

Toward a Reactant Library in Template-Directed Solid-State Organic Synthesis: Reactivity Involving a Monofunctional Reactant Based on a Stilbazole

Leonard R. MacGillivray,^{*,†} Jennifer L. Reid,[‡] John A. Ripmeester,[‡] and Giannis S. Papaefstathiou[†]

Department of Chemistry, University of Iowa, Iowa City, Iowa, 52242-1294, and Steacie Institute for Molecular Sciences, National Research Council of Canada, Ottawa, Ontario, Canada K1A 0R6

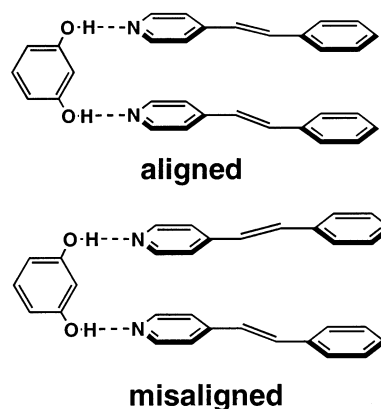
Cocrystallization of 4-chlorostilbazole (4-Cl-sbz) with either resorcinol (res) or 4-ethylresorcinol (4-Et-res) yields three-component molecular assemblies, (res)·2(4-Cl-sbz) and (4-Et-res)·2(4-Cl-sbz), held together by two O–H···N hydrogen bonds. The olefins of each assembly conform to the distance criterion of Schmidt for [2+2] photoreaction. In the former, the olefins lie antiparallel, whereas in the latter, the olefins lie parallel. Both solids are photoactive, leading to the regiocontrolled solid-state synthesis of *rctt*-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane (4-Cl-dpcb) in near or quantitative yield. The photoactivity of (res)·2(4-Cl-sbz) is attributed to the reactant undergoing a pedal-like change in conformation prior to cyclobutane formation. The ability to change the diol to achieve olefin alignment is expected to provide additional synthetic flexibility to this template approach.

The realization that covalent bonds can form in molecular solids¹ suggests a possibility that the solid state can be used as an environmentally friendly, or “green”, solvent-free² medium for conducting molecular syntheses with freedoms of the liquid phase (e.g., reliability, reactant diversity). Unfortunately, the constrained environment of the solid state,³ owing to subtle structural demands of close packing and weak intermolecular forces,^{3,4} has made it generally impossible to design molecules, a priori, that crystallize with certainty in position for reaction. This inability to reliably predict and, ultimately, control reactivity in molecular solids has placed severe limits on the sizes, shapes, and functionalities of targeted reactants and products, limits that are virtually nonexistent in solution.

We have introduced a flexible method for engineering [2+2] photoreactivity in the solid state that employs bifunctional molecules based on resorcinol (e.g., 5-methoxyresorcinol) in the form of linear templates⁵ that organize olefins linked to symmetrical bipyridines [e.g., *trans*-1,2-bis(4-pyridyl)ethylene (4,4'-bpe)] within discrete hydrogen-bonded molecular assemblies for reaction.⁶ By forcing reaction to occur within a discrete complex using relatively strong and directional forces,⁷ this approach eliminates many problems of intermolecular forces that have made such topochemical designs unreliable,⁸ the reactivity being determined by the ability of the template to preorganize⁷ the reactants in a position that conforms to Schmidt's¹ two geometry criteria for reaction, namely, separation of <4.2 Å between double bonds and olefin alignment.

To develop a reactant library,⁹ we now turn to stilbazoles. Owing to the presence of a single hydrogen bond acceptor site, we anticipated that a single template

Scheme 1



would be required to position two stilbazoles for a regiocontrolled (i.e., head-to-head) dimerization,¹⁰ which, in turn, would allow us to address the reliability of the approach owing to either slippage or flipping of terminal groups of the reactants, which can lead to olefin misalignment (Scheme 1).^{11–13} Although misalignment occurs, we have determined that alignment can be achieved by changing the template^{10,14} to a homologue with functionality placed away from the reaction center (i.e., in the 4, 5, or 6 position) such that olefin alignment is a consequence of the crystal-packing demands of the new template.¹⁴ In addition to expanding this method to monofunctional reactants, such an ability to achieve Schmidt's alignment criterion for reaction by placing a substituent along the periphery of the template is, owing to the modularity of this method,^{10,14} expected to increase the synthetic flexibility of this approach.¹⁴

Addition of 4-chlorostilbazole (4-Cl-sbz) (0.040 g)¹⁵ to resorcinol (res) (0.010 g) in a boiling aliquot of EtOH (3 mL) and chloroform (2 mL) yielded, upon slow cooling and solvent evaporation, colorless crystals of (res)·2(4-Cl-sbz) suitable for X-ray analysis (100% yield). The

* Corresponding author. Address: University of Iowa, Iowa City, IA, 52242. Telephone: (319) 335-3504. Fax: (319) 335-1270. E-mail: len-macgillivray@uiowa.edu.

