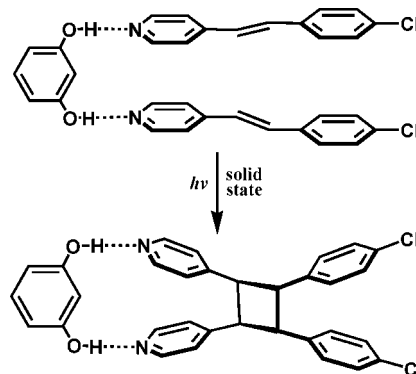

FIGURE 1. Space-filling view of the X-ray structure of 2(res)·(4,4′-tbcp).

SCHEME 6

The template-controlled solid-state reaction was also conducted in gram-scale amounts.

We then demonstrated that resorcinol could assemble an alkene with a single 4-pyridyl group.[15] In particular, resorcinol was used to assemble two stilbazoles in (resorcinol)·2(*trans*-1-(4-pyridyl)-2-(4-chlorophenyl)ethylene) in a head-to-head geometry for a regiocontrolled photodimerization that produced the corresponding head-to-head product *rctt*-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane in quantitative yield (Scheme 6). Cl···Cl interactions formed between the hydrogen-bonded complexes such that nearest neighbor assemblies constituted six-component assemblies held together by both O−H···N and Cl···Cl forces. As a consequence of these interactions, the olefins of the "superassembly" were organized in close proximity, with the C=C bonds being separated by 3.98 Å. Unlike 2(resorcinol)·2(4,4′-bpe), however, the olefins adopted an antiparallel orientation, which was expected to render the C=C bonds photostable. The generation of the photoproduct was attributed to the olefins undergoing pedal-like changes in conformation in the solid that enabled the C=C bonds to adopt a parallel orientation suitable to react and form the product.

IV. Target-Oriented Synthesis in the Solid State

Following our initial reports, we turned to apply the template method to more structurally diverse olefins. In particular, we studied di- and triolefins as reactants. We hypothesized that the self-assembly process involving the templates could adapt to the placement of additional C=C bonds between the pyridyl groups.

[2.2]Paracyclophane. We expected that we could use a resorcinol to construct a [2.2]paracyclophane. The framework, introduced by Cram, bears relevance to physical organic chemistry and materials science owing to its reactive, photochemical, electrochemical properties.[16] The syntheses of [2.2]paracyclophanes, however, has remained a synthetic challenge.

A "retrosynthetic analysis" of the targeted [2.2]paracyclophane, whereby the product forms in a single process via multiple photodimerizations, suggested that the molecule could be constructed from the bifunctional diene 1,4-bis[2-(4-pyridyl)ethenyl]benzene (1,4-bpeb). Cocrystallization of resorcinol, or a derivative, with 1,4-bpeb would give the four-component

SCHEME 7

SCHEME 8
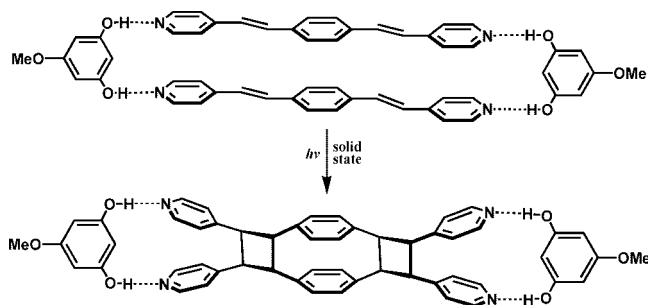
complex, 2(resorcinol)·2(1,4-bpeb), with the two dienes positioned for a double cycloaddition. UV irradiation would generate the cyclophane target tetrakis(4-pyridyl)-1,2,9,10-diethano-[2.2]paracyclophane (4,4′-tppcp). Ideally, the target would form in quantitative yield and gram quantities.

Cocrystallization of 5-methoxyresorcinol (5-OMe-res) with 1,4-bpeb produced the four-component assembly 2(5-OMe-res)·2(1,4-bpeb) (Scheme 7).[14] Similar to 2(resorcinol)·2(4,4′-bpe), the components were held together by four O−H···N hydrogen bonds with the C=C bonds being separated by 3.70 Å. The assemblies packed with C=C bonds of adjacent assemblies parallel and separated by 3.95 Å, a geometry also suitable for a photodimerization. As determined by ^{1}H NMR spectroscopy, UV irradiation of 2(5-OMe-res)·2(1,4-bpeb) produced 4,4′-tppcp in 60% yield. In addition to the paracyclophane, a monocyclized dimer and indefinable products formed. We attributed the formation of the side products to cross-reactions involving nearest neighbor hydrogen-bonded structures.

