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A Test for Homology: Photoactive Crystalline Assemblies Involving Linear Templates Based on a Homologous Series of Phloroglucinols

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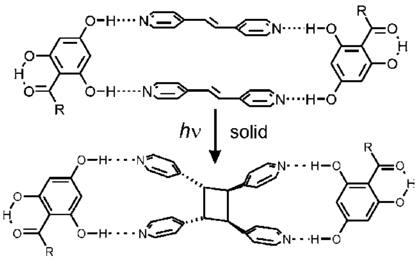
ABSTRACT



Cocrystallization of *trans*-1,2-bis(4-pyridyl)ethylene (4,4′-bpe) with eight members of a homologous series of phloroglucinols 1a–h yields molecular solids 2(1a–h)·2(4,4′-bpe) with components held together by four O–H···N hydrogen bonds. In each case, the molecules assemble to form a discrete four-component assembly with olefins preorganized for a [2 + 2] photodimerization. UV irradiation of each member in the series of solids produces *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb), stereospecifically, in up to 100% yield.

A fundamental basis for the success of synthetic organic chemistry is an ability to make covalent bonds using homologous series of compounds.[1] Homology enables chemists to make systematic changes to the structures of reactants (e.g., -methyl, -ethyl, and -propyl) while maintaining identical chemical reactivities. The ability to make systematic changes to reactants has, in turn, equipped chemists with a means to conduct molecular synthesis by design (e.g., natural products).[2]

Whereas homology has developed such that the concept is now “assumed” applicable in the liquid phase, the idea, although explored,[3,4] has been markedly less successful in the solid state. Indeed, the sensitivity of crystal packing to subtle structural changes to molecules[5,6] has meant that methods to organize molecules in the solid state to react have been largely based on “hit-or-miss” strategies which, de facto, have prohibited an ability to conduct molecular solid-state synthesis by design.[3] A general means to conduct molecular synthesis in the solid state could provide deliberate, solvent-free access to molecules and materials (e.g., switches), that may be difficult, or impossible, to achieve in the liquid phase.

We have introduced a method, based on principles of supramolecular chemistry, to direct the formation of covalent bonds in solids using molecules that function as linear templates.[7,8] The templates (e.g., resorcinol) assemble reactants (e.g., *trans*-1,2-bis(4-pyridyl)ethylene or 4,4′-bpe) via

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[1] Corey, E. J. *Pure Appl. Chem.* **1967**, *14*, 19.
[2] Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44.
[3] Schmidt, G. M. J. *Pure Appl. Chem.* **1971**, *27*, 647.
[4] (a) Ito, Y.; Borecka, B.; Trotter, J.; Scheffer, J. R. *Tetrahedron Lett.* **1995**, *36*, 6083. (b) Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755. (c) Tanaka, K.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K.; Toda, F. *Tetrahedron* **2000**, *56*, 6853. (d) Sharma, C. V. K.; Panneerselvam, K.; Shimoni, L.; Katz, H.; Carrell, H. L.; Desiraju, G. R. *Chem. Mater.* **1994**, *6*, 1282.
[5] Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.
[6] 6-Acetoxycoumarin, for example, is photoactive while 4-methyl-6-acetoxycoumarin is photostable (see: Gnanaguru, K.; Ramasubbu, N.; Venkatesan, K.; Ramamurthy, V. *J. Org. Chem.* **1985**, *50*, 2337).
[7] MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. *J. Am. Chem. Soc.* **2000**, *122*, 7817.
[8] Similar methods: (a) Shan, N.; Jones, W. *Tetrahedron Lett.* **2003**, *44*, 3687. (b) Amirsakis, D. G.; Garcia-Garibay, M. A.; Rowan, S. J.; Stoddart, J. F.; White, A. J. P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4256.

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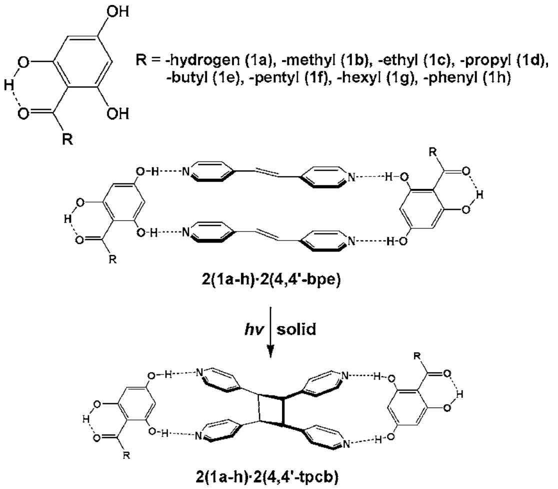

Figure 1. Schematic of the targeted assemblies.

hydrogen bonds within discrete molecular assemblies, such as 2(resorcinol)·2(4,4′-bpe), for single and multiple [2 + 2] photodimerizations. The flexibility of the approach, owing to the ability of the templates to assemble along the exteriors of the reactants and, in doing so, isolate reactants from vexatious effects of crystal packing, has enabled us to construct a [2.2]paracyclophane[7] and, very recently, [*n*]-ladderanes[9] (where $n = 3$ and 5) in solids.

