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Modularity in Organic Solid State and Supramolecular Chemistry

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Connection between the concept of modularity and how it relates to both organic solid state and supramolecular chemistry is discussed. It is demonstrated how the interrelationship between the three areas can be exploited to control chemical reactivity in the solid state. Specifically, it is shown how these areas can be used to achieve and fine-tune reactivity in organic solids. How modularity relates to other chemical systems, as well as to other areas of technology, is also discussed.

MODULARITY AS AN ELEMENT OF DESIGN

The design of functional systems, in the context of biology,[1] technology,[2] or informatics,[3] relies on a simple scheme of component parts that are mutually interconnected.[4] Assuming that the initial design of a functional system will not necessarily be the best one, either in the context of work- or cost-efficiency,[5] it becomes desirable to use a design that is readily amenable to improvements. A common strategy to achieve that goal is to employ a modular design (*i.e.,* to construct a system from several parts, each with a well-defined and distinct role that can readily be replaced) (Figure 1).[6] A modular system allows easy repair, as well as improvements to the function of the overall system through modulating a single component, rather than re-designing the entire system. The modular approach is extensively exploited by modern technologies, as demonstrated by the 'plug-and-play' concept of the electronics industry and the utilization of subroutine libraries and object programming by computer programmers.[7,8] Indeed, modularity is encountered in the design of biological systems, as exemplified by the processes of genetic recombination, and the structure of a living cell.[9,10] At the molecular level, modular design is found in protein assemblies composed of specialized protein molecules[11] that are held together by non-covalent forces, such as hydrogen bonds and $\pi \cdots \pi$ forces.[12,13]

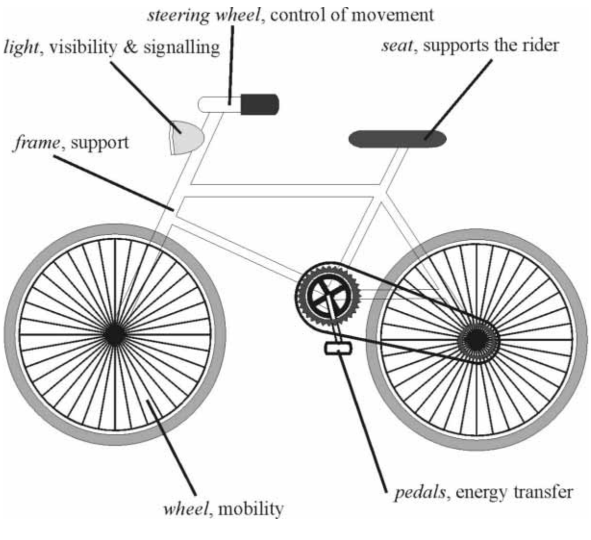

Figure 1. Modular construction of a functional device, illustrated using a simplified scheme of a bicycle. Several significant functional parts are indicated.

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MOLECULAR COCRYSTALS AS MODULAR SOLIDS

In recent years, concepts drawn from biology and supramolecular chemistry have been applied to design and construct organic solids. Molecular recognition and non-covalent forces have been utilized to construct functional solids in the form of multi-component crystals, or cocrystals.[14,15] With this in mind, we intend to illustrate, by providing an account of our own research, how the use of non-covalent interactions provides cocrystals with a property that can be achieved and improved owing to the modularity of the system.[16] The property that our research has focused upon is chemical reactivity in the form of the [2+2] photodimerization of carbon-carbon double bonds (C=C bonds).[17]

CRYSTAL ENGINEERING THE [2+2] PHOTODIMERIZATION

The [2+2] photodimerization in the solid state provides a cyclobutane ring from two olefins. The reaction is topochemically controlled (*i.e.,* reactivity is expected to occur between double bonds that are suitably pre-organized).[18] The issue of topochemical control means that the stereochemistry of the cyclobutane ring formed in the reaction is largely pre-determined by the organization of the C=C bonds in the reactant solid.[19] The geometrical parameters that describe the organization of C=C bonds for the photoreaction have been established by Schmidt and co-workers. The parameters have been compiled in a set of empirical rules known as the topochemical postulates.[20] According to the postulates, the bonds should be positioned in a parallel fashion with a spacing no more than 4.2 Å (Figure 2).[21] Consequently, the focus of crystal engineering in the context of achieving [2+2] photoreactions in the solid state has been to establish molecular packing of olefins that conform to the topochemical postulates.[22] In this context, many studies[23,24] have focused upon the application of non-covalent forces, such as hydrogen bonds, halogen···halogen forces, *e.g.,* Cl···Cl (Figure 3a), and π···π donor···acceptor interactions (Figure 3b) to engineer the [2+2] photoreaction in the solid state.[25]

