

Supramolecular Control of Reactivity in the Solid State: From Templates to Ladderanes to Metal–Organic Frameworks

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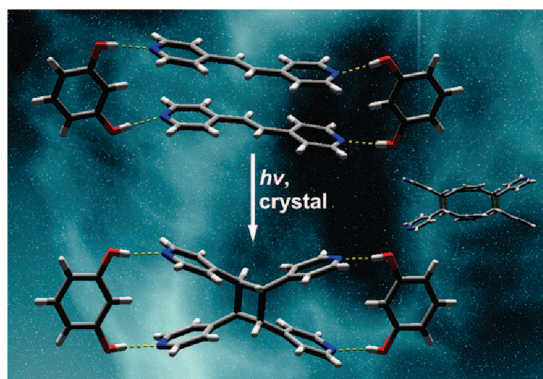
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We describe how reactivity can be controlled in the solid state using molecules and self-assembled metal–organic complexes as templates. Being able to control reactivity in the solid state bears relevance to synthetic chemistry and materials science. The former offers a promise to synthesize molecules that may be impossible to realize from the liquid phase while also taking advantage of the benefits of conducting highly stereocontrolled reactions in a solvent-free environment (i.e., green chemistry). The latter provides an opportunity to modify bulk physical properties of solids (e.g., optical properties) through changes to molecular structure that result from a solid-state reaction. Reactions in the solid state have been difficult to control owing to frustrating effects of molecular close packing. The high degree of order provided by the solid state also means that the templates can be developed to determine how principles of supramolecular chemistry can be generally employed to form covalent bonds. The paradigm of synthetic chemistry employed by Nature is based on integrating noncovalent and covalent bonds. The templates assemble olefins via either hydrogen bond or coordination-driven self-assembly for intermolecular [2 + 2] photodimerizations. The olefins are assembled within discrete, or finite, self-assembled complexes, which effectively decouples chemical reactivity from effects of crystal packing. The control of the solid-state assembly process affords the supramolecular construction of targets in the form of cyclophanes and ladderanes. The targets form stereospecifically, in quantitative yield, and in gram amounts. Both [3]- and [5]-ladderanes have been synthesized. The ladderanes are comparable to natural ladderane lipids, which are a new and exciting class of natural products recently discovered in anaerobic marine bacteria. The organic templates function as either hydrogen bond donors or hydrogen bond acceptors. The donors and acceptors generate cyclobutanes lined with pyridyl and carboxylic acid groups, respectively. The metal–organic templates are based on Zn(II) and Ag(I) ions. The reactivity involving Zn(II) ions is shown to affect optical properties in the form of solid-state fluorescence. The solids based on both the organic and metal–organic templates undergo rare single-crystal-to-single-crystal reactions. We also demonstrate how the cyclobutanes obtained from this method can be applied as novel polytopic ligands of metallosupramolecular assemblies (e.g., self-assembled capsules) and materials (e.g., metal–organic frameworks). Sonochemistry is also used to generate nanostructured single crystals of the multicomponent solids or cocrystals based on the organic templates. Collectively, our observations suggest that the organic solid state can be integrated into more mainstream settings of synthetic organic chemistry and be developed to construct functional crystalline solids.



Introduction

Noncovalent and covalent bonds are central to chemistry and life's processes.¹ The former are exploited in supramolecular chemistry for the construction of assemblies of molecules that exhibit properties and function beyond individual components.² The latter lies at the core of our understanding of the structures and properties of molecules.³ Nature combines noncovalent and covalent bonds to sustain life's processes. The synthesis of proteins, for example, requires a molecular code to be translated and transcribed via the formation and breakage of noncovalent (e.g., hydrogen bonds) and covalent bonds (e.g., peptide bonds).¹ The fidelity and generality with which Nature combines noncovalent and covalent bonds continues to inspire chemists⁴ to mimic such processes for the design of new catalysts,⁵ molecular machines and devices,⁶ and new forms of medicine.⁷

It is with these concepts in mind that we outline, in this Account, a method being developed in our laboratory that enables noncovalent bonds to be utilized, in a general way, to direct the formation of covalent bonds. In particular, we show how small organic molecules and metal-organic complexes act as templates to direct photochemically induced [2 + 2] cycloaddition reactions in the solid state.^{8,9} We demonstrate how the method enables molecules to be generated stereospecifically, in quantitative yield, and in gram amounts. A key to achieving this goal lies in the ability of the templates¹⁰ to assemble and preorganize reactant olefins within finite or zero-dimensional (0D) supramolecular assemblies, or supermolecules, for the reactions. We also show how this method enables bulk physical properties of solids (e.g., optical properties) to be modified and how the products can be employed as building blocks of porous metal-organic structures and materials. The application of sonochemistry to synthesize nanostructured reactive solids is also discussed.

Supramolecular Control of Solid-State Reactivity

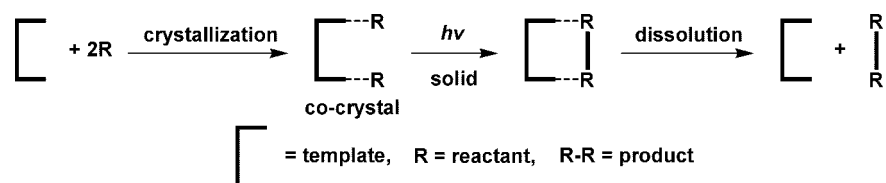
In 2000, we embarked to determine whether the solid state could be used as a medium to synthesize molecules by design. To achieve this goal, our plan was to identify a ditopic

molecule that preorganizes, via molecular recognition and self-assembly, two olefins in a position for an intermolecular [2 + 2] photodimerization (Scheme 1). The molecule would function as a linear template (cf. DNA)¹⁰ by assembling olefins within stacked or linear geometries for photo-reactions. Following a photoreaction, the template could be recycled for further synthesis.