[†] University of Iowa.

[‡] National Research Council of Canada.

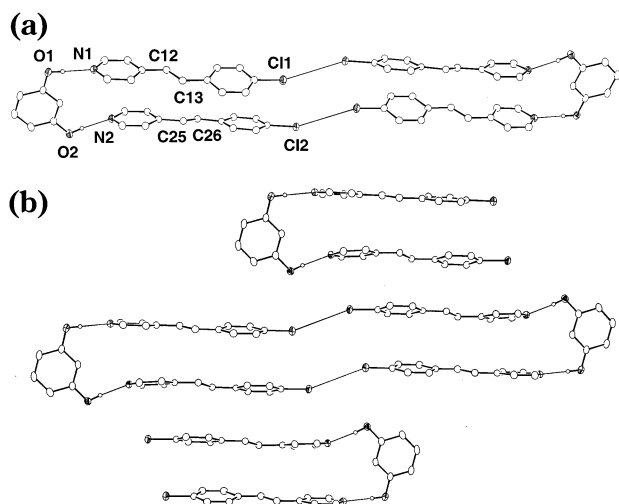


Figure 1. ORTEP perspectives of the X-ray crystal structure of (res)·2(4-Cl-sbz): (a) discrete three-component complex and (b) 2D layered structure. Selected interatomic distances (Å): O(1)···N(1), 2.689(2); O(2)···N(2), 2.741(2).

formulation of (res)·2(4-Cl-sbz) was confirmed by ^1H NMR spectroscopy and single-crystal X-ray diffraction.¹⁶

ORTEP perspectives of (res)·2(4-Cl-sbz) are shown in Figure 1. As anticipated, similarly to 2(res)·2(4,4'-bpe),^{6a} the components of (res)·2(4-Cl-sbz) assemble to form a three-component array held together by two intermolecular O—H···N hydrogen bonds [O···N separations (Å): O(1)···N(1), 2.689(2); O(2)···N(2), 2.741(2)]. Cl···Cl interactions [Cl···Cl separations (Å): Cl(1)···Cl(2), 3.84] have also formed such that nearest-neighbor assemblies constitute novel six-component complexes held together by a combination of Cl···Cl and O—H···N forces.¹⁷ As a consequence of these interactions, the olefins of the "superassembly" are organized such that the reactive sites lie in close proximity, with C···C separations between the olefins of 3.75 (C12···C25) and 4.40 (C13···C26) Å. Unlike 2(res)·2(4,4'-bpe),^{6a} however, the olefins adopt an antiparallel orientation such that the double bonds do not conform to Schmidt's alignment criterion for reaction.¹⁸ Adjacent assemblies of (res)·2(4-Cl-sbz) pack in a parallel fashion to form a 2D layered architecture, the carbon atoms of nearest-neighbor olefins being separated by 4.67 Å.

Although the olefins of (res)·2(4-Cl-sbz) do not conform to Schmidt's alignment criterion for [2+2] photoreaction, the stilbazoles are photoactive. UV irradiation of a powdered crystalline sample of (res)·2(4-Cl-sbz) (Hg lamp, 350 nm) for a period of 7 h produced a product consistent with a regiospecific dimerization that produces *rctt*-1,2-bis(4-pyridyl)-3,4-bis(4-chlorophenyl)cyclobutane (4-Cl-dpcb), as determined by ^1H NMR spectroscopy, in quantitative yield. Crystallization of a portion (0.005 g) of the reacted material from a solution of EtOH (3 mL) and chloroform (2 mL) yielded single crystals of (res)·(4-Cl-dpcb), with confirmation of the structure of the product by X-ray analysis.¹⁹ As shown in Figure 2, the photoproduct assembles with the linear template by way of O—H···N forces [O···N separations (Å): O(1)···N(1), 2.690(4); O(2)···N(2), 2.745(4)] to form a discrete four-component array where a hydroxyl group of the template, in contrast to 2(res)·(*rctt*-tetrakis(4-pyridyl)cyclobutane),^{6a} adopts a divergent conformation along the periphery of the molecule. We attribute the generation of 4-Cl-dpcb to the reactant undergoing a

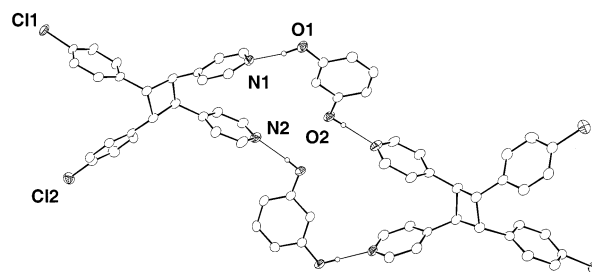


Figure 2. ORTEP perspective of the X-ray crystal structure of (res)·(4-Cl-dpcb). The photoproduct assembles with the template to form a discrete four-component molecular assembly. Selected interatomic distances: (Å): O(1)···N(1), 2.690(4); O(2)···N(2), 2.745(4).

pedal-like change in conformation in the solid,^{11–13} which enables the double bonds to adopt a parallel orientation and form the cyclobutane ring.