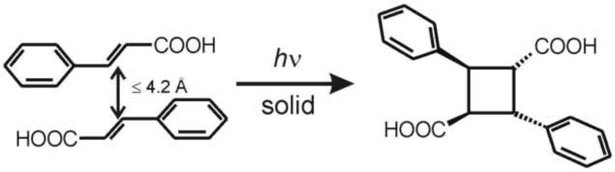


Figure 2. Schematic representation of [2+2] photodimerization in α-cinnamic acid, illustrating the topochemical postulates.

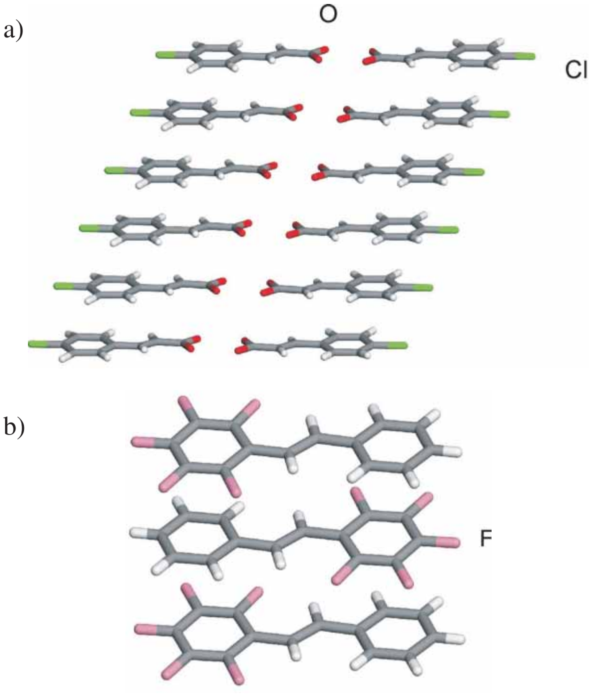


Figure 3. Solid-state structures illustrating the use of Cl···Cl and π···π interactions to achieve photoactive molecular arrangements: a) 4-chlorocinnamic acid and b) 2,3,4,5,6-pentafluorostilbene.

TEMPLATE-CONTROLLED SOLID-STATE SYNTHESIS

In recent years, we have shown that the [2+2] photodimerization can be reliably engineered in the organic solid state within molecular cocrystals. Specifically, we have shown that cocrystallization of resorcinol (res) with *trans*-1,2-bis(4-pyridyl)ethylene (4,4'-bpe) (ratio 1:1) results in the formation of cocrystals of composition 2(res)·2(4,4'-bpe). The cocrystals consist of four-component molecular assemblies held together by four O–H···N hydrogen bonds (Figure 4).[26] In each crystalline assembly, the res molecules act as linear templates by juxtaposing two molecules of 4,4'-bpe in positions suitable for intermolecular [2+2] photodimerization.[27] Upon exposure to ultraviolet (UV) light, the 4,4'-bpe molecules of 2(res)·2(4,4'-bpe) were shown to undergo stereospecific photodimerization to give the *rctt*-isomer of 1,2,3,4-tetrakis(4-pyridyl)cyclobutane (4,4'-tpcb) in quantitative yield and gram amounts (Scheme 1).[28]

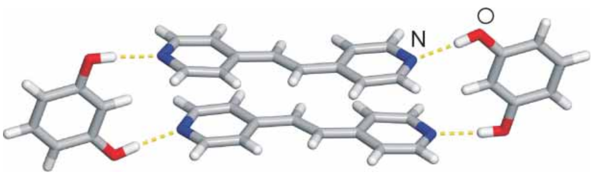
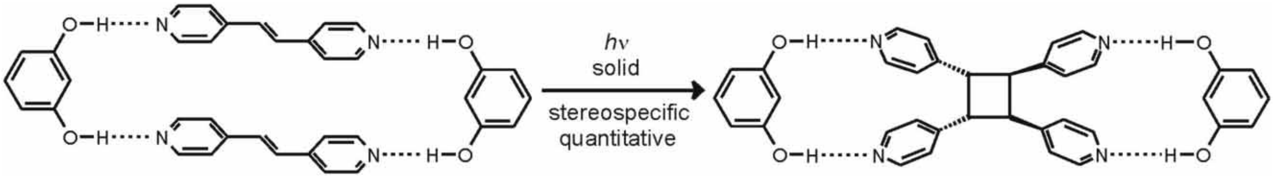


