Template-Controlled Synthesis in the Solid-State

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Abstract The application of molecular templates to direct reactivity in the solid state is described. Specifically, molecules that function as linear templates are demonstrated to provide control of the [2+2] photodimerization in the solid state such that it is possible to use the templates to conduct target-oriented molecular syntheses, or molecular syntheses by design. The degree of organization provided by the solid state is also shown to provide chemists a reliable means to capture and transform ordered complexes formed by way of hydrogen-bonded-driven self-assembly into complex covalent molecular and polymeric structures.

Keywords Linear templates · Photodimerization · Hydrogen-bonding · Preorganization · Molecular recognition · Self-assembly

List of Abbreviations

C=C	Carbon-carbon double
ht	Head-to-tail
hh	Head-to-head
4,4′-bpe	*trans*-1,2-Bis(4-pyridyl)ethylene
4,4′-tpcb	*rctt*-Tetrakis(4-pyridyl)cyclobutane
bpp-34-crown-10	Bisparaphenylene-34-crown-10
amm-stilb	Bis(dialkylammonium)-substituted stilbene
5-OMe-res	5-Methoxyresorcinol
1,8-nap	1,8-Napthalenedicarboxylic acid
4-Cl-sbz	4-Chlorostilbazole
4-Cl-dpcb	*rctt*-1,2-Bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane
2,2′-bpe	*trans*-1,2-Bis(2-pyridyl)ethylene
2,2′-tpcb	*rctt*-Tetrakis(4-pyridyl)cyclobutane
4-Cl-res	4-Chlororesorcinol
2,4-bpe	*trans*-1-(2-Pyridyl)-2-(4-pyridyl)ethylene
2,4-tpcb-hh	*rctt*-1,3-Bis(2-pyridyl)-2,4-bis(4-pyridyl)cyclobutane-hh
3,4-bpe	*trans*-1-(3-Pyridyl)-2-(4-pyridyl)ethylene
3,4-tpcb-hh	*rctt*-1,3-Bis(3-pyridyl)-2,4-bis(4-pyridyl)cyclobutane-hh
4,4′-bipyeth	1,2-Bis(4-pyridyl)ethane
4-Et-res	4-Ethylresorcinol
4,6-di-Cl-res	4,6-Dichlororesorcinol
1,4-bpeb	1,4-Bis(2-(4-pyridyl)ethenyl)benzene
4-benz-res	4-Benzylresorcinol

1
Introduction

The organized environment of the solid state is an intriguing medium within which to control the formation of covalent bonds [1]. Being virtually frozen in an environment with atom-to-atom separations on the order of angstroms, reactants in the solid state can, in principle, adopt geometries that may be difficult, or impossible, to achieve in the liquid phase, meaning that access to molecules less available or unavailable in solution can be achieved. That a toxic organic solvent is not required for a reaction to occur in the solid state also means reactions in the solid state are inherently environmentally-friendly, or green [2]. When combined with the fact that a reaction in the solid state results in a change in composition and, therefore, can affect a bulk physical property (e.g., color) of a solid [3], it becomes apparent that controlling the formation of covalent bonds in the solid state can bear relevance to both chemical synthesis and materials science.

Unfortunately, however, whereas the fluid environment of the liquid phase is routinely used to conduct target-oriented syntheses (e.g., natural products) [4], it has remained difficult, owing to subtle structure demands of close packing (i.e., the driving force that provides the cohesive energy for crystallization) [5], to control reactivity in the solid state [6]. Such lack of control has meant

Chemical Synthesis

	reaction homology	target-oriented synthesis
liquid phase	√	√
solid state	?	X

Fig. 1 Scheme illustrating the role of reaction homology and target-oriented synthesis in liquid phase and solid-state chemistry

that reactions involving members of a homologous series of compounds – an idea central to solution-phase synthesis – has been achieved with limited success [7] and a general ability to construct molecules of prescribed size, shape, and functionality – a signature of the liquid phase – has not been realized (Fig. 1). The process of controlling reactivity in the solid state has, moreover, largely evolved as being based on trial and error, relying, in most cases, on weak interactions between molecules to organize reactants in a suitable arrangement for reaction.

2
Overview

It is with these ideas in mind that we will provide here a review of work from our laboratory, and the laboratories of others, performed primarily during the past five years that focuses upon utilizing molecules, in the form of linear reaction templates [8], to control reactivity in the solid state. Specifically, upon identifying the ability of a linear template to position two molecules, by way of hydrogen bonds, in an arrangement suitable for a [2+2] photodimerization [7] that is largely independent of structure effects of close packing (Fig. 2), we have demonstrated that linear templates provide a means to direct reactivity in the solid state with synthetic freedoms akin to the liquid phase such that it is now possible to conduct target-oriented solid-state syntheses, or molecular solid-state syntheses by design.
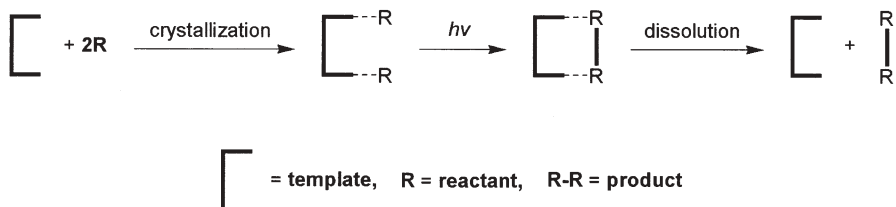

Fig. 2 Scheme showing the general synthesis behavior of a linear template

Our review will begin by outlining geometry criteria for a [2+2] photo-dimerization to occur in the solid state. We will then describe previous methods to control the [2+2] photoreaction and then present fundamentals of the template-controlled solid-state approach. We will also provide a brief account of the application of a similar method to control the formation of polymers, and then offer concluding remarks.