To place our method on firmer grounds, we believe it will be necessary to determine the tolerance of the assembly process to systematic changes to the constituent components. The modular nature of the approach means that the concept of homology can be applied to both the templates and reactants. Here, we describe our first test to determine the tolerance of the assembly process to a homologous series of components. Our focus is the template. Specifically, we have attached a series of -R groups (e.g., -alkyl) to a phloroglucinol (Figure 1) and demonstrate that the assembly process involving 4,4′-bpe is tolerant to the -R groups in 2(**1a**−**h**)·2(4,4′-bpe) and that photoreactivity, despite changes to packing of the crystalline assemblies, is maintained in all cases.

Our desire to modify the template stems from our demonstration of "template-switching".[10] We revealed that switching the template (e.g., resorcinol) to a derivative (e.g., 4-benzylresorcinol) can alter crystal packing so as to affect molecular orientation[10b] and product yield.[10a] Consequently, there is a need to modify the template to control structural and bulk physical properties of such reactive solids. Moreover, an ability to modify the template systematically could permit the properties of such reactive solids to be fine-tuned.

To develop a template amenable to systematic modification, we turned to commercially available phloroglucinaldehyde **1a** and its congeners. Houben−Hoesch reaction[11] of phloroglucinol with a homologous series of nitriles was anticipated to give **1b**−**h**. A search of the Cambridge Structural Database suggested that a hydroxyl group of **1a**−**h** could form an intramolecular O−H···O hydrogen bond with the carbonyl moiety[12] and thereby render **1a**−**h** a bifunctional template. Thus, cocrystallization of **1a**−**h** with 4,4′-bpe would give 2(**1a**−**h**)·2(4,4′-bpe) with olefins positioned linearly for a [2 + 2] photodimerization to form, stereospecifically, *rctt*-tetrakis(4-pyridyl)cyclobutane (4,4′-tpcb).

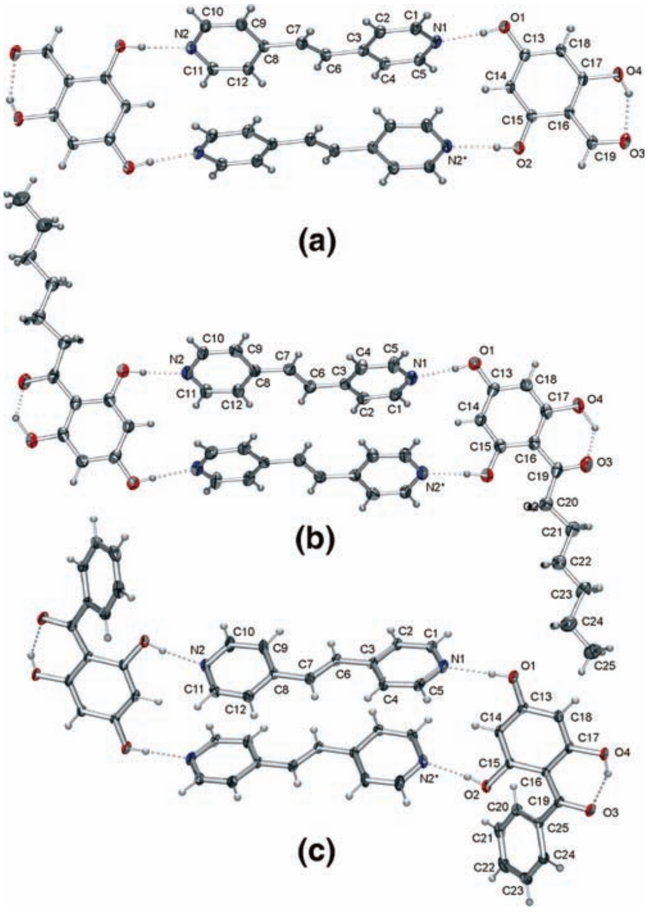

Figure 2. ORTEP perspectives of (a) 2(**1a**)·2(4,4′-bpe), (b) 2(**1g**)·2(4,4′-bpe), and (c) 2(**1h**)·2(4,4′-bpe). Color scheme: red = oxygen, blue = nitrogen, gray = carbon, white = hydrogen.