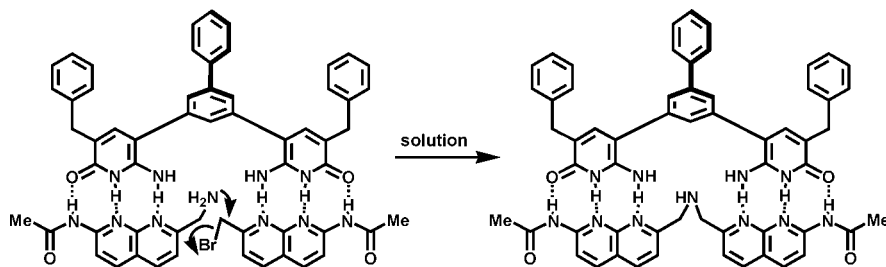
Our initial motivations to control reactivity in the solid state were twofold. First, the solid state, in contrast to the liquid phase, had been largely underutilized as a medium to construct molecules by design.¹¹ Although reactions had been known to proceed in the solid state for more than 100 years, frustrating effects of close packing¹² had thwarted efforts to control solid-state reactivity with the kinds of synthetic freedoms realized in solution. This meant that the benefits of employing the solid state as a medium for synthesis, which include high stereocontrol of reactivity, formation of unique products, and a solvent-free medium, remained largely underexploited.^{11,13} We hypothesized that a linear template could tackle problems of crystal packing since the template would assemble the olefins within a supermolecule,¹⁴ which would have a structure largely independent of long-range packing. At the same time, the template could be used to construct different products since the self-assembly process, with the template being located along the exteriors of the olefins,¹⁰ could accommodate structural changes (e.g., size) to the reactants. Our second motivation was that the field of supramolecular chemistry,² in which *molecules* direct covalent-bond formations, had remained largely unexplored as a general avenue to conduct organic synthesis. Work in the 1980s and 1990s showed that linear templates could assemble molecules in the liquid phase to react (Scheme 2).¹⁵ Binding of molecules in solution, however, is typically low owing to effects of entropy and solvent on structure.¹⁶ We hypothesized that the solid state could allow us to circumvent effects of entropy and solvent and, thereby, utilize linear templates¹⁰ as tools to direct the supramolecular construction of molecules.

Our aim to gain supramolecular control of reactivity in a medium sensitive to changes to molecular structure meant that we needed a reaction that was well understood and

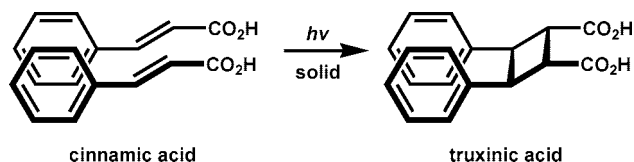
SCHEME 1



SCHEME 2



SCHEME 3



attractive for organic synthesis. We chose the [2 + 2] photodimerization of olefins.^{8,9} Pioneering work of Schmidt in the 1960s and 1970s provided topochemical postulates for olefins to photodimerize in solids. The work, which has provided roots for the field of crystal engineering,¹² comes from structure studies of cinnamic acids and generally states that two carbon–carbon double (C=C) bonds will photodimerize if the bonds lie approximately parallel and separated by <math><4.2 \text{ \AA}</math> (Scheme 3). Although the postulates are valuable¹⁷ for predicting whether a dimerization will occur, Schmidt showed that the reaction, in contrast to the liquid phase, is generally not maintained among closely related olefins. This was attributed to the sensitivity of crystal packing to molecular structure (e.g., substituent size). From a synthetic viewpoint, the importance of the cycloaddition in organic synthesis was evident.¹⁸ The cyclobutane ring from the reaction is an important building block in natural products and was emerging as a synthon of complex molecules (e.g., hydrocarbons). The ease with which cyclobutanes form and open also made the ring system synthetically valuable. Following the work of Schmidt and prior to our work studies aimed to control the cycloaddition in solids⁹ involved either covalently attaching substituents to C=C bonds¹⁹ or employing auxiliary components²⁰ to steer olefins for reaction. Hydrogen bonds^{19b,20} and charge-transfer forces,^{19c} as well as chlorine–chlorine^{19d} and benzene–perfluorobenzene^{19a} interactions, had been employed with different levels of success.

Template-Controlled Solid-State Reactivity

To develop a linear template that directs the [2 + 2] photodimerization in the solid state, we hypothesized that 1,3-dihydroxybenzene, or resorcinol (res), could direct *trans*-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) to react (Scheme 4). Our

hypothesis was based on three findings. First, in 1988, Aoyama reported a cocrystal²¹ wherein a bis(resorcinol)anthracene directed stacking of quinones via hydrogen bonds.²² The quinones were stacked at a separation of 3.80 Å, which was within the distance of Schmidt for a photodimerization. We concluded that res could be used to direct stacking of other heterocycles; specifically, pyridines via O–H···N hydrogen bonds. Second, in 1995, Ito described coerced stacking of cinnamates in diammonium salts.^{20c,d} Although the solids often afforded product mixtures, it was clear that forced stacking of olefins was possible. In the same year, Feldman described a J-shaped naphthalene dicarboxylic acid that formed a hydrogen-bonded dimer with two C=C bonds pre-organized for a photodimerization.^{19b} The dimer isolated the olefins from crystal packing. The olefins reacted in quantitative yield and generated a single product (Scheme 5).

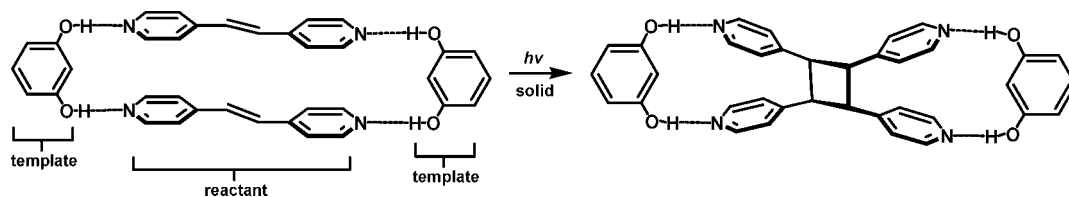
With the studies of Aoyama, Ito, and Feldman established, we cocrystallized res with 4,4'-bpe. The result was a four-component supermolecule with two C=C bonds of two olefins positioned via four O–H···N hydrogen bonds for an intermolecular [2 + 2] photodimerization (Figure 1).²³ Ultraviolet (UV) radiation of a powdered sample resulted in the stereocontrolled formation of *rac*-tetrakis(4-pyridyl)cyclobutane (4,4'-tpcb) in 100% yield and gram quantities. Res was separated from the cyclobutane product through basic extraction.²⁴

Generality of Template-Controlled Solid-State Reactivity

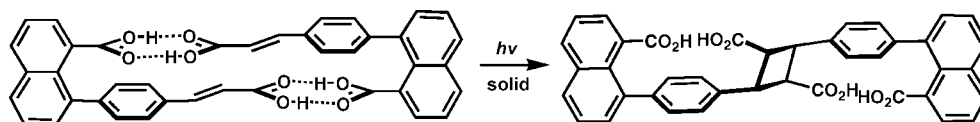
Since our initial report, we have determined that the templates and reactants can be generalized. We have developed templates that assemble olefins via hydrogen bonds (1,8-nap, 2,3-nap, Reb-im) and coordination bonds (Zn₂L, Ag₂) (Scheme 6). We have modified the templates to tailor the self-assembly processes and modify physical properties of the solids. We have changed the recognition sites and number of reactive centers attached to the olefins. We have also modified the reactants to construct molecules by design.

