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Supramolecular Control of Reactivity in the Solid State Using Linear Molecular Templates[†]

Leonard R. MacGillivray,* Jennifer L. Reid, and
John A. Ripmeester

Steacie Institute for Molecular Sciences
National Research Council of Canada
Ottawa, Ontario, Canada, K1A 0R6

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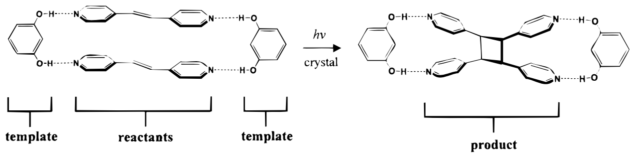
Since the work of Schmidt which delineated a "topochemical principle" for [2 + 2] photoreactions in the solid state,[1] chemists have strived to design molecules that will predictably crystallize to allow such reactions to occur. Such an approach to synthesis can lead to the formation of covalent bonds 'at will' in solids to facilitate the high yield, solvent-free synthesis[2] of molecules available either in low yields, as part of mixtures, or are not accessible in the liquid phase. Despite this realization, there remains no method to align olefins in solids that is reliable and may be used with reactants of diverse size, shape, and functionality,[3] criteria which, in principle, could offer synthetic freedoms realized in solution. The process has, moreover, largely remained one of trial and error,[4] often requiring weak intermolecular interactions between substituents[4−6] or constraining environments of cavities[7,8] to steer double bonds for reaction.

With this in mind, we describe a method involving a linear template,[9] based on 1,3-dihydroxybenzene (resorcinol),[10] to enforce topochemical alignment[1] of olefins in the solid state, by way of hydrogen bonds,[9−12] such that they undergo [2 + 2] photoreaction. We reasoned that an approach that exploits the strength and directionality of hydrogen bonds,[11,12] in the form of a molecule that enforces alignment of two sites within a discrete complex for reaction,[12] would largely eliminate consequences of intermolecular forces that have made topochemical designs unreliable.[4−6,13] Moreover, by separating the steering and reacting part supramolecularly, we reasoned that it should be possible to transfer a reaction between appropriately functionalized reactants in which the template may be used in diverse chemical environments[9] and, following reaction, recycled for further synthesis.[7] This method permits activation of molecules photostable as pure solids and we demonstrate how the method provides an entry to the regio- and stereocontrolled[12] solvent-free synthesis of cyclic molecules.[14] Whereas linear templates have been applied in solution, such an approach to engineering reactivity, where a single molecule organizes two molecules within a discrete complex for reaction, has not been realized in the solid state.[9,15]

Scheme 1



trans-1,2-Bis(4-pyridyl)ethylene (4,4′-bpe) crystallizes to form a layered structure in which olefins of neighboring layers lie orthogonal and separated by 6.52 Å.[16] 4,4′-bpe does not conform to the topochemical principle and is photostable.

To orient the olefins of 4,4′-bpe such that they are photoactive, we turned to structure studies based on resorcinol.[10] Such studies suggested that cocrystallization of 4,4′-bpe with resorcinol would yield a four-component assembly, 2(4,4′-bpe)·2(resorcinol) **1**, held together by four $O-H\cdots N$ hydrogen bonds, in which two pyridine units of 4,4′-bpe lie approximately orthogonal to the diol, interacting by way of $\pi-\pi$ interactions (Scheme 1). The olefins of the complex would be arranged in a parallel fashion, separated by ∼4 Å. Photoreaction of the complex would give, in contrast to the liquid phase,[17] a single product, *rctt*-tetrakis(4-pyridyl)cyclobutane (tpcb).