Later, we showed that 4-benzylresorcinol (4-bn-res) affords 4,4′-tppcp stereospecifically in 100% yield.[17] Similar to 2(5-OMe-res)·2(1,4-bpeb), cocrystals of 2(4-bn-res)·2(1,4-bpeb) consisted of dienes positioned for a double [2 + 2] photodimerization. In contrast to 2(4-bn-res)·2(1,4-bpeb), the closest separation between C=C bonds of adjacent assemblies was 5.4 Å. This distance was outside the criterion of Schmidt for a reaction. The different packing of the hydrogen-bonded assemblies was attributed to steric and electronic influences of the benzyl group of the resorcinol template. UV irradiation of 2(4-bn-res)·2(1,4-bpeb) produced 4,4′-tppcp in 100% yield. The structure of the cyclophane was confirmed via X-ray diffraction (Figure 2).

Ladderanes. In addition to a [2.2]paracyclophane, we anticipated that a resorcinol could be used to construct [n]ladderanes (where n = 3 or 5). Near the time of this work, ladderanes were discovered in intracellular membrane lipids of anaerobic ammonium-oxidizing, or *anammox*, bacteria.[18] The ladderanes were shown to rigidify the membrane of an organelle that allows the bacteria to participate in the oceanic N_2 cycle. A retrosynthetic analysis of a ladderane suggested that a template-controlled [2 + 2] photodimerization of the conjugated diene *trans,trans*-1,4-bis(4-pyridyl)-1,3-butadiene (1,4-bpbd) would yield the corresponding [3]-ladderane all-*trans*-tetrakis(4-pyridyl)[3]ladderane (4-tp-3-lad). Likewise, a templated [2 + 2] photodimerization of the triene *trans,trans,trans*-1,6-bis(4-pyridyl)-1,3,5-hexatriene (1,6-bpht) would produce [5]ladderane all-*trans*-tetrakis(4-pyridyl)[5]ladderane (4-tp-5-lad) (Scheme 8).

5-OMe-res was determined to afford the stereospecific and quantitative construction of both the [3]- and [5]ladderanes.[19] Cocrystallization of 5-OMe-res with either 1,4-bpbd or 1,6-bpht
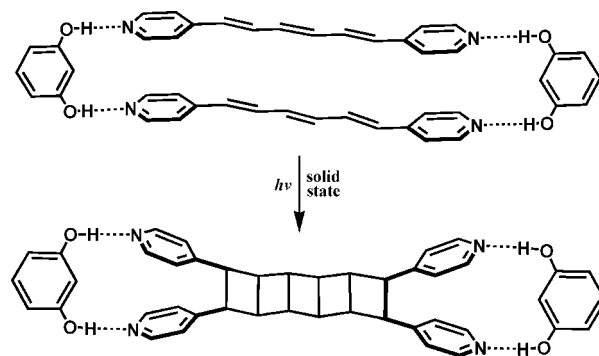
produced the four-component assemblies 2(5-OMe-res)·2(1,4-bpbd) and 2(5-OMe-res)·2(1,6-bpht), respectively. The C=C bonds of each assembly were organized in appropriate positions for the photoreaction. As established by ^{1}H NMR spectroscopy, UV irradiation of each solid produced the targeted [3]- and [5]ladderane in gram amounts and 100% yield. Each ladderane was characterized via X-ray analysis (Figure 3). The template-controlled solid-state [2 + 2] photodimerization of 1,4-bpbd in 2(5-OMe-res)·2(1,4-bpbd) provided the first example of a high-yielding solid-state synthesis of a [3]ladderane, while the reaction within 2(5-OMe-res)·2(1,6-bpht) represented the first example of a solid-state synthesis of a [5]ladderane.

Importantly, Corey, in more recent work, has described the first total syntheses of a naturally occurring ladderane; namely, the methyl ester of pentacycloannamoxic acid (Scheme 9). Overall yields were approximately 1%, which can be ascribed to difficulties synthesizing the ladder portion of the molecule.