Hydrogen-Bond Templates. We first extended linear templates to 1,8-naphthalenedicarboxylic acid (1,8-nap) (Fig-

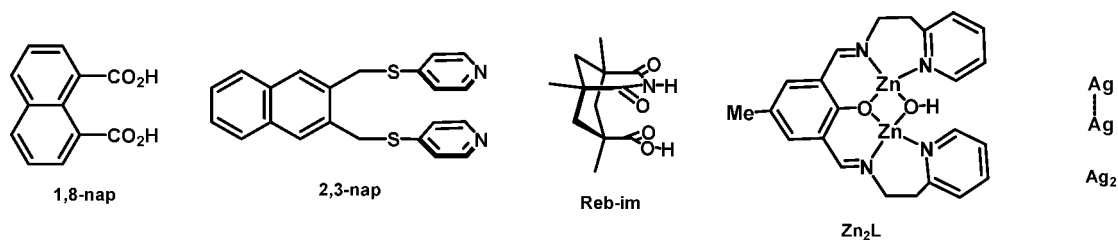
SCHEME 4



SCHEME 5



SCHEME 6



ure 2).²⁵ Cocrystallization of 1,8-nap with 4,4'-bpe produced the four-component assembly $2(1,8\text{-nap}) \cdot 2(4,4'\text{-bpe})$. Each carboxylic acid interacted with 4,4'-bpe via an $O-H \cdots N$ hydrogen bond (Figure 2a). The $C=C$ bonds were organized parallel and separated by 3.73 Å. UV-irradiation produced 4,4'-tpcb in quantitative yield.

We also reversed the "code" of the self-assembly to a hydrogen-bond acceptor.²⁶ In particular, cocrystallization of 2,3-bis(4-methylenepyridyl)naphthalene (2,3-nap) with fumaric acid (fum) produced $2(2,3\text{-nap}) \cdot 2(\text{fum})$ with $C=C$ bonds parallel and separated by 3.84 Å (Figure 2b). UV-irradiation produced *rctt*-1,2,3,4-cyclobutanetetracarboxylic acid in up to 70% yield. The reaction occurred via a rare single-

crystal-to-single-crystal (SCSC) transformation.²⁷ This study also demonstrated that carboxylic acid groups could be incorporated within a photoproduct.

Whereas res, 1,8-nap, and 2,3-nap are symmetrical, we also developed an unsymmetrical template. From studies of induced π -stacking,²⁸ we expected Rebek's imide (Reb-im) to function as an unsymmetrical template.²⁹ Each different "hand" of Reb-im would assemble and interact with two different 4-pyridyl groups of 4,4'-bpe. Cocrystallization of Reb-im

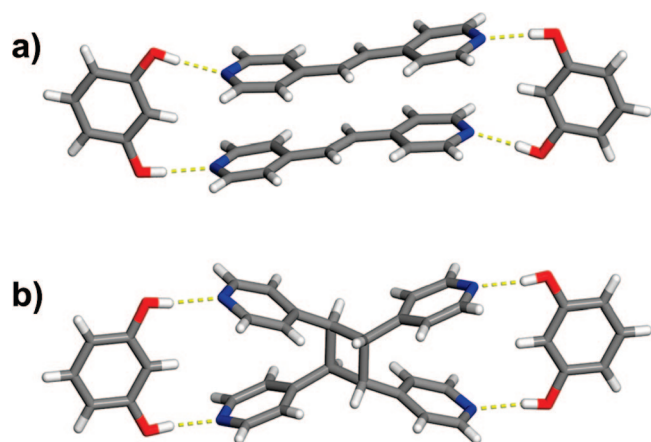


FIGURE 1. X-ray structures: (a) $2(\text{res}) \cdot 2(4,4'\text{-bpe})$ and (b) $2(\text{res}) \cdot (4,4'\text{-tpcb})$ (color scheme: C, gray; H, white; N, blue; O, red).

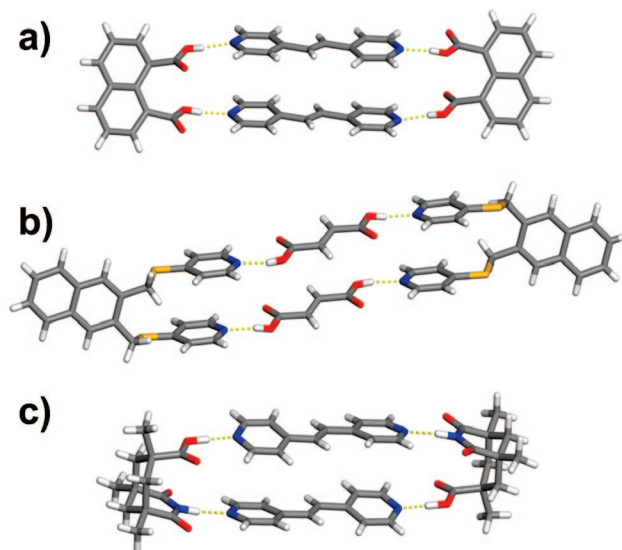


FIGURE 2. X-ray structures: (a) $2(1,8\text{-nap}) \cdot 2(4,4'\text{-bpe})$; (b) $2(2,3\text{-nap}) \cdot 2(\text{fum})$; (c) $2(\text{Reb-im}) \cdot 2(4,4'\text{-bpe})$ (color scheme: C, gray; H, white; N, blue; O, red; S, yellow).