An ORTEP perspective of **1** is shown in Figure 1.[18] As anticipated, the components assemble to form a cyclic array held together by four $O-H\cdots N$ hydrogen bonds.[19] In this arrangement, the olefins lie parallel and separated by 3.65 Å. Olefins of adjacent complexes pack such that they lie offset and are separated by 4.71 Å. As a result, the double bonds of the assembly are the sole olefins of the solid that conform to the topochemical principle.[1]

UV irradiation of a powdered crystalline sample of **1** placed between two glass plates (Hg lamp) produced tpcb, stereospecifically (yield: 100%), after a period of 42 h, as determined by ^{1}H NMR spectroscopy and ESI$^+$-MS.[20] As confirmed by structure analysis of a recrystallized portion of the reacted material,[21] photoreaction of **1**, as shown in Figure 2, produced tpcb. Interestingly, the template and product assemble to form a three-component array, (tpcb)·2(resorcinol) **2**, held together by four

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[*] Author for correspondence. Steacie Institute for Molecular Sciences. Telephone: (613) 993-4406. Fax: (613) 998-7833. E-mail: lmacgil@ned1.sims.nrc.ca. New address: Department of Chemistry, University of Iowa, Iowa City, IA, 52242. Telephone: (319) 335-3504. Fax: (319)335-1270. E-mail: len-macgillivray@uiowa.edu.

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(1) For photodimerization to occur in the solid state, olefins should be parallel and separated by < 4.2 Å. See: Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.

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(18) Single crystals of **1** were grown by cocrystallization of 4,4-bpe with resorcinol in EtOH/MeCN (1:1). Crystal data for **1**: crystal size 0.3 × 0.3 × 0.4 mm, triclinic, space group $P\bar{1}$, $a = 8.070(1)$ Å, $b = 9.832(1)$ Å, $c = 10.876(1)$ Å, $\alpha = 73.119(1)°$, $\beta = 72.563(1)°$, $\gamma = 66.184(1)°$, $U = 738.8(1)$ Å^3, $2\theta = 45°$, Mo Kα radiation ($\lambda = 0.71070$ Å) for $Z = 2$ and $R = 0.054$.

(19) **1** may form a divergent, polymeric assembly. Studies are underway to determine factors that contribute to formation of the convergent, discrete structure.

(20) For details, see Supporting Information.

(21) Single crystals of **2** were grown by recrystallizing a portion of reacted **1** from EtOH/toluene (10:1). Crystal data for **2**: crystal size 0.2 × 0.2 × 0.2 mm, monoclinic, space group $P2_1/n$, $a = 11.367(1)$ Å, $b = 9.749(1)$ Å, $c = 14.273(1)$ Å, $\beta = 111.668(3)°$, $U = 1469.7(3)$ Å^3, $2\theta = 45°$, Mo Kα radiation ($\lambda = 0.71070$ Å) for $Z = 2$ and $R = 0.064$.

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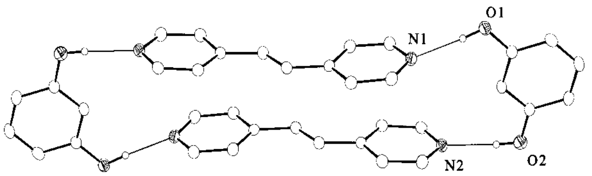


Figure 1. ORTEP perspective of **1**. Selected interatomic distances (Å): O1···N1 2.734(2), O2···N2 2.753(2).

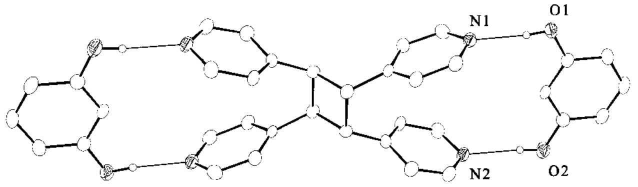
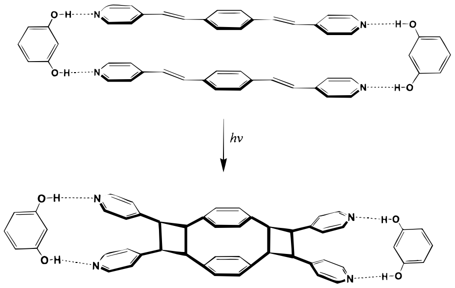


Figure 2. ORTEP perspective of the photoactivated complex **2**. Selected interatomic distances (Å): O1···N1 2.718(1), O2···N2 2.788(1).