3
The Solid-State [2+2] Photodimerization

For a [2+2] photodimerization to occur in the solid state, two carbon-carbon double (C=C) bonds should conform to specific geometry criteria outlined by Schmidt [7]. Specifically, following crystal structure studies involving cinnamic acid, Schmidt has revealed that two C=C bonds should be aligned parallel and separated by <4.2 Å (Fig. 3). These criteria place the four *p*-orbitals of two C=C bonds in close enough proximity and proper orientation to undergo the photoreaction. Schmidt has also shown that the photoreaction is regioselective, the stereochemical relationship of reactants being preserved in the photoproducts. Thus, UV-irradiation of crystalline α-*trans*-cinnamic acid, a polymorph of cinnamic acid wherein the olefins are arranged head-to-tail (ht), produces α-truxillic acid while irradiation of β-*trans*-cinnamic acid, wherein the olefins are arranged head-to-head (hh), produces β-truxinic acid. These geometry criteria, which are based on a wealth of crystallographic data, make up the 'topochemical postulates' [6].

3.1
Approaches to Control the [2+2] Photodimerization in the Solid State

Past approaches to control the [2+2] photodimerization in the solid state have fallen into two general categories; specifically, methods that employ either (i) intramolecular substitution or (ii) cavities.

3.1.1
Intramolecular Substitution

In the first approach, substituents have been covalently attached to molecules to 'steer' reactants, upon crystallization, in a necessary arrangement for reaction.

Schmidt, for example, has revealed that Cl atoms when attached to an aromatic ring tend to steer a molecule, by way of Cl···Cl interactions, such that the molecule assembles head-to-head, in a β-structure, wherein neighboring olefins are photoactive [9]. Following this work, electrostatic, as well as donor-acceptor, interactions have been used for steering the synthesis of molecules and, in some cases, polymers [10–15] (Fig. 4).
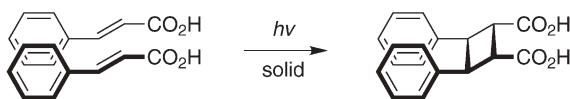
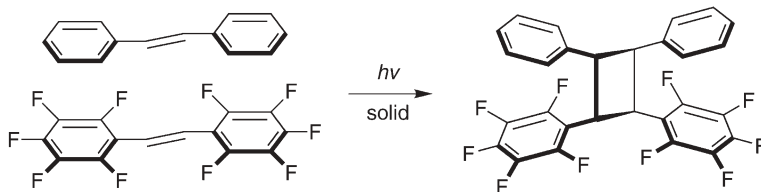**Fig. 3** Solid-state photoreaction of β-cinnamic acid to produce β-truxinic acid

Fig. 4 Phenyl-perfluorophenyl interactions that orient two stilbenes in the solid state for a [2+2] photodimerization
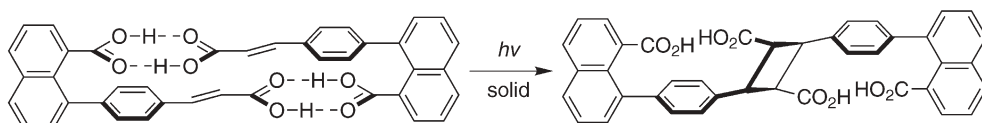

Fig. 5 'J'-shaped cinnamic acid that aligns two olefins within a hydrogen-bonded complex

In a notable success, a 'J'-shaped dicarboxylic acid has been shown by Feldman to self-assemble to form a dimer held together by four O-H⋯O hydrogen bonds wherein two C=C bonds conformed to the topochemical postulates (Fig. 5) [16]. The naphthalene unit served to preorganize the olefins at a separation distance suitable for the photoreaction. UV irradiation of the solid produced the expected photoproduct in quantitative yield.

3.1.2
Cavities

In the second approach, an auxiliary component has been employed to produce a cavity in the solid state that serves to host two molecules that undergo a [2+2] photoreaction.

Host cavities based on cyclodextrins [17] and saponite [18], for example, have been used to organize stilbenes by way of van der Waals and electrostatic forces, respectively. In the former, the host accommodated the guests within a tubular framework while, in the latter, the clay-like silicate accommodated the guests by swelling. In each case, the guest dimerized upon UV irradiation.

Extensive work involving auxiliary molecules that interact with reactants by way of hydrogen bonds and assemble to form solid-state cavities has also been described [19]. Specifically, tetraaryl diols have been shown by Toda to accommodate ketones within cavities wherein each host interacted with two guests by way of two O-H⋯O hydrogen bonds (Fig. 6). The guests packed within the
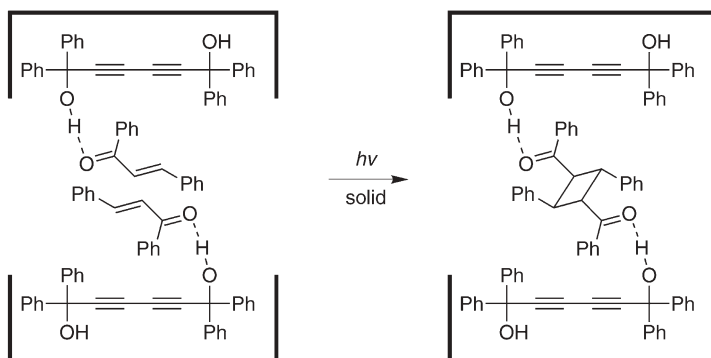
Fig. 6 Tetraaryl diol that forms cavities and interacts with olefins by way of hydrogen bonds

cavities such that two C=C bonds of two guests conformed to the topochemical postulates and photodimerized.

4
Solid-State Reactivity and Molecular Synthesis by Design

Although substituents and cavities have been successfully employed to direct the [2+2] photodimerization in the solid state, both methods have fallen short as general, or 'universal' [6], means to direct the solid-state reaction. In the former, the approach has typically involved steering forces that are relatively weak. This has made the method difficult to control since such forces are sensitive to, and therefore have difficulty competing with, subtle structure demands of close packing [5]. Numerous substituents have also been typically required to steer olefins for reaction which, in addition to yielding products with properties different than the parent reactant framework, can limit derivatization of the products. In the latter, the approach has required reactants that 'fit' within the cavities. This has limited the range of guests (i.e., sizes and shapes), and therefore products, accessible using the approach. Indeed, such lack of generality has meant that it is has remained difficult to synthesize molecules in the solid state [7] with degrees of synthetic freedom common to the liquid phase (e.g., reliability, functional groups). In effect, the products of [2+2] photodimerizations conducted in the solid state have been limited to each topochemical strategy, a fact that has thwarted efforts toward an ability to conduct target-oriented synthesis, or molecular solid-state synthesis by design [4].