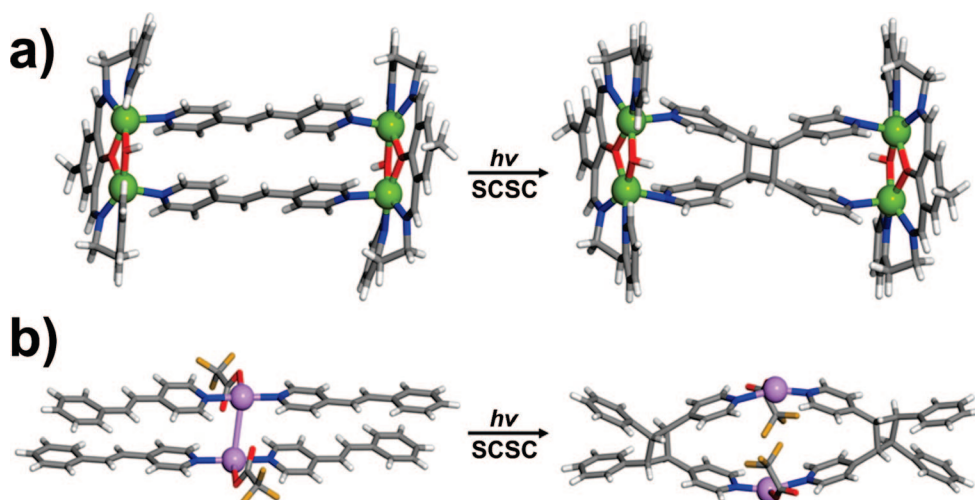


FIGURE 3. SCSC reactions: (a) $[Zn_4L_2(OH)_2(4,4'-bpe)_2]^{4+}$ and (b) $[Ag_2(4-stilbz)_4]^{2+}$ (color scheme: Zn, green; Ag, lavender; C, gray; H, white; F, orange; N, blue; O, red).

with 4,4'-bpe produced $2(\text{Reb-im}) \cdot 2(4,4'-bpe)$ (Figure 2c). The supermolecule formed via $O-H \cdots N$ and $N-H \cdots N$ forces wherein Reb-im adopted an antiparallel orientation within the hydrogen-bonded structure. The solid reacted to give 4,4'-tpcb stereospecifically and in quantitative yield. The material also exhibited a partial SCSC transformation in up to 28% conversion.²⁷ We showed that the reactivity could be maintained following removal of an included toluene molecule. This suggested that such a reactive system may be developed in media less organized than a crystal (e.g., polymers).

We have also attached functional groups to the templates. Specifically, homologous templates based on phloroglucinol maintained reactivity in all cases.³⁰ Alkyl and aryl groups were attached to the templates. In a related study, *ortho* substitution preorganized res in a *syn* conformation to generate a finite structure.³¹

Following our initial work, other bifunctional templates were used to assemble olefins for $[2 + 2]$ cycloadditions in the solid state.³² These studies involved hydrogen bonds,^{32a-d} halogen bonds,^{32e} and host cavities.^{32f}

Metal–Organic Templates. The field of coordination-driven self-assembly has experienced rapid growth in recent years.³³ As with organics, the goal is to construct multicomponent assemblies with properties that transcend the individual components. Coordination bonds are stronger than hydrogen bonds, while metal ions exhibit distinct physical properties (e.g., magnetic properties).

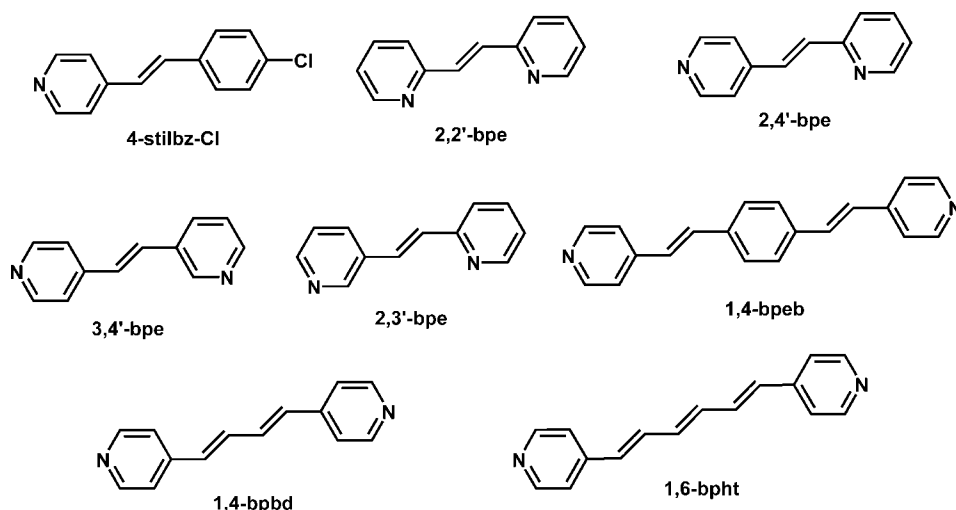
To address whether a self-assembled coordination complex could function as a template, we turned to the Schiff base $[M_2L(OH)]$ (where $L = 2,6\text{-bis}[N\text{-(2-pyridylethyl)formimidoyl}]-4\text{-methylphenol}$) (Figure 3a). The ligand, introduced by Robson and Okawa,³⁴ had been used to position two metal atoms

on the order of 3.15 Å. We showed that the Zn(II) complex $[Zn_2L(OH)]^{2+}$ stacks two molecules of 4,4'-bpe within 3.64 Å in the tetranuclear assembly $[Zn_4L_2(OH)_2(4,4'-bpe)_2]^{4+}$ (Figure 3a).³⁵ UV-irradiation produced 4,4'-tpcb via a SCSC photodimerization in quantitative yield. The photodimerization also induced a remarkable red shift in fluorescence. The solid emitted at 464 and 520 nm before and after the photoreaction, respectively. This material was the first metal–organic solid to exhibit photocontrolled fluorescence. Later, and following a report by Vittal,³⁶ we described a metal–organic framework (MOF) with reactive olefins (Figure 3b).³⁷ Specifically, reaction of the same Zn(II) complex with an additional equivalent of 4,4'-bpe produced a 1D MOF with olefins that formed 4,4'-tpcb stereospecifically in 95% yield.

To expand the metal–organic approach, we demonstrated that Ag(I) ions can assemble *trans*-1-(4-pyridyl)-2-(phenyl)ethylene (4-stilbz) in $[Ag_2(4-stilbz)_4][CO_2CF_3]_2$ for a regiocontrolled head-to-head photodimerization to give *rctt*-1,2-bis(4-pyridyl)-3,4-bis(phenyl)cyclobutane (4-pyr-ph-cb) in quantitative yield (Figure 3b).³⁸ The ions engaged in argentophilic forces, being separated by 3.41 Å, while the C=C bonds exhibited a crossed arrangement, being separated by 3.82 Å (Figure 3b). That the photoreaction proceeded despite the crossed C=C bonds was attributed to the olefins undergoing a pedal-like rotation. The reaction proceeded via a SCSC transformation with the dinuclear complex being converted to a 1D MOF. The MOF formed through the breakage and formation of the $Ag \cdots Ag$ and $Ag \cdots C$ forces, respectively. Vittal has since demonstrated the ability of Ag(I) ions to mediate a $[2 + 2]$ photodimerization of 4,4'-bpe in crystalline and desolvated 1D MOFs.^{39,40}

Olefins and Photoproducts. That a linear template assembles exterior to the reactants means that the template

SCHEME 7



can accommodate structural changes to the reactants. In principle, reactant size, shape, or functionality can be changed. Changes in functionality can involve, for example, addition of a substituent, C=C bond, or 'handle' group. Deliberate changes can provide a means to construct molecules by design. To date, we have modified the olefins in three ways. We have changed the number of pyridyl groups, modified the position of the N-nuclei (2,2', 2,4', 2,3', and 3,4'-bpe), and added functionalities in the form of a phenyl group (1,4-bpeb) and C=C bonds (1,4-bpbd, 1,6-bpht) (Scheme 7). The functionalities have yielded a [2.2]paracyclophane and ladderanes, respectively. The olefins were assembled using hydrogen bonds.