V. Other Templates

In addition to the olefins, we have turned to increase the scope of the templates. We reasoned that additional templates could increase the synthetic flexibility of the method. Different
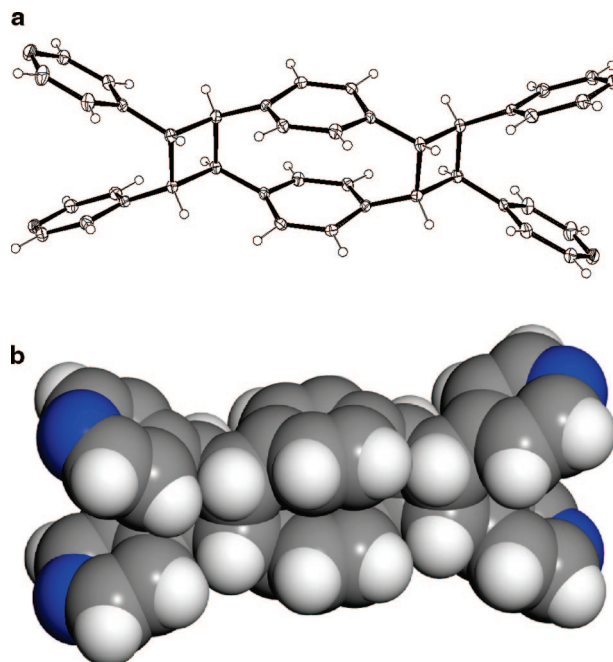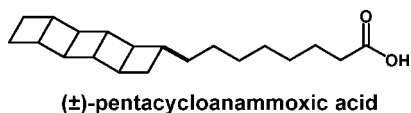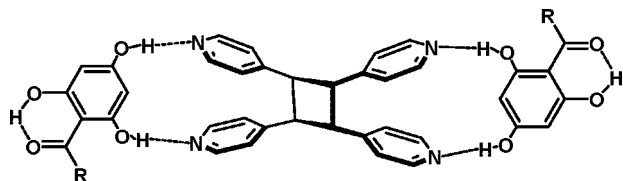
a

b

FIGURE 2. (a) ORTEP perspective of the targeted tetrakis(4-pyridyl)[2.2]paracyclophane and (b) space-filling view of the cyclophane.

SCHEME 9

(±)-pentacycloanammoxic acid

SCHEME 10

R = -H, -methyl, -ethyl, -propyl, -butyl, -pentyl, -hexyl, -phenyl

templates could, for example, provide means to increase product yields where other resorcinols may be less effective. Recognition sites other than 4-pyridyl groups could be designed, based on new systems of templates, and attached to the olefins. Different recognition sites could be used to increase the structural diversity of the photoproducts. Thus, in addition to various resorcinols,[20] we have determined that 1,8-napthalenedicarboxylic acid (1,8-nap),[21] 2,3-bis(4-methylenethiopyridyl)naphthalene (2,3-nap),[22] and Rebek's imide (Reb-im)[23] act as linear templates in the solid state.