Compounds **1b**−**h** were synthesized via Houben-Hoesch reaction with the appropriate nitrile. Single crystals of 2(**1a**−**c**)·2(4,4′-bpe) and 2(**1e**−**h**)·2(4,4′-bpe) were grown by allowing a saturated solution of 4,4′-bpe and **1a**−**h** (ratio 1:1) in MeCN to stand during 1 day. Single crystals of 2(**1d**)·2(4,4′-bpe) were grown by allowing a saturated solution of the components in ethyl acetate to evaporate at 50 °C over 1 day. The formulations of 2(**1a**−**h**)·2(4,4′-bpe) were confirmed via single-crystal[13] X-ray diffraction and ^{1}H NMR spectroscopy.

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(10) (a) Friščić, T.; MacGillivray, L. R. *Chem. Commun.* **2003**, 1306. (b) MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A.; Papaefstathiou, G. S. *Ind. Eng. Chem. Res.* **2002**, *41*, 4494.

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(12) Begley, M. J.; Crombie, L.; King, R. W.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, *21*, 2393. CCDC reference codes: FORCIT10 and ACCITR10.

Table 1. Structure Data and Yields for 2(**1a-h**)·2(4,4′-bpe)

template	R	O(1,2)···N(1,2) distances (Å)		d_1[a] (Å)	d_2[b] (Å)	yield (%)
1a	H	2.693(3)	2.733(3)	3.79	7.44	96
1b	CH_3	2.720(3)	2.718(3)	3.69	4.79	65
1c	C_2H_5	2.724(3)	2.718(3)	3.87	4.95	65
1d	C_3H_8	2.743(3)	2.694(3)	3.88	5.16	92
1e	C_4H_9	2.714(2)	2.745(2)	3.92	4.71	87
1f	C_5H_{11}	2.714(3)	2.733(3)	3.76	4.95	100
1g	C_6H_{13}	2.741(6)	2.707(6)	3.91	4.23	81
1h	C_6H_5	2.752(2)	2.693(2)	3.95	5.85	50

[a] d_1 represents the distance between carbon atoms of double bonds within a hydrogen-bonded assembly. [b] d_2 represents the distance between carbon atoms of double bonds between adjacent assemblies.

Structure studies reveal (Figure 2) that the components of each solid assemble to form discrete four-component molecular assemblies 2(**1a**−**h**)·2(4,4′-bpe), held together by four O−H···N hydrogen bonds. As anticipated, a single hydroxyl group of **1a**−**h** participates in an intramolecular O−H···O hydrogen bond with each carbonyl moiety, which enables each triol to serve as a ditopic receptor[14] and participate in the O−H···N forces (Table 1). Each -R group is projected away from the center of **1a**−**h** and the olefins of each assembly lie parallel and separated by <4.2 Å, geometries that conform to the topochemical postulates of Schmidt for [2 + 2] photoreaction.[3] Moreover, these observations demonstrate that the assembly process involving **1a**−**h** and 4,4′-bpe is tolerant to the series of -R groups which, in turn, enables each triol to position each olefin for reaction.

The tolerance of the assembly process to each -R group translates into reactivity in each solid. Ultraviolet (UV) irradiation (broadband Hg lamp) of powdered crystalline samples of 2(**1a**−**h**)·2(4,4′-bpe) reveals that each olefin reacts to give, stereospecifically, 4,4′-tpcb, as confirmed by ^{1}H NMR spectroscopy (Figure 3). The identity of 4,4′-tpcb is confirmed by the emergence of cyclobutane protons at 4.66 ppm (singlet, DMSO-d_6). Similar to 2(*R*-resorcinol)·2(1,4-bpeb) (where R = 5-methoxy, 4-benzyl),[10] the yields of the photoreactions are different, ranging from 50% to 100%.[15]

That each photoreaction of 2(**1a**−**h**)·2(4,4′-bpe) occurs within each hydrogen-bonded assembly is further realized by the packing of the assemblies in each solid (Figure 4).

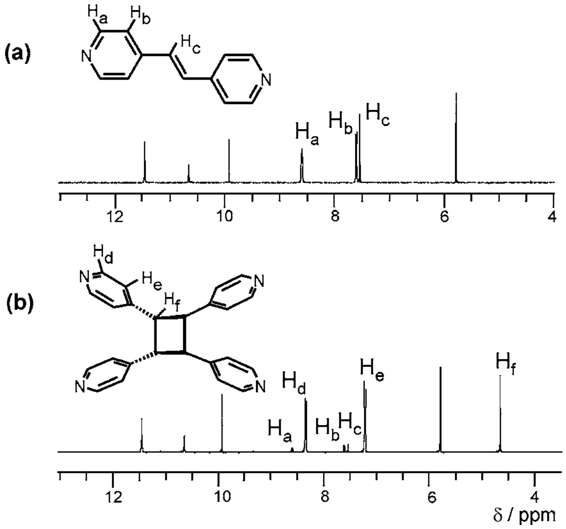

Figure 3. ^{1}H NMR spectra of 2(**1a**)·2(4,4′-bpe) (a) before and (b) after photoreaction (yield 96%).