An olefin with a single pyridyl group was assembled to react.⁴¹ Cocrystallization of 4-ethylres with *trans*-1-(4-pyridyl)-2-(4-chloro-phenyl)ethylene (4-stilbz-Cl) produced (4-ethylres) · 2(4-stilbz-Cl) (Figure 4a). The olefins were aligned head-to-head and formed *rctt*-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane (4-pyr-ph-cb-Cl) in quantitative yield.

In addition to 4,4'-bpe, we have employed linear templates to assemble 2,2',²³ 2,4',⁴² 3,4',⁴³ and 2,3'-bpe⁴⁴ for reaction. As with 4,4'-tpcb, the olefins formed the *rctt* photoproducts. For the unsymmetrical reactants (i.e., 2,4'- and 2,3'-bpe), the olefins assembled head-to-head and formed head-to-head products. Thus, cocrystallization of 1,8-nap with 3,4'-bpe produced 2(1,8-nap) · 2(3,4'-bpe), which reacted to give 3,4'-tpcb (Figure 4b). The reaction proceeded via a SCSC reaction in quantitative yield.

Our first incorporation of functional groups involved the synthesis of a [2.2]paracyclophane.²³ Introduced by Cram, the cyclophane continues to pose synthetic challenges and exhibits promising applications in areas such as catalysis and poly-

mer chemistry.⁴⁵ We anticipated that reaction of a bipyridine with two C=C bonds separated by a phenyl group, namely, 1,4-bis[2-(4-pyridyl)ethenyl]benzene (1,4-bpeb), would give a supermolecule that reacts to form tetrakis(4-pyridyl)-1,2,9,10-diethano[2.2]paracyclophane (4,4'-tppcb). The assembly would be lengthened compared with 2(res) · 2(4,4'-bpe). Cocrystallization of 4-methoxyres with 1,4-bpeb produced 2(5-methoxyres) · 2(1,4-bpeb), wherein the C=C bonds were preorganized for photoreaction. UV irradiation produced 4,4'-tppcb in 60% yield.²³ The relatively low yield was attributed to cross reactions between supermolecules in the solid. Later, we increased the yield to 100% using 4-benzylres (Figure 5a,b),⁴⁶ where cross reactions were prohibited. The process of changing the template to modify yield was termed "template-switching".

We have also constructed ladderanes.⁴⁷ Ladderanes are potential building blocks of optoelectronics and have, very

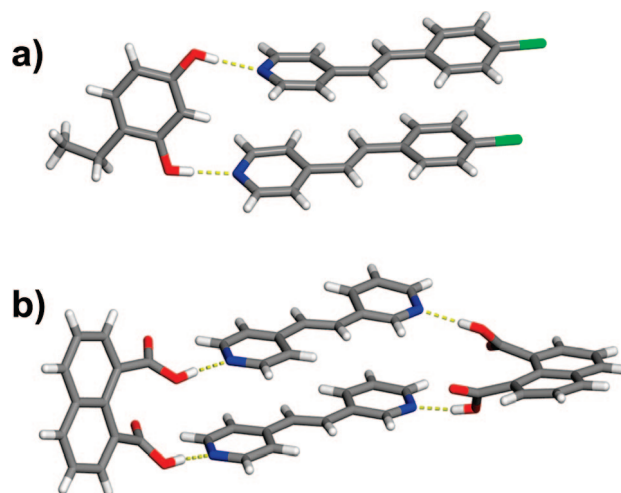


FIGURE 4. X-ray crystal structures: (a) (4-ethyl-res) · 2(4-stilbz-Cl) and (b) 2(1,8-nap) · 2(3,4'-bpe) (color scheme: C, gray; H, white; N, blue; O, red; Cl, green).

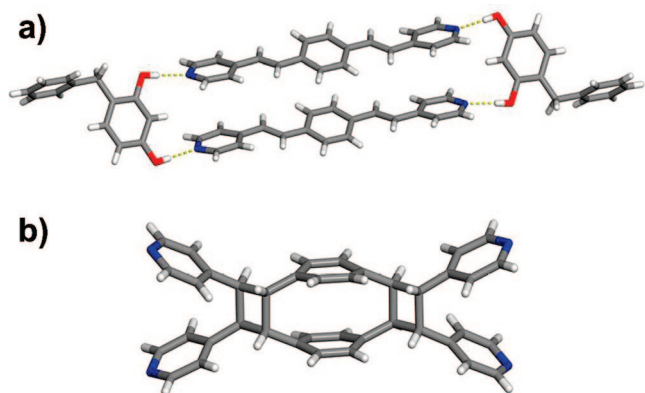


FIGURE 5. X-ray structures: (a) 2(5-benzylres) · 2(1,4-bpbe) and (b) 4,4'-tppcp (color scheme: C, gray; H, white; N, blue; O, red).

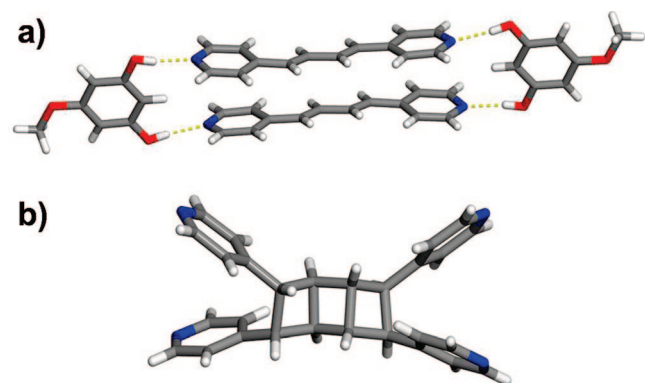


FIGURE 6. X-ray crystal structures: (a) 2(5-methoxyres) · 2(1,4-bpbd) and (b) 4-tp-3-lad (color scheme: C, gray; H, white; N, blue; O, red).