Scheme 2



O−H···N hydrogen bonds, analogous to **1**. The structure of **2** favors the onward progress of the reaction and we suggest accounts for the quantitative conversion of 4,4′-bpe to tpcb.[12,22]

We have expanded the approach to additional reactants and templates.[20] *trans*-1,2-bis(2-pyridyl)ethylene (2,2′-bpe), upon cocrystallization with resorcinol is a suitable reactant, while 5-methoxyresorcinol (5-OMe-resorcinol), upon cocrystallization with 4,4′-bpe is a suitable template. 2,2′-bpe is photostable as a pure compound,[17] and reactivity experiments reveal that the olefins of both complexes, the sole bonds of each solid that conform to the topochemical principle, photodimerize, stereospecifically (yield: 100%), to yield *rctt*-isomers.[22]

With the realization that this approach permits reliable engineering of reactivity achieved, we set out to design a system involving two reaction centers. We anticipated that photoreaction of 1,4-bis[2-(4-pyridyl)ethenyl]benzene (1,4-bpeb)[23] would give a tricyclic [2.2]paracyclophane (Scheme 2).[24,25] If successful, the approach, in addition to displaying tolerance to lengthening of the reactant, would provide a novel entry to cyclic molecules[14] where low yields often requiring large batches of solvent are encountered in solution.

An ORTEP perspective of 2(1,4-bpeb)·2(5-OMe-resorcinol) **3** is shown in Figure 3.[26] As with **1**, the components form a four-component complex held together by four O−H···N hydrogen bonds. The olefins of 1,4-bpeb, one of which lies disordered across two positions (occupancies: 70:30), are aligned within the assembly such that the olefin of the major site meets the topochemical principle[1] with the ordered olefin, the two double bonds being separated by 3.70 Å. Two ordered olefins of two neighboring assemblies lie parallel and within 3.95 Å.

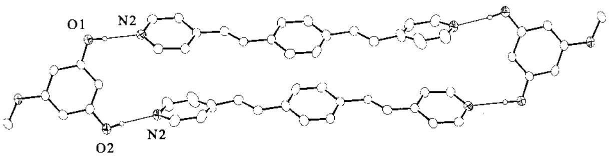


Figure 3. ORTEP perspective of **3** which leads to a [2.2]paracyclophane. Selected interatomic distances (Å): O1···N1 2.731(4), O2···N2 2.736(4).

UV irradiation of **3** produced the expected cyclophane (60%), along with a monocyclized dimer (30%) and indefinable products (10%), after 49 h. The cyclophane is characterized by pairs of doublets at 8.35 and 7.25 ppm, 7.07 and 6.78 ppm, and 4.74 and 4.61 ppm which correspond to the pyridyl, phenylene, and cyclobutane protons, respectively. The splitting pattern of the phenylene moiety is indicative of an *exo*, rather than an *endo*, isomer,[25] while the good yield of the cyclophane is consistent with a dynamic model of disorder.[27] The synthesis has, moreover, been regio- and stereoselective, proceeding by way of a monocyclized product in which the indefinable materials may be attributed to photoreactions involving nearest neighbor assemblies.[22] To our knowledge, **3** represents the first example in which a linear template has been used to organize more than one reaction center, in this case two sites for the designed synthesis of a molecule with an inner cyclic framework.[9]

We have presented a reliable method for aligning olefins in the solid state. The method utilizes linear templates[9] to organize single or multiple reaction centers to conduct regio- and stereocontrolled molecular synthesis in solids. Experiments are underway to modify the components of the system such that further analogies between solution and solid-state synthesis may be explored (e.g., functional group tolerance).[28] We are also investigating whether this approach may be applied to other reactions to devise templates that will allow the solid state to be used for the designed synthesis of molecular frameworks of increasing size and complexity.

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Supporting Information Available: Crystallographic reports and tables of positional and thermal parameters, bond lengths and angles, NMR data, and ESI$^+$-MS data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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