5
Linear Templates

To develop a general means to control the [2+2] photodimerization in the solid state, and thereby provide a means to conduct molecular solid-state synthesis by

design, recent efforts by us, and others, have focused on employing bifunctional molecules, in the form of linear templates [8], to direct the photoreaction (Fig. 2). It was anticipated that such molecules would offer a means to preorganize, according to principles of molecular recognition [20] and self-assembly [21], two molecules linearly within a discrete, solid-state complex for reaction. By enforcing the photoreaction to occur within a discrete complex using strong and directional noncovalent forces (e.g., hydrogen bonds), the approach could eliminate many vexatious problems of close packing that have made previous methods unreliable. Moreover, that the template would assemble along the periphery of the complex would mean that access to a variety of molecules may be achieved since the template could, in principle, adapt to changes to size (e.g., lengthening) and shape (e.g., bending) of the reactants. By making such changes systematically, an ability to conduct target-oriented solid-state synthesis could then be realized.

6
Linear Templates in the Solid State

The first study that illustrated that a linear template could be employed to direct a [2+2] photodimerization in the solid state was by Ito and Scheffer [22, 23]. Specifically, diamines (e.g., ethylenediamine) were revealed to undergo acid-base reactions with substituted cinnamic acids (e.g., *o*-methoxycinnamic acid), wherein each ammonium group formed an N^+-$H\cdots O^-$ hydrogen bond with a cinnamate (Fig. 7). Combinations of base and acid were photoactive, which was accounted for by the formation of three-component complexes wherein each base, in a *gauche* conformation, positioned two cinnamates for a [2+2] photo-
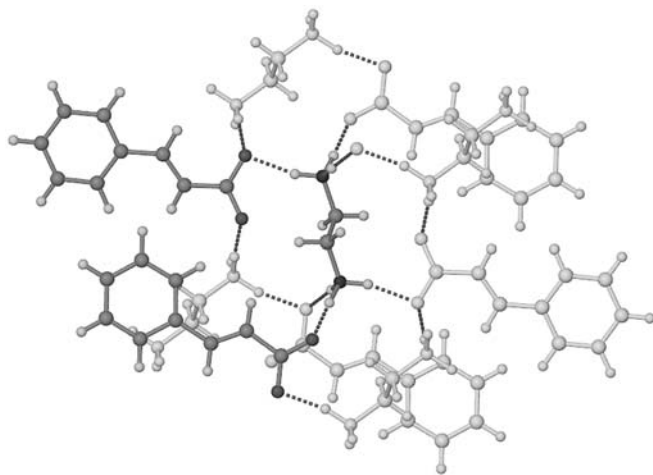

Fig. 7 Perspective of crystal structure of ethylenediammonium cinnamate. The dications and anions of a reactive complex are *highlighted in black*

reaction. It was also revealed that the ammonium ions could adopt an *anti* conformation that forced the cinnamates into an unreactive orientation while, in some cases, the cations participated in N^+-H$\cdots$O$^-$ forces with other components of the lattice to produce infinite assemblies that were photostable. Nevertheless, features of a linear template chemistry were demonstrated by the Ito and Scheffer approach.

Inspired by work of Ito and Scheffer, we turned to develop a linear template that could reliably organize two olefins for a [2+2] photoreaction. To achieve this goal, we anticipated that a rigid molecule with no more than two hydrogen bond donor groups separated at a distance consistent with the topochemical postulates [7] could serve as such a template. Specifically, from a structure study involving a bis(resorcinol)anthracene co-crystallized with anthraquinone [24], we anticipated that co-crystallization of resorcinol with *trans*-1,2-bis(4-pyridyl)ethylene (4,4′-bpe) would produce a discrete, four-component complex, 2(resorcinol)·2(4,4′-bpe), held together by four O-H$\cdots$N hydrogen bonds wherein two molecules of 4,4′-bpe would be positioned for a [2+2] photodimerization (Fig. 8). Similar to Ito and Scheffer, the design would employ a bifunctional molecule to direct the photoreaction. In contrast to Ito and Scheffer, the rigidity of the aromatic ring and presence of only two hydrogen bond donor groups would largely ensure that 4,4′-bpe would be organized independent of structure effects of close packing in a solid.
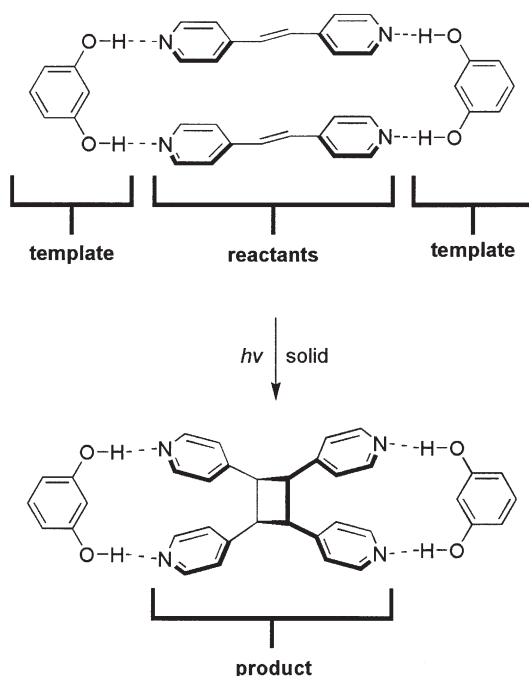

Fig. 8 Schematic of 2(resorcinol)·2(4,4′-bpe)

In line with our strategy, co-crystallization of resorcinol with 4,4′-bpe produced the discrete, four-component complex 2(resorcinol)·2(4,4′-bpe) (Fig. 9) [25]. In this arrangement, the four pyridyl units of the two olefins were stacked and twisted approximately orthogonal to the diol such that the two C=C bonds were oriented parallel and separated by 3.65 Å, an ideal position for a [2+2] photodimerization. UV-irradiation of the solid produced the anticipated photoproduct, *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb), in 100% yield. The structure of the photoproduct was also determined by way of single-crystal X-ray analysis where 4,4′-tpcb was shown to assemble with resorcinol in a three-component complex, 2(resorcinol)·(4,4′-tpcb), held together by four O-H···N hydrogen bonds. The template-controlled reaction was also conducted on a gram scale where resorcinol and 4,4′-tpcb were separated by way of a liquid phase extraction.