Phloroglucinols. To gain systematic control of the [2 + 2] photodimerization using linear templates, we studied a homologous series of phloroglucinols.[20] In particular, we turned to phloroglucinaldehyde, and its congeners, as templates. Houben–Hoesch reaction of the aldehyde with a series of nitriles produced eight homologous R-phloroglucinols (R = alkyl, aryl). Cocrystallization of each phloroglucinol with 4,4′-bpe afforded a hydrogen-bonded assembly with a structure analogous to 2(resorcinol)·2(4,4′-bpe) (Scheme 10). In each case, 4,4′-bpe photodimerized to give 4,4′-tpcb stereospecifically and in up
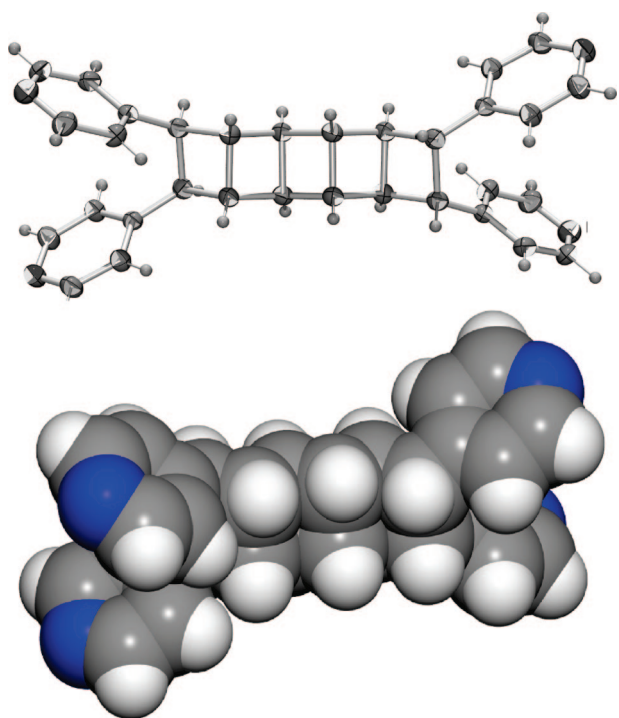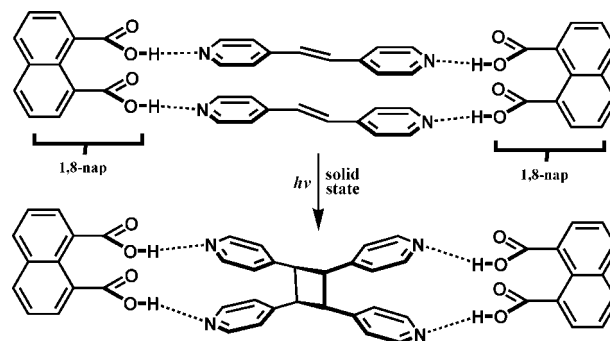

FIGURE 3. (a) ORTEP perspective of the tetrakis(4-pyridyl)[5]ladderane and (b) space-filling view of the ladderane.
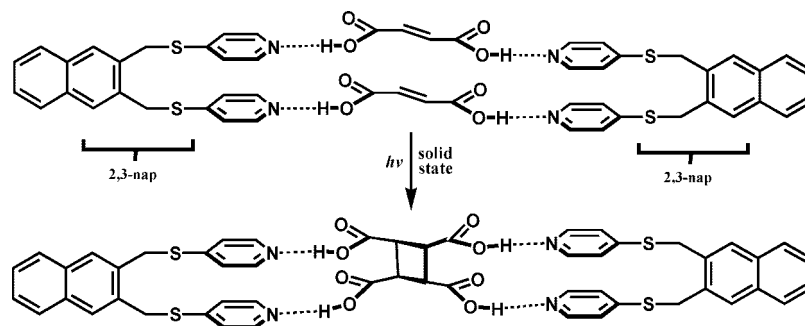
SCHEME 11

to quantitative yield. An intramolecular hydrogen bond also formed along the backbone of each template. These findings attested to the tolerance of the self-assembly process to R-groups on the templates.

1,8-nap. To extend linear templates beyond the 1,3-diol functionality, we turned to 1,8-nap (Scheme 11).[21] Similar to 2(resorcinol)·2(4,4′-bpe), cocrystallization of 1,8-nap with 4,4′-bpe was expected to produce the four-component assembly 2(1,8-nap)·2(4,4′-bpe). That the 1,8-naphthalene framework had been used to enforce face-to-face stacking of aromatics and that the diacid was known to form a hydrogen-bonded dimer in the solid state provided measures of support for our hypothesis.[24,25] We expected that carboxylic acid groups of the diacid would interact with the 4-pyridyl groups of 4,4′-bpe via O–H···N hydrogen bonds. Cocrystallization of the components produced a four-component molecular assembly with two C≡C bonds organized parallel and separated by 3.73 Å. UV irradiation of the solid produced 4,4′-tpcb stereospecifically in 100% yield.[21]

2,3-nap. It occurred to us that the hydrogen bonding, or code, of the self-assembly process could be reversed. Thus, we aimed to develop a template that acts as a hydrogen-bond acceptor. We determined that code reversal could be achieved using 2,3-nap (Scheme 12).[22] Cocrystallization of 2,3-nap with fumaric acid (fum) produced the assembly 2(2,3-nap)·2(fum) held together by four O–H···N hydrogen bonds. Two acid molecules were juxtaposed by the bipyridines, with the C≡C bonds being separated by 3.84 Å. UV irradiation of the solid produced *rctt*-1,2,3,4-cyclobutanetetracarboxylic acid in up to 70% yield. The photoreaction was also determined to proceed via a rare single-crystal-to-single-crystal (SCSC) transformation.[25]