recently, been discovered in intracellular membrane lipids of *anamnox* bacteria. The bacteria participate in the oceanic N_2 cycle.⁴⁸ We anticipated that a linear template could preorganize poly-*m*-enes (where: $m = 2$ or 3) to form [n]-ladderanes (where: $n = 3$ or 5), respectively. Cocrystallization of 5-methoxyres with the conjugated diene *trans,trans*-1,4-bis(4-pyridyl)-1,3-butadiene (1,4-bpbd) and triene *trans,trans,trans*-1,6-bis(4-pyridyl)-1,3,5-hexatriene (1,6-bpht) produced the hydrogen-bonded assemblies 2(5-methoxyres) · 2(1,4-bpbd) and 2(5-methoxyres) · 2(1,6-bpht) (Figure 6a).⁴⁷ UV-irradiation of each solid generated the corresponding ladderanes all-*trans*-tetrakis(4-pyridyl)-[3]-ladderane (4-tp-3-lad) and all-*trans*-tetrakis(4-pyridyl)-[5]-ladderane (4-tp-5-lad) stereospecifically and in quantitative yield (Figure 6b).

Applications of the Products

The products of templated solid-state reactions form with perfect stereocontrol and in gram quantities. This makes the products available for applications *beyond the solid-state syntheses*. This contrasts previous work, where reactivity has been difficult to control in terms of structures and yields of products; consequently, applications of molecules synthesized in the solid state have been limited.¹⁰ That the cyclobutanes are

lined with pyridyl groups made the products initially attractive as building units of metallosupramolecular assemblies and materials (e.g., MOFs).^{33,49} We envisaged that a product could assemble with a transition metal ion to form a MOF wherein the cyclobutane functions as a node.⁴⁹ Such molecules can be difficult or impossible to obtain in the liquid phase or without the template.⁵⁰ Thus, the method could generate novel 'downstream' supramolecular materials. To date, we have determined that the products can serve as building units of MOFs, as well as metal-organic polyhedra and polygons.

MOFs. The compound 4,4'-tpcb has functioned as a four-connected node of two 2D MOFs (Figure 7). Reaction with the Cu(II) paddle-wheel complex $[Cu_2(CO_2CH_3)_4]$ produced the 2D grid $[Cu_4(CO_2CH_3)_8(4,4'-tpcb)]_\infty$ with identical rhombic cavities (Figure 7a).⁵¹ The cavities hosted benzene molecules within 1D channels. The guests were removed via a SCSC process.⁵² Owing to the linear geometry of the dicopper unit, the organic groups of the carboxylate ions pointed into the cavities. We termed the framework an inverted MOF (IMOF) since the metal complex acted as a linear bridge and the cyclobutane a node. Thus, the structural roles of the metal and organic components, as compared with more conventional MOFs, were inverted. Since the terminal anion can be easily changed, an IMOF enables the internal pore structures of MOF solids to be engineered.⁵¹ Reaction of 4,4'-tpcb with $[Co(CO_2CH_3)_2]$ produced the 2D grid $[Co(CO_2CH_3)_2(4,4'-tpcb)]_\infty$ (Figure 7b).⁵³ The MOF possessed two different rhombic cavities, with each angle of the cyclobutane ring defining a different cavity. The framework maintained crystallinity upon guest removal.

The [2.2]paracyclophane 4,4'-tppcp has been used to generate a 2D MOF.⁵⁴ The MOF contained two different nodes and two different cavity types; consequently, the topology conformed to a nonregular net (Figure 7c). In particular, reaction of 4,4'-tppcp with $[Co(CO_2CH_3)_2]$ produced the grid $[Co(CO_2CH_3)_2(4,4'-tppcp)]_\infty$, which contained both rhombus (R) and hexagon (H) cavities. The topology was based on three- and four-connected nodes, with two three-connected nodes being covalently fused via the cyclophane. That the MOF involved two fused three-connected nodes meant that the formation of higher-symmetry MOFs based exclusively upon connections between three- and four-connected nodes was prohibited. Thus, the cyclophane provided a means to code^{49b} the formation of a relatively low-symmetry MOF. The two different cavities hosted different solvent molecules as guests.

Metal-Organic Polyhedra and Polygons. Finite metallosupramolecular assemblies have gained widespread atten-

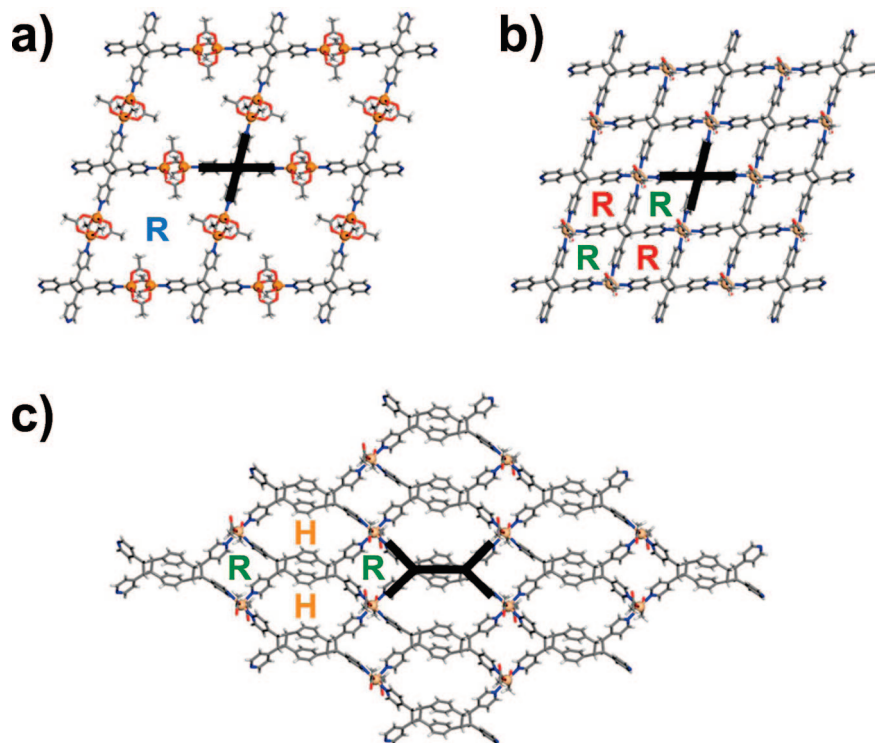


FIGURE 7. X-ray crystal structures: (a) $[\text{Cu}_4(\text{CO}_2\text{CH}_3)_6(4,4'\text{-tpcb})]_{\infty\infty}$ (b) $[\text{Co}(\text{CO}_2\text{CH}_3)_2(4,4'\text{-tpcb})]_{\infty\infty}$ and (c) $[\text{Co}(\text{CO}_2\text{CH}_3)_2(4,4'\text{-tppcp})]_{\infty\infty}$ (color scheme: Co, pink; Cu, orange; C, gray; H, white; N, blue; O, red). Cyclobutane connector highlighted in black (R = rhombus, H = hexagon).