Following our report, a flexible template based on a crown ether was shown to organize two C=C bonds within a discrete complex in the solid state for a [2+2] photoreaction [26]. Specifically, Garcia-Garibay and Stoddart demonstrated that reaction of a bisparaphenylene-34-crown-10 (bpp-34-crown-10) with a bis(dialkylammonium)-substituted stilbene (amm-stilb) produced the four-component complex 2(bpp-34-crown-10)·2(ammon-stilb) held together by eight N^+-H···O hydrogen bonds (Fig. 10). In this design, the cavity of the
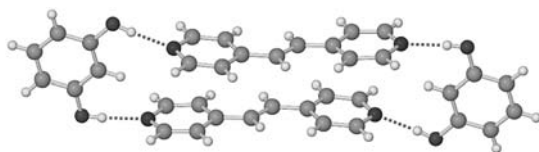

Fig. 9 Perspective of the four-component complex 2(resorcinol)·2(4,4′-bpe) (hydrogen bonds *dotted*)
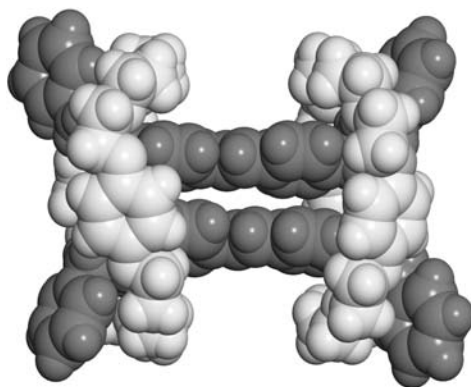

Fig. 10 A crown ether that directs a [2+2] photodimerization in the solid state: space-filling view of the four-component complex 2(bpp-34-crown-10)·2(ammon-stilb) (crown ether *light gray*; olefins *dark gray*)

crown ether was filled with the two reactants, the olefinic bonds being aligned parallel and separated by approximately 4.20 Å. UV irradiation of the solid resulted in a stereospecific dimerization of ammon-stilb to give a single diastereo-isomer in approximate 80% yield, as confirmed by way of X-ray crystallography.

6.1
Fundamentals

To expand the scope of molecules accessible using linear templates, we anticipated that it would be necessary to determine the tolerance [27] of the self-assembly process to structural changes to the templates and reactants. Such modifications could, for example, introduce functionalities (e.g., lone pairs) that may interfere with the interaction between the template and reactants. In the ideal case, the template would interact preferentially with complementary sites of the reactants despite structural changes to the components of the complex. Moreover, with basic knowledge of structural changes tolerated by the assembly process, the designed synthesis of molecules that may be less available or completely inaccessible using conventional solution-based synthesis could be realized.

6.1.1
Modifying the Template

We have revealed that the assembly process is tolerant to substituents placed along the periphery of the template. In particular, derivatives of resorcinol with substituents largely unable to disrupt the hydrogen bonds between the templates and reactants (e.g., -R, -OR) have been shown to serve as templates. Thus, co-crystallization of 5-methoxyresorcinol (5-OMe-res) with 4,4′-bpe produced the four-component complex 2(5-OMe-res)·2(4,4′-bpe) with two C=C bonds aligned parallel and separated by 3.66 Å. UV-irradiation of the solid with broad-band UV-radiation produced 4,4′-tpcb in quantitative yield [25].

In addition to resorcinol, we have shown that 1,8-naphthalenedicarboxylic acid (1,8-nap) serves as a template. Similar to 2(resorcinol)·2(4,4′-bpe), co-crystallization of 1,8-nap with 4,4′-bpe produced the four-component complex 2(1,8-nap)·2(4,4′-bpe) held together by four O-H···N hydrogen bonds (Fig. 11) [28]. The two carboxylic acid groups, each of which was twisted out of the plane

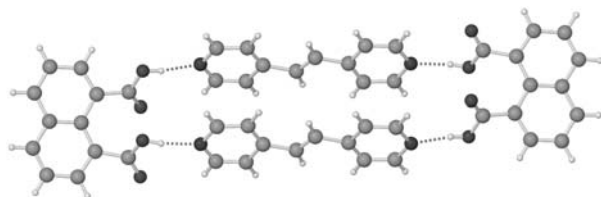**Fig. 11** Perspective of the four-component complex 2(1,8-nap)·2(4,4′-bpe)

of the naphthalene unit, positioned the reactants for reaction, the two C=C bonds being aligned parallel and separated by 3.73 Å. UV-irradiation of the solid using broadband UV radiation produced 4,4′-tpcb in quantitative yield.

6.1.2
Modifying the Reactants

We anticipated that the reactants could be modified by changing the number and/or position of the hydrogen bond acceptors sites, as well as by adding, or removing, functional groups. In this context, we have shown that the self-assembly process is tolerant to changes to both the number and position of the acceptor sites. A study involving the addition of alkyl groups to a hydrogen bond acceptor substrate has also been conducted.

6.1.2.1
Number of Hydrogen Bond Acceptor Sites

The minimalist olefins that may be organized by a linear template within a complex for reaction possess a single hydrogen bond acceptor site. Thus, a single template may organize two stilbazoles in a head-to-head arrangement for a regiocontrolled photodimerization to produce a head-to-head cyclobutane product.

Similar to 2(resorcinol)·2(4,4′-bpe), co-crystallization of resorcinol with 4-chlorostilbazole (4-Cl-sbz) produced the three-component complex (resorcinol)·2(4-Cl-sbz) held together by three O-H···N hydrogen bonds. Cl···Cl interactions also formed between the complexes such that nearest-neighbor assemblies constituted six-component complexes held together by Cl···Cl and O-H···N forces (Fig. 12) [29]. The complexes assembled to form offset linear stacks. As a consequence of these forces, the C=C bonds of the 'super-complex' were organized in close proximity, the two C=C bonds being separated by 3.98 Å. Unlike 2(resorcinol)·2(4,4′-bpe), however, the olefins of the complex adopted an antiparallel orientation, which was expected to render the C=C bonds photostable.