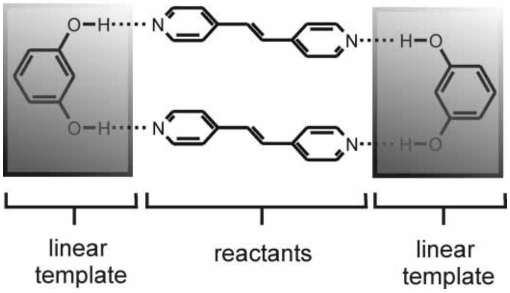
Figure 4. Capped-stick representation of a single crystalline assembly of 2(res)·2(4,4'-bpe).



Scheme 1.

MODULARITY OF TEMPLATE-CONTROLLED SOLID-STATE SYNTHESIS

The architecture of the hydrogen-bonded assembly 2(res)·2(4,4'-bpe) is inherently modular. Specifically, two parts that exhibit different functions are present within the solid-state assembly: the template (res) and the reactant (4,4'-bpe). The two parts are held together by a molecular recognition motif based on O–H···N hydrogen bonds (Scheme 2).



Scheme 2.

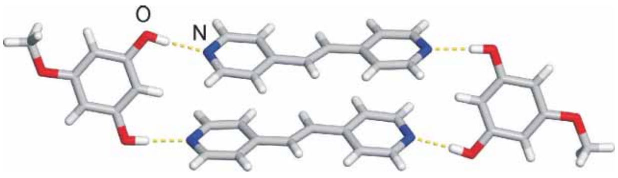


Figure 5. Capped-stick representation of the crystalline assembly 2(5-OMe-res)·2(4,4'-bpe).

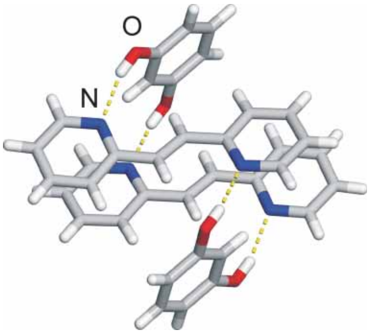
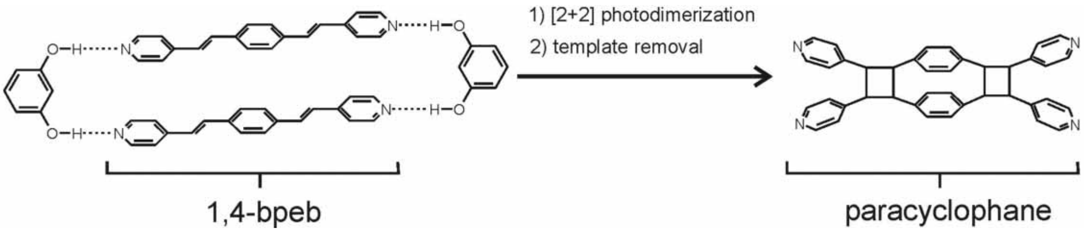


Figure 6. Wireframe model of a single assembly of 2(res)·2(2,2'-bpe) in the crystal.