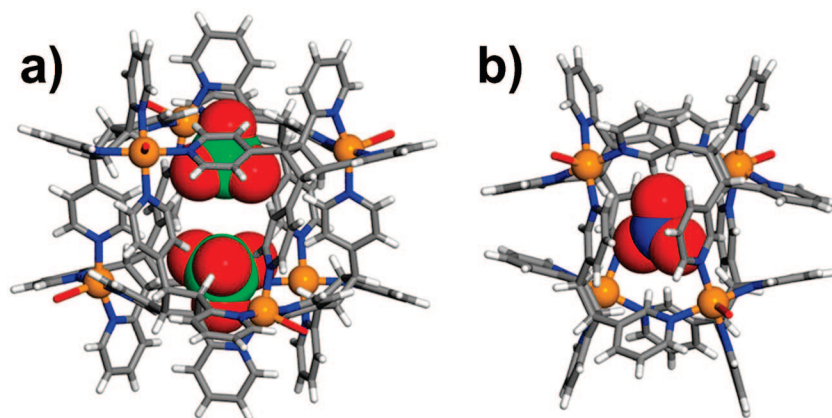


FIGURE 8. X-ray structures: (a) $[\text{Cu}_6(2,4'\text{-tpcb})_6(\text{H}_2\text{O})_6]^{12+}$ (trigonal antiprism) encapsulating two ClO_4^- ions and (b) $[\text{Cu}_4(2,4'\text{-tpcb})_4(\text{H}_2\text{O})_4]^{8+}$ (tetrahedron) encapsulating a NO_3^- ion (color scheme: Cu, orange; C, gray; H, white; Cl, green; N, blue; O, red).

tion (e.g., recognition, catalysis).³³ The synthesis of a finite or discrete self-assembled structure is achieved using a building unit with obtuse or acute corner angles (e.g., 90° , 120°).³³ We have utilized products of template-controlled solid-state reactions as corners of metal–organic polyhedra and polygons.

In particular, reaction of 2,4'-tpcb with $\text{Cu}(\text{ClO}_4)_2$ produced the hexanuclear polyhedron $[\text{Cu}_6(2,4'\text{-tpcb})_6(\text{H}_2\text{O})_6]^{12+}$. The topology conformed to a trigonal antiprism (Figure 8a).⁴² Each cyclobutane interacted with three different Cu(II) ions wherein the 4-pyridyl and 2-pyridyl groups served as monodentate and chelating ligands, respectively. The corners were, thus,

provided by the chelation of the 2-pyridyl groups. Each Cu(II) ion adopted a square pyramidal coordination geometry and occupied a vertex of the polyhedron. The polyhedron was filled by two ClO_4^- ions. Similarly, reaction of 2,3'-tpcb with $\text{Cu}(\text{NO}_3)_2$ produced the tetranuclear polyhedron $[\text{Cu}_4(2,4'\text{-tpcb})_4(\text{H}_2\text{O})_4]^{8+}$ with a structure that conformed to a tetrahedron.⁴⁴ The topology was chiral. The chirality was a result of the geometric fit of the cyclobutane ligands. The central cavity was occupied by a NO_3^- ion.

The photoproducts have also been corners of molecular polygons.⁵⁵ Reaction of 2,4'-tpcb with $\text{Cu}(\text{hfac})_2$ produced a tetranuclear rhomboid. The edges were defined by the 4-py-

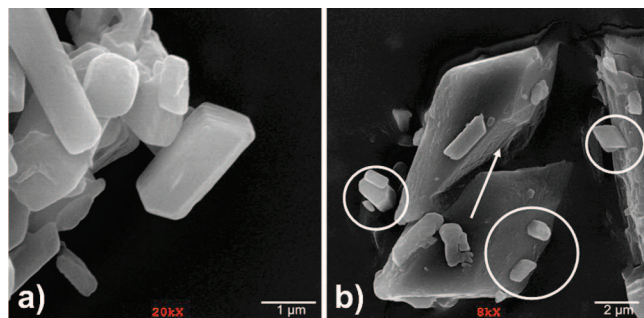


FIGURE 9. Microscopy images of $2(\text{res}) \cdot 2(4,4'\text{-bpe})$ nanostructured cocrystals (a) before and (b) after UV irradiation (circles and arrow highlight crystals that remain intact and crack, respectively).

ridyl groups, while opposite corners were defined by two Cu(II) ions and two cyclobutane rings. The 2-pyridyl groups chelated metal ions along the periphery. This approach was also extended to 4-pyr-ph-cb-Cl. 2,4'-Tpcb represented a rare example of a ligand that supports both a polyhedron and polygon.^{42,55}

Nanostructured Cocrystals

Reactions that proceed in the solid state involve movements of atoms.^{11,27} For a topochemical $[2 + 2]$ photodimerization, each C atom moves on the order of 0.70 Å to form a cyclobutane ring. The movements are accompanied by accumulations of stress and strain in the solids, which can cause single crystals to turn opaque or form powders. Although methods to affect whether an organic solid-state reaction proceeds via a SCSC transformation have emerged (e.g., tail-end absorption),⁵⁶ crystals that undergo SCSC $[2 + 2]$ photodimerizations and SCSC reactivity in general²⁷ remain rare.

Following work of Nakinishi,⁵⁷ we aimed to achieve a SCSC reaction of the cocrystal $2(\text{res}) \cdot 2(4,4'\text{-bpe})$ by reducing crystal size. Studies had shown that organic crystals can exhibit SCSC reactivity by reducing crystal sizes to nanometer-scale dimensions.⁵⁷ Rapid precipitation is typically used to generate such solids. We discovered, however, that rapid precipitation did not afford nanocrystals of $2(\text{res}) \cdot 2(4,4'\text{-bpe})$.⁵⁸ Micro- and millimeter-sized cocrystals with irregular morphologies formed, and the crystals cracked upon photoirradiation. The formation of the large and irregular crystals was attributed to a mismatch of solubilities of the res and 4,4'-bpe components of the solid.