Although the olefins of (resorcinol)·2(4-Cl-sbz) were misaligned, the stilbazoles were photoactive. UV irradiation of (resorcinol)·2(4-Cl-sbz) using 350 nm radiation produced *rctt*-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl) cyclobutane (4-Cl-dpcb) in 100% yield. The generation of 4-Cl-dpcb was attrib-
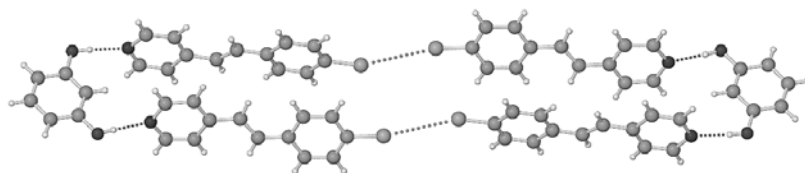

Fig. 12 Perspective of the six-component 'super-complex' 2(resorcinol)·4(4-Cl-sbz)

uted to the reactant undergoing a pedal-like change in conformation in the solid that enabled the C=C bonds to adopt a parallel orientation suitable to form the cyclobutane.

6.1.2.2
Position of the Hydrogen Bond Acceptor Sites

In addition to the number of hydrogen bond acceptor sites, we have demonstrated that the assembly process is tolerant to changes to the positions of the acceptor sites. Such changes were anticipated to force the templates to assemble so as to occupy different positions along the peripheries of the reactants.

Co-crystallization of 1,8-nap with *trans*-1,2-bis(2-pyridyl)ethylene (2,2′-bpe), for example, produced the discrete, four-component complex 2(1,8-nap)·2(2,2′-bpe) held together by four O–H·N hydrogen bonds (Fig. 13a) [28]. The C=C bonds of the complex were organized parallel and separated by 3.91 Å. In contrast to 2(1,8-nap)·2(4,4′-bpe), each template assembled in close proximity to each olefinic bond. UV-irradiation of the solid with broadband UV-radiation produced *rctt*-tetrakis(2-pyridyl)cyclobutane (2,2′-tpcb) in quantitative yield.

The ability of a linear template to orient two identical pyridyl units in a face-to-face stacked arrangement suggested that a linear template could assemble two reactants with two different pyridyl units for a head-to-head photodimerization. Since different combinations of hydrogen bond acceptor sites could be employed for the photoreaction (i.e., *trans*-1-(*n*-pyridyl)-2-(*m*-pyridyl)ethylene (where: *n*, *m*=2, 3, or 4; *n*≠*m*), a general means to establish regiocontrol of the photoreaction could be achieved.
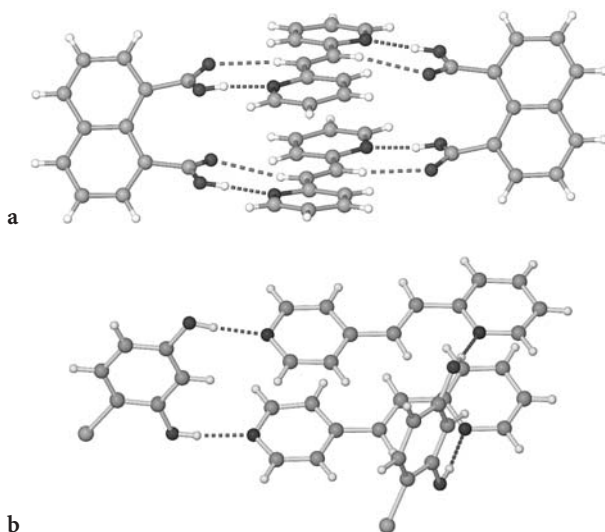

Fig. 13a, b Perspective of complexes based on different hydrogen bond acceptor sites: **a** 2(1,8-nap)·2(2,2′-bpe); **b** 2(4-Cl-res)·2(2,4-bpe)

Thus, co-crystallization of 4-chlororesorcinol (4-Cl-res) with *trans*-1-(2-pyridyl)-2-(4-pyridyl)ethylene (2,4-bpe) produced the four-component complex 2(4-Cl-res)·2(2,4-bpe) (Fig. 13b) [30]. The bipyridine was organized within the complex in a head-to-head fashion, each diol interacting with either a 2-pyridyl or 4-pyridyl unit. The C=C bonds were aligned parallel and separated by 3.89 Å. UV-irradiation of the solid using broadband UV radiation produced the head-head photoproduct 2,4-tpcb-hh in quantitative yield. Similar to 2(4-Cl-res)·2(2,4-bpe), co-crystallization of 1,8-nap with *trans*-1-(3-pyridyl)-2-(4-pyridyl)-ethylene (3,4-bpe) produced the four-component complex 2(1,8-nap)·2(3,4-bpe) wherein the two olefins were organized head-to-head [31]. The two C=C bonds were aligned parallel and separated by 3.58 Å. UV-irradiation of 2(1,8-nap)·2(3,4-bpe) produced the head-to-head cycloproduct, 3,4-tpcb-hh, in quantitative yield.

6.1.2.3
Functional Groups

Our first study to determine tolerance of the assembly process to functional groups has involved methylene linkages. Specifically, co-crystallization of resorcinol with 1,2-bis(4-pyridyl)ethane (4,4′-bipyeth) produced, in contrast to 2(resorcinol)·2(4,4′-bpe), an infinite 1D polymer, (resorcinol)·(4,4′-bipyeth) [32]. In this arrangement, the hydroxyl groups of the resorcinol unit adopted a divergent conformation. Similar to neat crystalline 4,4′-bipyeth [33], the ethane moiety and pyridyl units of the bipyridine were twisted approximately orthogonal (Fig. 14). Notably, the closest N(bipyridine)···C-H(resorcinol) separations of the 1D array involved the 4- and 6- positions of the diol. Thus, the flexibility of the methylene linkages, as realized by the twisting of the ethane moiety, enabled the diol and bipyridine to form the 1D array, largely prohibiting the components to assemble to form the targeted discrete structure.