To explore the modularity of the template-controlled solid-state approach, we decided to test the tolerance of the structure of the hydrogen-bonded assembly to a change to the template. To achieve this goal, we have shown that 5-methoxyresorcinol (5-OMe-res) can be used as a template. Thus, cocrystallization of 5-OMe-res with 4,4'-bpe produced cocrystals composed of finite molecular assemblies of composition 2(5-OMe-res)·2(4,4'-bpe). In each assembly, 5-OMe-res functioned as a template, positioning the 4,4'-bpe reactants for stereospecific [2+2] photodimerization, which produced 4,4'-tpcb quantitatively and in gram amounts (Figure 5).[26,29]

In addition to modifying the template, we have also tested the tolerance of the structure of the molecular assembly to changes to the reactants. Specifically, we speculated that photoactive assemblies involving res could be formed despite changes to the position of the hydrogen-bond acceptor group of the reactant bipyridine. Thus, we have shown that 2,2'-bpe and 2,4'-bpe can function as reactants.[26] Cocrystallization of either 2,2'-bpe or 2,4'-bpe with res resulted in the formation of four-component hydrogen-bonded molecular assemblies held together by four O–H···N hydrogen bonds. In each case, res positioned the C=C bonds of the olefins for a stereospecific [2+2] photodimerization that occurred in quantitative yield (Figure 6), with the unsymmetrical 2,4'-bpe producing the corresponding head-to-head photoproduct.



Scheme 3.

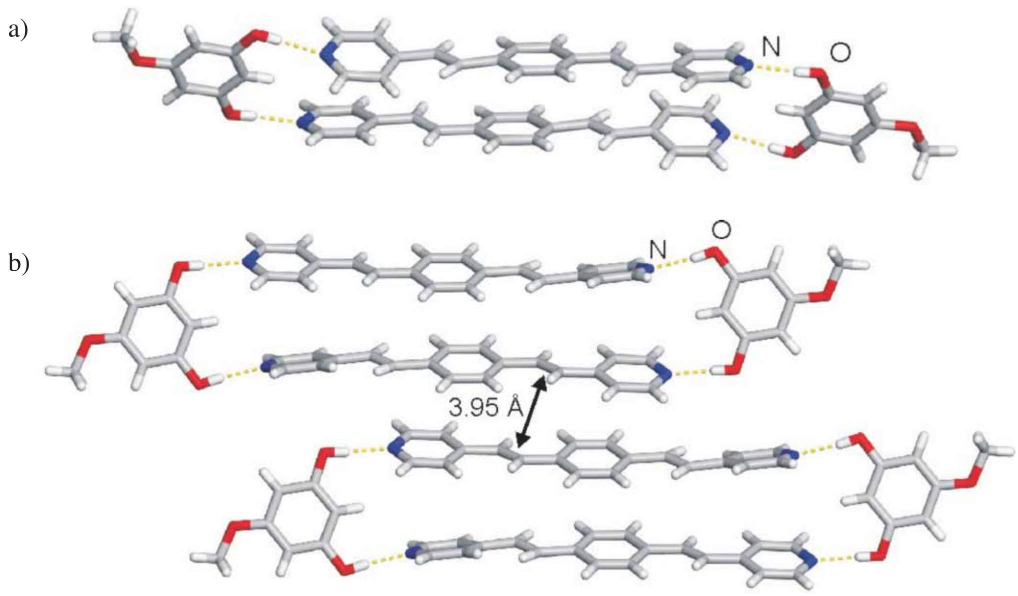


Figure 7. Capped-stick representations of crystalline (1,4-bpeb)· 2(5-OMe-res): a) single assembly, and b) nearest-neighbor assemblies.