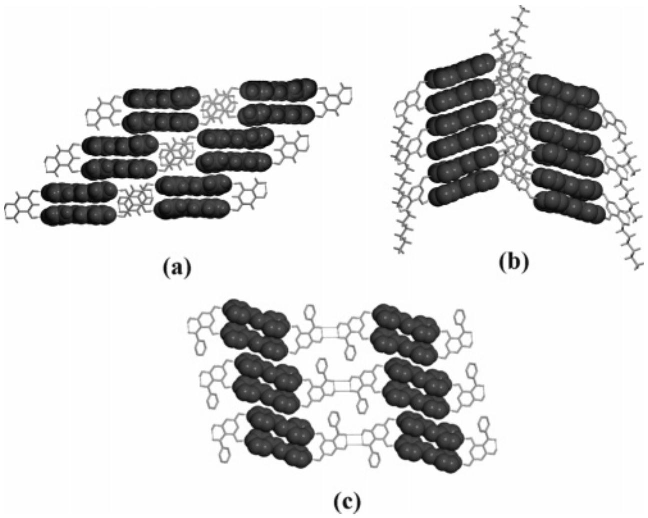

Figure 4. Mixed wireframe (template) and space-filling (olefin) perspectives of the packing of (a) 2(**1a**)·2(4,4′-bpe), (b) 2(**1g**)·2(4,4′-bpe), and (c) 2(**1h**)·2(4,4′-bpe).

Specifically, the assemblies form sheets held together, depending on the -R group, by four different bonding motifs. In 2(**1a**)·2(4,4′-bpe), adjacent assemblies participate in C−H···π forces involving aldehyde and pyridine units of nearest-neighbor assemblies while in 2(**1b**−**c**)·2(4,4′-bpe) the C−H···π interactions are effectively replaced by C−H···O forces[16] between the terminal methyl groups and hydroxyl groups involved in the intramolecular hydrogen bond. Further lengthening of the aliphatic chain in 2(**1d**−**g**)·2(4,4′-bpe) results in interdigitation[17] of the chains while the phenyl group of **1h** enables weak O−H···O hydrogen bonds between neighboring assemblies [d(O4···O3^i) = 3.262 Å, symmetry operator $i = -x + 3, -y - 1, -z - 1$]. Despite these structural differences, however, the separation between carbon atoms of double bonds of nearest-neighbor assemblies in each solid is larger than the corresponding distance within the assembly (Table 1). Thus, in addition to supporting the

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(13) See the Supporting Information for 2(**1a**−**h**)·2(4, 4′-bpe) crystal data.

(14) (a) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744. (b) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (c) Bassani, D. M.; Darcos, V.; Mahony, S.; Desvergne, J.-P. *J. Am. Chem. Soc.* **2000**, *122*, 8795.

(15) A correlation of yield with the orientation of reactive carbon−carbon double bonds was not observed (see the Supporting Information), which suggests that mechanical properties of each solid may play a role in determining the yield; see: (a) McBride, J. M. *Acc. Chem. Res.* **1983**, *16*, 304. (b) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433.

(16) Desiraju, G. R. *Acc. Chem. Res.* **1996**, *29*, 441.

formation of each discrete structure, each −R group serves a secondary role of prohibiting cross-reactions between adjacent assemblies by giving rise to different crystal packing arrangements in each solid.[18]

In this report, we have established that an assembly process involving a series of components is tolerant to systematic changing of −R groups. Specifically, all members of a homologous series of phloroglucinols have been shown to function as linear templates by assembling 4,4′-bpe via hydrogen bonds within discrete molecular assemblies in the solid state for [2 + 2] photoreaction. With an ability to systematically modify the template achieved, we are now targeting functional groups of increasing complexity to engineer templates with applications in chemical synthesis (e.g., chiral groups) and materials science (e.g., chromophores).

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Supporting Information Available: Crystallographic reports and tables of positional and thermal parameters, bond lengths and angles, parameters describing the positioning of double bonds, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Menger, F. M.; Lee, J.-J.; Hagen, K. S. *J. Am. Chem. Soc.* **1991**, *113*, 4017.

(18) Photoreactivities in solids based on cinnamic acid have been classified according to α-, *β*-, and *γ*-packing motifs (see ref 3).