6.1.3
Template-Switching

Although the goal to organize two reactants within a discrete hydrogen-bonded complex was formulated as a means to isolate two reactive olefins from structure effects of close packing, it was evident that such a complex was not completely independent of such packing effects. Indeed, in the case of (resorcinol)·
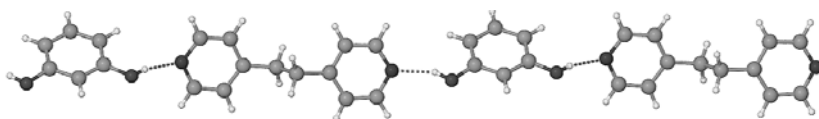

Fig. 14 Perspective of the infinite 1D polymer (resorcinol)·(4,4′-bipyeth)

2(4-Cl-sbz) [29], the C=C bonds of the complex, although photoactive, assembled misaligned while the components of 2(resorcinol)·2(4,4′-bipyeth) [32] assembled to give an infinite, rather than a discrete structure.

To confront further effects of close packing, and thereby establish further control of the [2+2] photodimerization [7], we anticipated that changing the template to derivative, by adding a substituent along the periphery of the template, could be used to promote the formation of a discrete complex that exhibits desired photoreactivity. The addition of a substituent to the template would effectively modify the shape of the template which, de facto, would be expected to lead to a different crystal packing environment [34] that may support the formation of a desired photoactive structure. Although an ability to predict successfully solid-state packing has remained elusive, we anticipated that such 'template-switching' [35] would, in effect, exploit unpredictable structural consequences of crystal packing, enabling the approach to provide a means to increase the likelihood of achieving the topochemical postulates of Schmidt for a [2+2] photoreaction.

6.1.3.1
Olefin Alignment

In line with our template-switching strategy, co-crystallization of 4-ethyl-resorcinol (4-Et-res) with 4-Cl-sbz produced the three-component complex (4-Et-res)·2(4-Cl-sbz) held together by three O-H···N hydrogen bonds (Fig. 15) [29]. Unlike (resorcinol)·2(4-Cl-sbz), the C=C bonds of the complex, which were separated by 3.92 Å, were aligned parallel. That the C=C bonds of 4-Cl-sbz assembled parallel was consistent with the ability of stacked C=C bonds to adopt either a parallel or nonparallel orientation in a solid [29]. UV irradiation of the solid produced the targeted product, 4-Cl-dpcb, in near quantitative yield.

6.1.3.2
Assembly Process

That 4,4′-bipyeth and resorcinol formed a 1D array also prompted us to apply template-switching to generate a discrete complex involving the bipyridine.
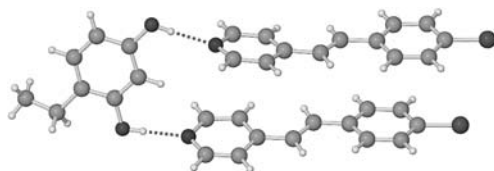

Fig. 15 Achieving olefin alignment: Perspective of the three-component complex (4-Et-res)·2(4-Cl-sbz)
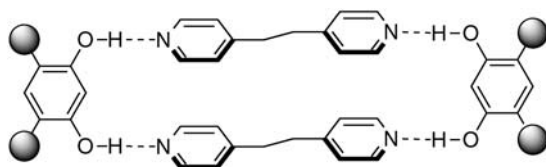
Fig. 16   Scheme of a discrete assembly achieved using a resorcinol derivative

Stacking of methylene groups in the solid state was established [36] while the known flexibility of 4,4′-bipyeth [37] suggested that the bipyridine could be forced to adopt a planar conformation suitable for a discrete structure. Moreover, it was reasoned that substituents placed in the 4- and/or 6- positions of a resorcinol may enable the diol to direct stacking of 4,4′-bipeth within a discrete complex (Fig. 16). In addition to making a 1D assembly energetically unfavorable by sterically protecting each 'side' of the diol [38], the positioning of the substituents adjacent to the hydroxyl groups would promote the diol to adopt a convergent conformation. In effect, the substituents would largely preorganize [39] a resorcinol to form a targeted discrete structure.

As anticipated, co-crystallization of either 4-Cl-res or 4,6-dichlororesorcinol (4,6-di-Cl-res) with 4,4′-bipyeth produced the four-component complexes 2(4-Cl-res)·2(4,4′-bipyeth) and 2(4,6-di-Cl-res)·2(4,4′-bipyeth), respectively, held together by four O-H···N hydrogen bonds. The bipyridines stacked alongside each resorcinol unit such that the methylene linkages were aligned and separated by 4.13 Å [32]. In contrast to (resorcinol)·(4,4′-bipyeth), the bipyridines adopted an approximate planar conformation wherein the ethane moiety and pyridyl units were twisted toward co-planarity (Fig. 17). Thus, in addition to promoting the formation of the discrete complex, the presence of the substituents along the periphery of each diol affected the conformation of the bipyridine.
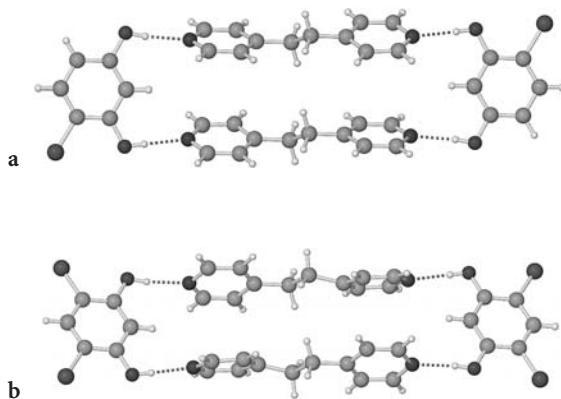

Fig. 17a, b   Achieving a discrete complex: Perspectives of: **a** 2(4-Cl-res)·2(4,4′-bipyeth); **b** 2(4,6-di-Cl-res)·2(4,4′-bipyeth)

6.2
Target-Oriented Synthesis

The tolerance of the assembly process to structural changes to the templates and reactants demonstrated that linear templates could be used to direct reliably the [2+2] photodimerization in the solid state. Moreover, that the templates assembled along the peripheries of the hydrogen-bonded complexes suggested that the templates could be used to synthesize molecules of varying size (e.g., lengthening) and shape (e.g., bending) since the templates could, in principle, adapt to changes to size and shape of the reactants. An increase in size to the reactants could also be accompanied by attachment of additional reactive sites (i.e., C=C bonds) to the reactants. Indeed, such abilities to dictate the size and shape of a molecule would be reminiscent of synthetic flexibilities of the liquid phase where such synthetic 'freedoms' are routinely employed to synthesize molecular targets [4]. In the case of the solid state, the linear templates would effectively serve as molecular-level tools that enable molecular syntheses by design.