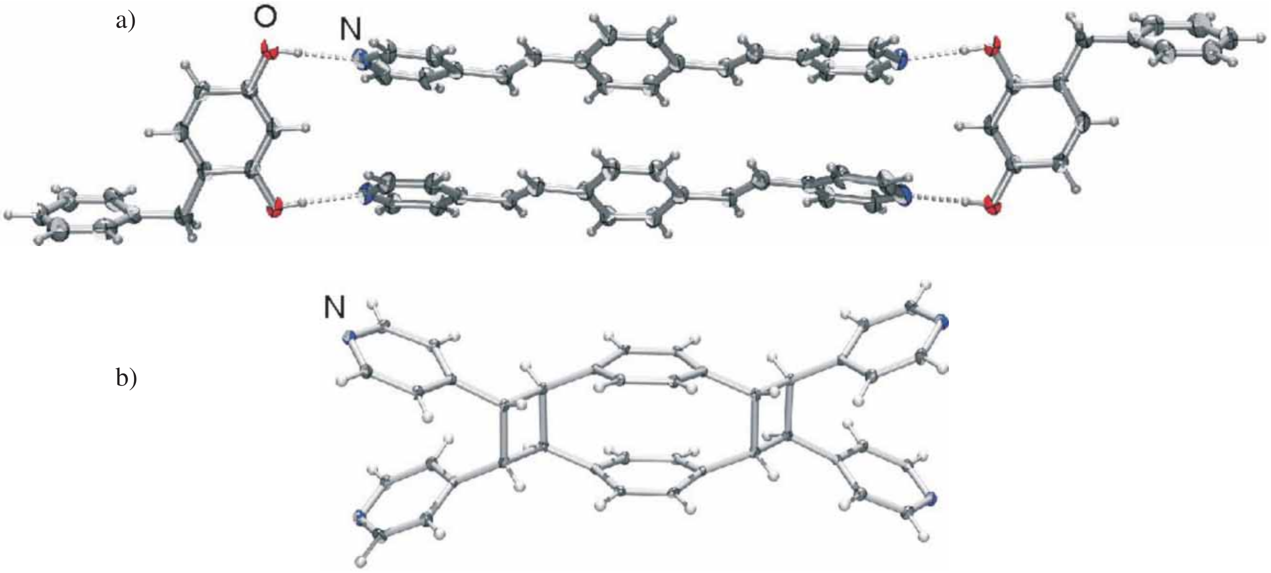


Figure 8. ORTEP representations: a) a single assembly of 2(4-bn-res)·2(1,4-bpeb), and b) the [2.2]paracylophane photoproduct.

To explore the synthetic versatility of the template-controlled method, we have made changes to the size of the reactants by utilizing 1,4-bis(4-pyridylethenyl)benzene (1,4-bpeb) as a reactant. Cocrystallization of 1,4-bpeb with res, or a derivative, was expected to produce a photoactive assembly of a length longer than the assemblies involving simple mono-olefins. Moreover, such an assembly was expected, upon exposure to UV-radiation and template removal, to produce a [2.2]paracyclophane by way of a double photodimerization (Scheme 3).[26,30] Indeed, a single-crystal X-ray structure analysis of the resulting cocrystals of 2(1,4-bpeb)·2(5-OMe-res) confirmed the formation of the expected assembly (Figure 7a). In each assembly, the res juxtaposed two of the diolefins, by way of O–H···N hydrogen bonds, for double [2+2] photodimerization. Exposure of the solid to UV-radiation produced the targeted cyclophane in 60 % yield, along with oligomeric and polymeric by-products. Formation of the by-products was attributed to unwanted photoreactions that occurred between C=C bonds of nearest-neighbor hydrogen-bonded structures (Figure 7b).

TEMPLATE SWITCHING STRATEGY

We expected the modularity of our template-based method to allow us to direct the synthesis of the paracyclophane