Reb-im. Whereas resorcinol, 1,8-nap, and 2,3-nap are symmetrical, we expected that an unsymmetrical molecule could be used to direct a [2 + 2] photodimerization in the solid state. In particular, we hypothesized that Reb-im could be used to assemble two molecules of 4,4′-bpe for a [2 + 2] photodimerization. In this design, the template would interact with 4,4′-bpe via a combination of N–H···N and O–H···N hydrogen bonds (Scheme 13). Related work by our group had shown that Reb-im self-assembles in the solid state, similar to 1,8-nap, as a hydrogen-bonded dimer,[25] while the cyclohexane scaffold had been used to direct reactivity in solution.[27,28] Cocrystallization of Reb-im with 4,4′-bpe produced the hydrogen-bonded assembly, 2(Reb-im)·2(4,4′-bpe), wherein the two olefins were parallel and separated by 3.70 Å. A toluene molecule was also trapped within the lattice. UV irradiation of the solid produced 4,4′-tpcb

SCHEME 12

SCHEME 13
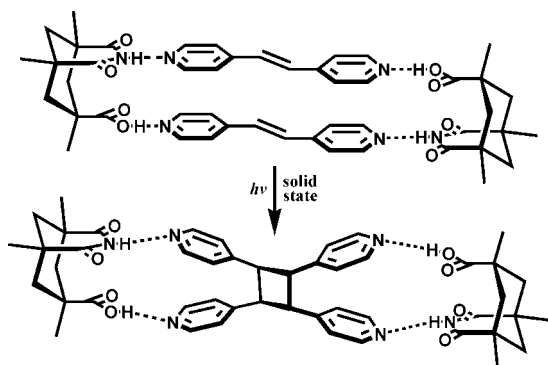
stereospecifically in 100% yield. The reaction was also shown to occur via a SCSC transformation (Figure 4).

VI. Conclusions

In this Perspective, it has been shown that hydrogen-mediated self-assembly involving linear templates can be used to direct and control reactivity in the organic solid state. The templates are used in a modular way to direct [2 + 2] photodimerizations in solids.[30] The templates generate, stereospecifically and in quantitative yield, molecules such as a [2.2]paracyclophane and [*n*]ladderanes. Indeed, the ability of the solid state to enable molecules to be "locked" in position to react, when combined with the directing ability of the templates, provides fertile grounds for chemists to synthesize molecules. For example, there are, in principle, *unlimited* olefins that could be studied using this approach. The olefins can be developed to incorporate various hydrogen-bond acceptor and/or donor sites, substituents, and numbers of C=C bonds. These possibilities are made real since structure effects associated with crystal packing—the nemesis of the crystal engineer—are largely diminished. Moreover,
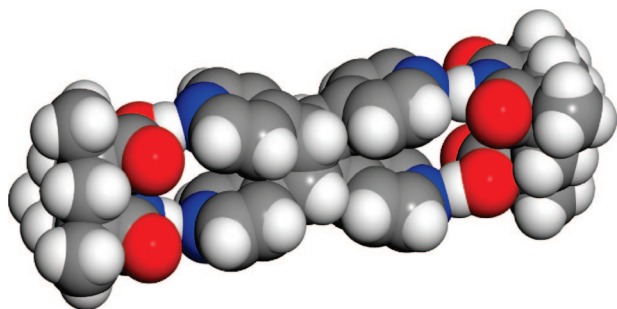
when one considers recent advances in the fields of supramolecular chemistry and self-assembly, where new geometries for self-assembly are now becoming routinely realized,[6] it is possible to envisage this method as a general means to convert geometries the result of molecular recognition and self-assembly into covalent bonds. In that way, a true bridge between the noncovalent and covalent bond is within our grips and can be deliberately developed and established. We are currently working to develop new templates, construct new targets, and exploit new strategies to make these exciting prospects a reality.

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FIGURE 4. Space-filling view of the X-ray structure of 2(Reb-im)·2(4,4′-bpe) from the single-crystal transformation.

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