6.2.1
Cyclophane

To employ a linear template as a tool to construct a molecule, we focused upon a [2.2]paracyclophane as a target (Fig. 18). The cyclic molecule is a member of a general class of layered aromatic compounds that has gained widespread interest owing to the ability of such molecules to provide challenging targets in organic chemistry and find applications in areas ranging from chemical syn-
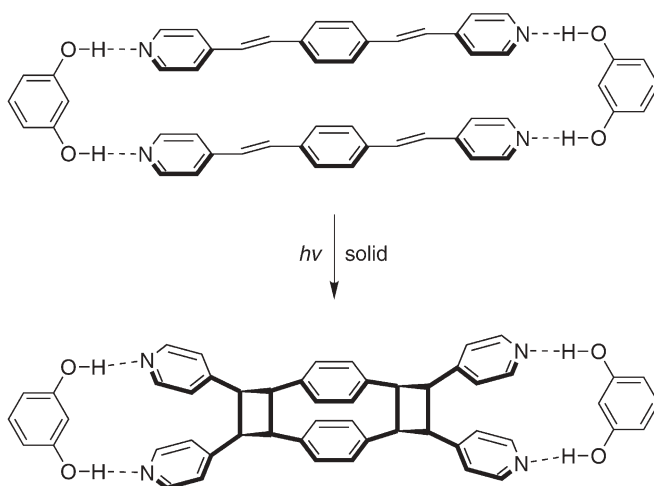

Fig. 18 Scheme illustrating the template-controlled solid-state synthesis of a [2.2]paracyclophane
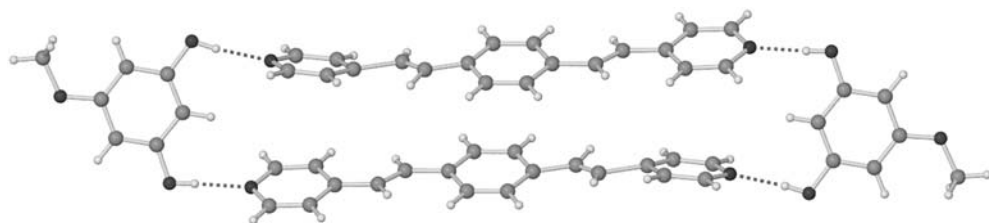
Fig. 19 Perspective of the four-component complex 2(5-OMe-res)·2(1,4-bpeb)

thesis (e.g., catalysis) to materials science (e.g., optical materials) [40]. Specifically, we anticipated that co-crystallization of a resorcinol, or a 1,8-nap, with the diolefin 1,4-bis(2-(4-pyridyl)ethenyl)benzene (1,4-bpeb) would produce the four-component complex 2(resorcinol)·2(1,4-bpeb) with two olefins positioned for a 'double' [2+2] photodimerization. UV-irradiation of the solid would give a tricyclic product with an inner cyclic core reminiscent of a [2.2]paracyclophane. The periphery of the product would, in effect, possess an imprint of the two templates along the exterior of the molecule [8]. The method would also provide a novel entry to cyclic molecules where low yields often requiring high dilution conditions (i.e. large batches of solvent) are common in solution [41].

As anticipated, co-crystallization of 1,4-bpeb with 5-OMe-res produced the discrete, four-component complex 2(5-OMe-res)·2(1,4-bpeb) held together by four O-H···N hydrogen bonds (Fig. 19) [25]. In this arrangement, the olefins of 1,4-bpeb, one of which was disordered across two positions (occupancies: 70:30), were aligned such that the olefinic bond of the major site conformed to the geometry criteria of the topochemical postulates with the ordered olefin, the two C=C bonds being separated by 3.70 Å. UV-irradiation of 2(5-OMe-res)·2(1,4-bpeb) produced the targeted [2.2]paracyclophane, along with a monocyclized dimer and indefinable products, in 60% yield. The formation of the monocyclized product was attributed to face-to-face stacking of the complexes which introduced close contacts (i.e., <4.2 Å) of C=C bonds in the solid. Thus, by adapting to the size of a lengthened reactant, the template served as a tool, providing regio- and stereocontrolled access to a lengthened cyclophane target.

6.2.1.1
Template-Switching to Influence Yield

With a target-oriented synthesis of a paracyclophane realized, we anticipated that template-switching could be used to generate a packing environment that, in contrast to 2(5-OMe-res)·2(1,4-bpeb), could accommodate the cyclophane in quantitative yield. The ability to generate the cyclophane in quantitative yield could also be employed to provide ready access to gram quantities of the product.
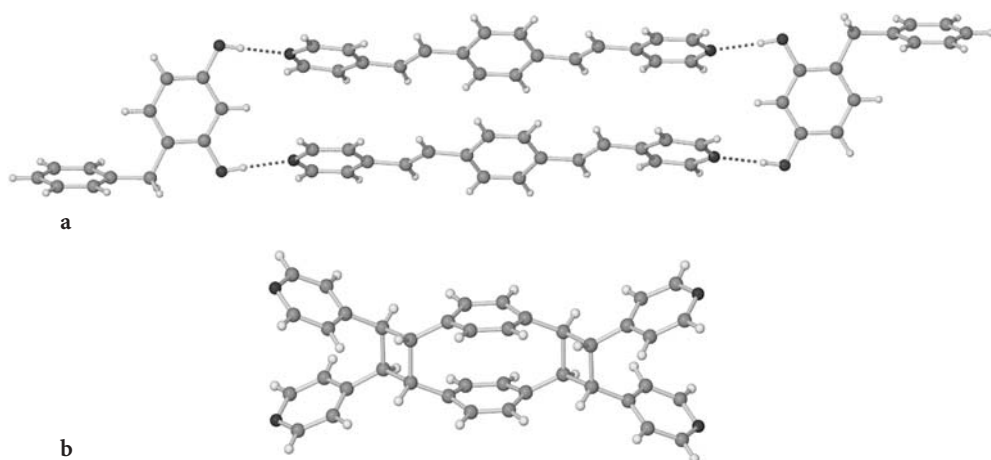
Fig. 20a, b Achieving 100% yield and gram quantity construction of a cyclophane: **a** perspective of the four-component complex 2(4-benz-res)·2(1,4-bpeb); **b** the targeted [2.2]paracyclophane