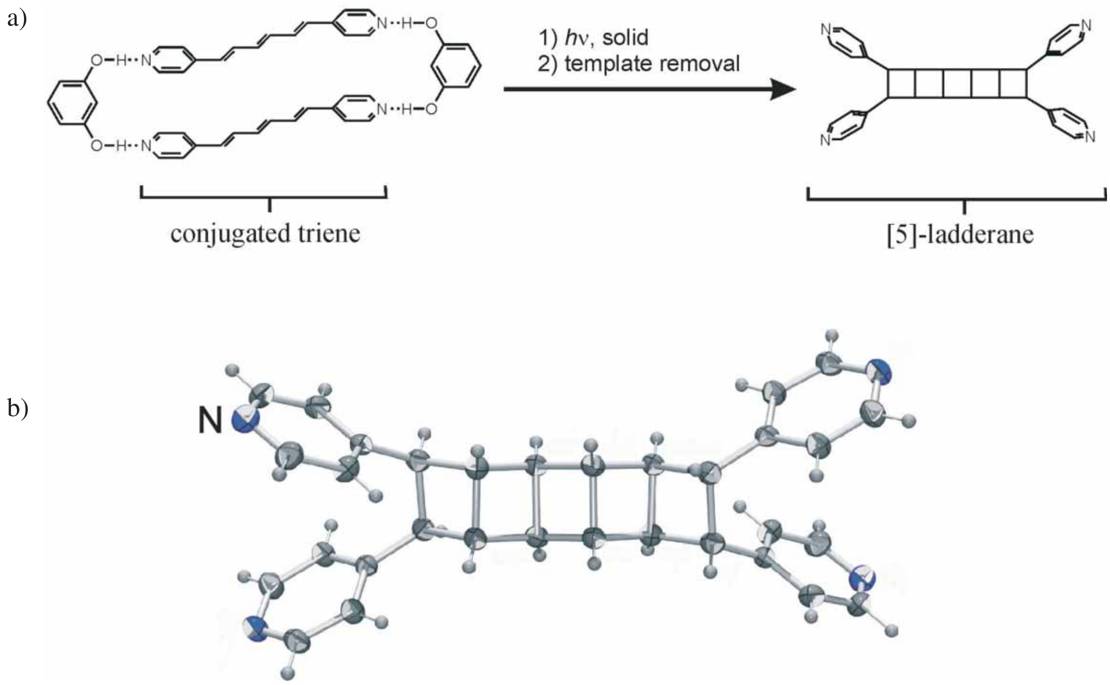


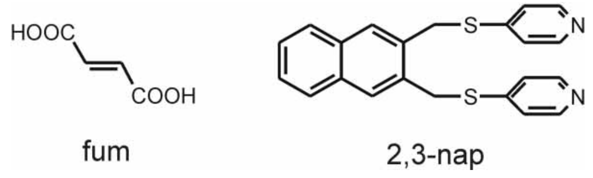
Figure 9. a) Schematic representation of the template-controlled synthesis of [5]-ladderane in the solid state, and b) ORTEP representation of the [5]-ladderane product.

target in quantitative yield. In particular, we anticipated that replacing 5-OMe-res with a different resorcinol could lead to a molecular assembly that adopts a different packing structure. As a result, a different resorcinol as the template would enable us to explore the landscape of crystal-packing motifs to search for a structure that supports quantitative formation of the cyclophane. Application of such a template-switching[31] strategy led to the identification of 4-benzylresorcinol (4-bn-res) as a template that provides access to the paracyclophane target in 100 % yield (Figure 8). The crystal structure analysis of cocrystals involving 1,4-bpeb and 4-bn-res revealed the hydrogen-bonded molecular assembly 2(4-bn-res)·2(1,4-bpeb). The structure of the assembly was analogous to 2(5-OMe-res)·2(1,4-bpeb) (Figure 8a). Analysis of the crystal structure of 2(4-bn-res)·2(1,4-bpeb) revealed that C=C bonds of nearest-neighbor assemblies were positioned at a separation beyond the upper limit (5.8 Å) for [2+2] photodimerization (Figure 8b). Thus, the template-switching strategy enabled us to fine-tune the reactivity of a given molecule in an organic solid. In this way, template-switching permitted the solid-state reactivity to be decoupled from crystal packing. We also applied template-switching to conjugated diene and triene reactants for the quantitative construction of [3]- and [5]-ladderanes (Figure 9).[32,33] How template-switching can be used to produce numerous crystal packing motifs was also demonstrated in cocrystals involving 4,4'-bpe as the reactant and a homologous series of phloroglucinols as templates.[34]

MODIFICATION OF THE RECOGNITION MOTIF

In the examples described above, the templates function as hydrogen-bond donors, giving rise to cyclobutane products that bear hydrogen-bond acceptor groups in the form of pyridines. To enable the use of our template-based method as a general means to control reactivity in the solid state, the method should be applicable to the construction of a variety of molecules. Indeed, we anticipated that such generality would require modifying the recognition motif (*i.e.,* supramolecular forces) that holds the components of the hydrogen-bonded assemblies together.

To test the tolerance of the assembly process to a change in the hydrogen bonding, we studied the ability of inverting hydrogen bonding between the template and the reactants. As a suitable reactant, we employed a dicarboxylic acid analogue of 4,4'-bpe, namely fumaric acid (fum), as the reactant, and a bis(pyridine), in the form of 2,3-bis(4-methylenethiopyridyl)naphthalene (2,3-nap), as the template (Scheme 4).[35] Cocrystallization of 2,3-nap with fum produced cocrystals, of composition 2(2,3-nap)·



Scheme 4.