Nanostructured cocrystals of $2(\text{res}) \cdot 2(4,4'\text{-bpe})$ did form, however, via sonocrystallization (Figure 9).⁵⁸ In particular, we applied ultrasonication during a rapid precipitation of $2(\text{res}) \cdot 2(4,4'\text{-bpe})$. The resulting single crystals exhibited uniform morphologies with sizes ranging from 200 nm to 5 μm (Figure 9a). That nanostructured solids formed using sonoc-

rySTALLIZATION was attributed to effects of cavitation, which can provide an environment that favors both rapid solubilization and precipitation of the components. UV irradiation resulted in a SCSC transformation of the nanocrystals, while the larger crystals exhibited cracks (Figure 9b).

Summary and Outlook

In this Account, a method to control reactivity using principles of supramolecular and organic solid-state chemistry has been outlined. The method employs templates that juxtapose olefins for intermolecular $[2 + 2]$ photodimerizations. Success lies in the ability of the templates to enforce stacking within 0D supramolecular assemblies, or supermolecules, which have structures largely independent of long-range packing. The reliability and generality of the approach has enabled us to readily form products and use the products to construct metallosupramolecular assemblies and MOF materials. We are currently expanding this method such that a toolbox of non-covalent bonds and recognition motifs can be applied as synthons to assemble and preorganize a wider range of olefins. The roles of cocrystals in supporting this approach will continue to be developed.

BIOGRAPHICAL INFORMATION

Len MacGillivray was born in Nova Scotia, Canada, where he received a B.Sc., Hons. (Chemistry) from Saint Mary's University in 1994. After receiving a Ph.D. from the University of Missouri—Columbia in 1998 while working in the lab of Professor Jerry L. Atwood, he joined the Functional Materials Program at the Steacie Institute of Molecular Science, National Research Council of Canada, Ottawa, where he was a Research Associate from 1998 to 2000. In 2000, he joined the Department of Chemistry at the University of Iowa as an Assistant Professor and was promoted to his current rank of Associate Professor in 2005. His research focuses upon the field of supramolecular chemistry, particularly as it relates to the design and construction of organic solids. In 2004, he was awarded the Young Investigator Award of the Inter-American Photochemical Society and the Etter Early Career Development Award of the American Crystallographic Association. He was elected a Fellow of the Royal Society of Chemistry in 2006 and was just awarded a 2007 Arthur C. Cope Scholar Award of the American Chemical Society.

Giannis S. Papaefstathiou obtained his B.Sc. in 1998 and his Ph.D. in 2002 from the University of Patras, Greece, working with Professor Spyros P. Perlepes. He moved to the University of Iowa in 2002 to work with Professor Leonard R. MacGillivray as a post-doctoral fellow for 2 years. He then moved back to Greece to work as a temporary Lecturer at the University of Patras and as an Associate Instructional Personnel at the Hellenic Open University. He joined the faculty at the Department of Chemistry of the National and Kapodistrian University of Athens in 2006 as a Lec-

turer. His current research interests are in aspects of coordination chemistry and supramolecular chemistry.

Tomislav Friščić obtained his undergraduate degree in General and Inorganic Chemistry in 2001 from the University of Zagreb, Croatia, studying metal complexes of first row transition metals. In 2002, he became a doctoral fellow of the Center for Biocatalysis and Bioprocessing at the University of Iowa under the supervision of Professor Leonard R. MacGillivray, who inspired his interest in supramolecular chemistry. During his doctoral studies, he became acquainted with the intricacies of modern synthetic organic chemistry and, in 2006, completed a thesis on molecular self-assembly as a way to control solid-state organic photoreactions. Since 2006, he has been a postdoctoral researcher with William Jones at the University of Cambridge. His interests have shifted to developing mechanochemical methods for the synthesis of hydrogen- and halogen-bonded cocrystals as functional solids.

Tamara D. Hamilton was born in Nova Scotia, Canada, in 1979. In 2001, she graduated from Acadia University with a Bachelor of Science degree with Honors. In 2005, she obtained her Ph.D. degree from the University of Iowa for studies on the coordination chemistry of products from template-directed synthesis in the solid state with Leonard R. MacGillivray. Currently, she is a Natural Sciences and Engineering Research Council of Canada (NSERC) postdoctoral researcher in the group of James D. Wuest at Université de Montréal. Her research involves engineering crystals built from molecular tectons with pyrogallol functionalities.

Dejan-Krešimir Bučar was born in Zagreb, Croatia, in 1975. He obtained a B.Sc. degree in chemistry from the University of Zagreb in 2004. In 2005, he joined the research group of Prof. Leonard R. MacGillivray at the University of Iowa as a graduate student. His principal research interests concern various aspects of organic solid-state chemistry with particular focus on template-directed solid-state synthesis and pharmaceutical cocrystals. He is also interested in synthetic organic chemistry, single-crystal X-ray crystallography, and coordination-driven self-assembly.

Qianli Chu was born in 1975. He performed his undergraduate studies in organic chemistry at Shanghai University, P. R. China (1993–1997). He then spent four years at the Shanghai Institute of Organic Chemistry (SIOC) as a research assistant with Prof. Shizheng Zhu. He joined the research group of Prof. Leonard R. MacGillivray at the University of Iowa to obtain his Ph.D. degree in supramolecular chemistry (2001–2005). He is currently a postdoctoral fellow under the guidance of Prof. Dennis P. Curran at University of Pittsburgh with research efforts that mainly focus on fluororous organocatalysis and molecular recognition. His research interests are concentrated at the interface of organic chemistry and supramolecular chemistry.

Dushyant B. Varshney received his B.Pharm. degree (Pharmaceutical Sciences) from the University of Pune in 1997 and completed his M.Pharm. (Pharmaceutical Chemistry) from University of Mumbai in 1999. In 2005, he obtained his Ph.D. degree

(Organic Solid-state Chemistry) from the University of Iowa with Prof. Leonard R. MacGillivray. Upon completing postdoctoral work with Prof. Raj Suryanaryanan at the University of Minnesota (Pharmaceuticals) in 2006, he joined Eli Lilly & Co. (Preformulations). He is currently a Senior Research Investigator at Sanofi-Aventis (Formulation Development).

Ivan G. Georgiev was born in Bulgaria in 1973. He received his B.A. in Chemistry from Missouri State University in 2002. He then graduated with a M.A. degree from the same university conducting research with Prof. Eric Bosch on the design and synthesis of supramolecular complexes. He will graduate with his Ph.D. degree in 2007 under the supervision of Prof. Leonard R. MacGillivray. He is currently a researcher with SoPharma pharmaceuticals in Bulgaria. His research interest lies in the area of supramolecular chemistry and organic solid-state reactivity.

FOOTNOTES

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