The observation that the double bonds of the discrete assembly (res)·2(4-Cl-sbz) do not conform to Schmidt's geometry criteria for reaction prompted us to employ an alternative strategy to achieve olefin alignment. Although the olefins of (res)·2(4-Cl-sbz) are photoactive, we reasoned that such an approach would be useful for achieving reaction involving olefins of a discrete assembly that might be misaligned and photostable.¹³ To achieve olefin alignment, we turned to modifying the shape of the template by the addition of a substituent in a position away from the reaction center.²⁰ We anticipated that such a change to the shape of the template would alter the crystal-packing environment of the assembly, and therefore of the reactant, which, owing to specific packing demands of the template,¹⁴ could then result in olefin alignment.¹³ Moreover, although an ability to successfully predict solid-state packing remains elusive,²¹ such switching of the template would, in effect, exploit unpredictable consequences of crystal packing, enabling this modular approach to increase the likelihood of achieving Schmidt's alignment criterion for a [2+2] reaction.¹

Addition of 4-chlorostilbazole (0.031 g) to 4-ethylresorcinol (4-Et-res) (0.010 g) in a boiling aliquot of EtOH (3 mL) and chloroform (2 mL) yielded, upon slow cooling and solvent evaporation, colorless crystals of (4-Et-res)·2(4-Cl-sbz) suitable for X-ray analysis (100% yield). The formulation of (4-Et-res)·2(4-Cl-sbz) was confirmed by ^1H NMR spectroscopy and single-crystal X-ray diffraction.²²

ORTEP perspectives of (4-Et-res)·2(4-Cl-sbz) are shown in Figure 3. Similarly to (res)·2(4-Cl-sbz), the components of (4-Et-res)·2(4-Cl-sbz) form a discrete three-component array held together by two O—H···N hydrogen bonds [O···N separations (Å): O(1)···N(1), 2.752(4); O(2)···N(2), 2.707(4)]. In this arrangement, the olefins of (4-Et-res)·2(4-Cl-sbz) conform to Schmidt's distance criterion for photoreaction, the olefin C···C separations being 4.00 (C14···C27) and 3.84 (C15···C28) Å. In contrast to (res)·2(4-Cl-sbz), however, the olefins of the complex are aligned such that adjacent assemblies form a 2D herringbone motif,²¹ the carbon atoms of nearest-neighbor olefins being separated by 4.79 and 4.93 Å. Indeed, UV irradiation of a powdered crystalline sample of (4-Et-res)·2(4-Cl-sbz) produced the targeted product, 4-Cl-dpcb, in near-quantitative yield, as confirmed by ^1H NMR spectroscopy. Thus, placement of the alkyl group along the periphery of the template in the 4-position has resulted in a change in packing of the

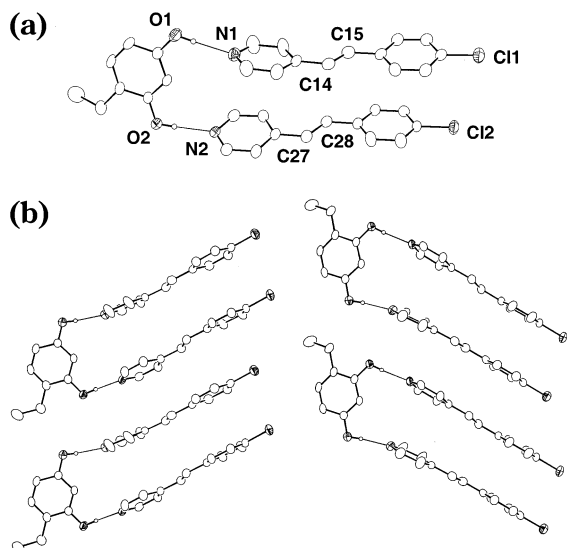


Figure 3. ORTEP perspective of the X-ray crystal structure of (4-Et-res)·2(4-Cl-sbz). Selected interatomic distances (Å): O(1)···N(1), 2.752(4); O(2)···N(2), 2.707(4).

reactants, which, in turn, has induced olefin alignment. Moreover, because a virtually limitless number of such resorcinol derivatives are accessible,²³ such observations suggest that such switching of the template can be exploited as a general means of achieving alignment of double bonds using this approach.⁶ From a synthetic perspective, this observation is important because such an ability to achieve olefin alignment is expected to increase the synthetic flexibility of this method, providing alternative supramolecular²⁴ pathways to targeted molecular products.²⁵