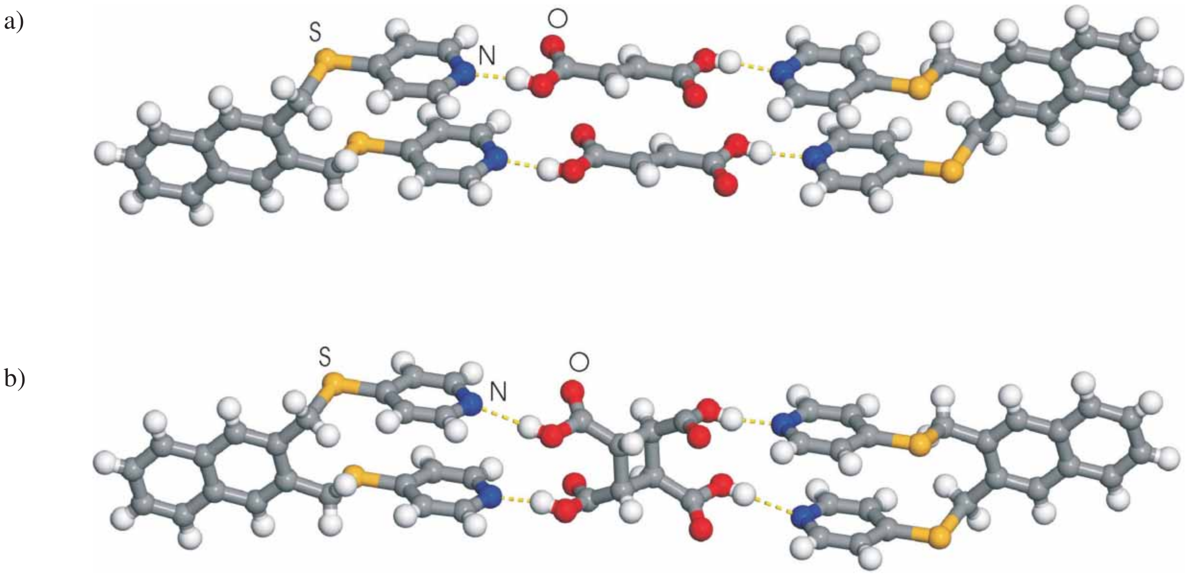


Figure 10. Ball-and-stick representations of crystalline assemblies of 2(2,3-nap)·2(fum): a) before reaction, and b) 36 % yield.

2(fum), which consisted of hydrogen-bonded molecular assemblies analogous to 2(res)·2(4,4'-bpe). The C=C bonds of fum were organized, by way of O–H···N hydrogen bonds, in a position suitable for topochemical [2+2] photodimerization. UV-irradiation of the solid using UV-radiation of 350 nm produced *rctt*-1,2,3,4-cyclobutanetetracarboxylic acid (cbta) by way of a rare single-crystal-to-single-crystal transformation (Figure 10).[36]

SUMMARY AND OUTLOOK

Modularity allows improvements to operating and functional systems. In this context, principles of supramolecular chemistry permit construction of cocrystals, which provide a route to reactive solids. The ability to achieve and refine the reactivity of such cocrystals stems from the modular design inherent to a multi-component solid. Whereas the examples presented here illustrate how the modular nature of cocrystals can be exploited to accomplish and refine the [2+2] photodimerization, the concepts presented here may also be used to refine additional properties of organic solids, such as conductivity,[37] solubility,[38] porosity,[39] and/or crystal morphology.[40,41] These concepts may also be applied, in principle, to higher-order crystals (*e.g.,* ternary solids), as well as to solids with components held together by coordination bonds,[42,43] π···π forces,[44] and halogen bonds.[45] Consequently, we anticipate that the properties of organic solids will continue to be exploited through modularity, particularly as the diversity of supramolecular systems continues to expand and develop.

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SAŽETAK

Koncepcija modula u organskoj kemiji čvrstog stanja i supramolekulskoj kemiji

Tomislav Friščić i Leonard R. MacGillivray

Prikazana je koncepcija modula u organskoj kemiji čvrstog stanja i supramolekulskoj kemiji. Pomoću odabranih primjera prikazana je mogućnost uporabe modulske građe supramolekulskih struktura u svrhu upravljanja reakcijama u čvrstom stanju. Primjeri pokazuju da se reaktivnost molekula u čvrstom stanju može ne samo potaknuti već i pažljivo usmjeriti/nadzirati. Također se daje i kratki pregled koncepcije modula u ostalim kemijskim odnosno tehnologijskim sustavima.