In line with our strategy, co-crystallization of 4-benzylresorcinol (4-benz-res) with 1,4-bpeb produced the discrete, four-component complex 2(4-benz-res)· 2(1,4-bpeb) held together by four O-H···N hydrogen bonds (Fig. 20a) [35]. The olefinic groups of the complex assembled parallel and separated by 3.60 Å. In contrast to 2(5-OMe-res)·2(1,4-bpeb), the C=C bonds of the complex were ordered and nearest-neighbor complexes assembled offset such that there were no close C=C contacts involving neighboring complexes in the solid. Moreover, UV-irradiation of 2(4-benz-res)·2(1,4-bpeb) resulted in the quantitative conversion of 1,4-bpeb to the targeted [2.2]paracyclophane, as confirmed by way of single-crystal X-ray analysis (Fig. 20b). Indeed, the quantitative generation of the cyclophane in 2(4-benz-res)·2(1,4-bpeb) provided ready access to gram quantities of the target which enabled us to determine the structure of the product.

7
Solid-State Polymerization of Acetylenes

For a thermal polymerization of a diacetylene to give a polydiacetylene to occur, the diacetylenes, similar to a [2+2] photodimerization, must be organized in a prescribed geometry to react [42]. Specifically, the carbon atoms of a diacetylene must adopt a linear arrangement with an intermolecular repeat spacing of approximately 5.0 Å and tilt angle of 45° (Fig. 21). Most diacetylenes, similar to olefins, however, do not crystallize in an arrangement suitable for solid-state reaction. Moreover, the application of molecules that assemble and, in effect, serve as linear templates has offered a solution to this problem.
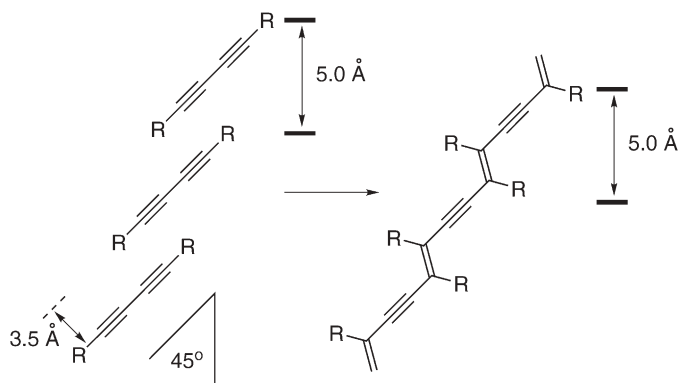
Fig. 21 Topochemical requirement for the polymerization of diacetylenes in the solid state

7.1
Templates to Direct Di- and Triacetylene Polymerization

A strategy based on host molecules that assemble and function as templates that direct the thermal polymerization of diacetylenes has been described by Fowler and Lauher [43]. The method has involved molecules that self-assemble into 1D hydrogen-bonded polymers. The polymers have been shown to impose a characteristic intermolecular repeat distance and tilt angle upon diacetylenes such that the reactants conform to the geometric requirements for solid-state polymerization. Thus, co-crystallization of the oxalamide of glycine with a bis-pyridyl substituted diacetylene was revealed to impose a repeat distance and tilt angle of 4.97 Å and 43°, respectively, upon the diacetylene (Fig. 22) [43]. The resulting solids slowly polymerized at room temperature to give the targeted diacetylene polymer. Notably, thermal annealing at a slightly elevated temperature increased the rate of conversion. In addition to a diacetylene, the
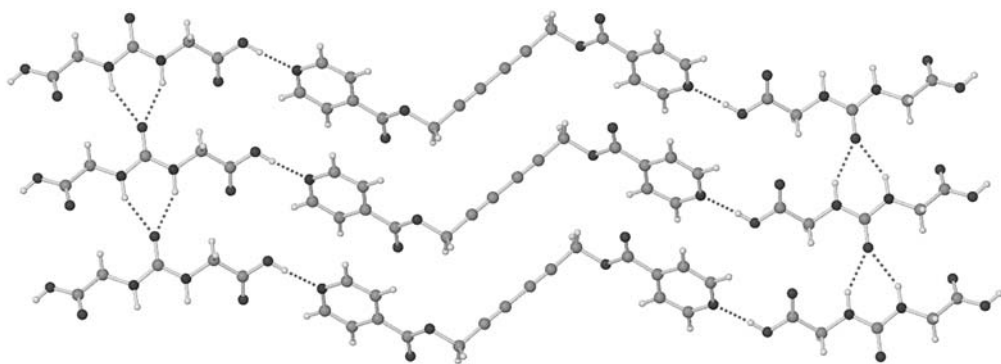

Fig. 22 Perspective of a co-crystal involving an oxalamide of glycine and a bis-pyridyl substituted diacetylene

method has been applied a triacetylene in an unprecedented polymerization that gives a triacetylene polymer [44].

8
Summary and Outlook

Linear templates have served as tools that control reactivity in the solid state. By preorganizing olefins within discrete hydrogen-bonded complexes for [2+2] photodimerization [22, 23, 25, 26], linear templates have been shown to provide a means to isolate reactants from subtle structural effects of close packing such that it is now possible to conduct molecular solid-state synthesis by design [25]. The approach has also been applied to direct polymerizations in the solid state, yielding both di- and triacetylenes [49, 50].

Whereas an early goal of applying linear templates to the solid state has been to control reactivity, it has become clear that the method has also provided an equally intriguing means to employ principles of molecular recognition [20] and self-assembly [21] to direct the syntheses of molecules and polymers. Indeed, the degree of organization provided by the solid state has enabled multiple equilibria involving noncovalent complexes normally encountered in the liquid phase to be avoided such that it is now possible to reliably capture and transform self-assembled complexes [3] into complex covalent structures. Consequently, it now possible to address what kinds of covalent structures can be predesigned and constructed using the approach. Notably, the hydrogen bond acceptor sites attached to the products also present functionality intimately connected to the functions of the templates which makes the products attractive building blocks [21] in coordination- and hydrogen-bond-driven self-assembly [30, 45], while the imprints of the templates, upon removal, may yield 'true' targets. Studies are underway to assess these, and related, possibilities of the linear template, solid-state approach.

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