In this report, we have expanded a template⁵ approach for controlling reactivity in the solid state to monofunctional reactants, and we have demonstrated the ability of this method to achieve Schmidt's alignment criterion¹ for solid-state reaction by placing a substituent along the periphery of the template.^{9,10,14} With a library⁹ of reactants now emerging, experiments are underway to apply this method to the targeted⁵ solvent-free synthesis of complex mono- and bifunctional products (e.g., nanostructures). Owing to the increasing reliability of this method, the deliberate solvent-free² design of such targets should be feasible, so that access to molecules, and materials, less accessible using more traditional approaches can be realized.

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Supporting Information Available: Crystallographic reports and tables of positional and thermal parameters, bond lengths and angles, and ¹H NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Literature Cited

- Schmidt, G. M. J. Photodimerization in the Solid State. *Pure Appl. Chem.* **1971**, *27*, 647.
- (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (b) Moulton, B.; Zaworotko, M. J. From Molecules to Crystal Engineering: Supramolecular Isomerism and Polymorphism in Network Solids. *Chem. Rev.* **2001**, *101*, 1629.
- Joy A.; Ramamurthy, V. Chiral Photochemistry within Zeolites. *Chem. Eur. J.* **2000**, *6*, 1287.
- Coates, G. W.; Dunn, A. R.; Henling, L. M.; Ziller, J. W.; Lobkovsky, E. B.; Grubbs, R. H. Phenyl-Perfluorophenyl Stacking Interactions: Topochemical [2+2] Photodimerization and Photopolymerization of Olefinic Compounds. *J. Am. Chem. Soc.* **1998**, *120*, 3641.
- Anderson, S.; Anderson, H. L. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 2000; pp 1–38.
- (a) MacGillivray, L. R.; Reid, J. L.; Ripmeester, J. A. Supramolecular Control of Reactivity in the Solid State Using Linear Templates. *J. Am. Chem. Soc.* **2000**, *122*, 7817. (b) Papaefstathiou, G. S.; Kipp, A. J.; MacGillivray, L. R. Exploiting Modularity in Template-Controlled Synthesis: A New Linear Template to Direct Reactivity Within Discrete Hydrogen-Bonded Molecular Assemblies in the Solid State. *Chem. Commun.* **2001**, 2462.
- Feldman, K. S.; Campbell, R. F. Efficient Stereo- and Regiocontrolled Alkene Photodimerization through Hydrogen Bond Enforced Preorganization in the Solid State. *J. Org. Chem.* **1995**, *60*, 1924.
- Venkatesan, K.; Ramamurthy, V. In *Photochemistry in Organized and Confined Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; pp 133–184.
- Fowler, F. W.; Lauher, J. W. A Rational Design of Molecular Materials. *J. Phys. Org. Chem.* **2000**, *13*, 850.
- For a study involving salts based on diamines that aid alignment of olefins within infinite assemblies, see: Ito, Y.; Borecka, B.; Trotter, J.; Scheffer, J. R. Control of Solid-State Photodimerization of Trans-Cinnamic Acid by Double Salt Formation with Diamines. *Tetrahedron Lett.* **1995**, *36*, 6083.
- Using a conceptually similar approach, phthalic acid has been employed to organize *trans*-cinnamide within an infinite ribbon assembly such that the olefins adopt an antiparallel orientation and react to produce a photodimer in 13% yield. See: Ohba, S.; Hosomi, H.; Ito, Y. In Situ X-ray Observation of Pedal-like Conformational Change and Dimerization of Trans-Cinnamide in Cocrystals with Phthalic Acid. *J. Am. Chem. Soc.* **2001**, *123*, 6349.
- (a) Desiraju, G. R.; Pedireddi, V. R. Solid-State Dimerization of β -Nitrostyrene: A Disordered Photoreactive Crystal. *Chem. Commun.* **1989**, 1112. (b) Murthy, G. S.; Arjunan, P.; Venkatesan, K.; Ramamurthy, V. Consequences of Lattice Relaxability in Solid State Photodimerizations. *Tetrahedron* **1987**, *43*, 1225.
- Orientation of the double bond of stilbene and derivatives is sensitive to crystal environment. This suggests that olefins of a discrete assembly similar to the hydrogen-bonded arrays described here can readily adopt either a parallel or antiparallel orientation in the solid state (see: Galli, S.; Mercandelli, P.; Sironi, A. Molecular Mechanics in Crystalline Media: The Case of (E)-Stilbenes. *J. Am. Chem. Soc.* **1999**, *121*, 3767), being either photoactive or photostable.
- For a discussion on using an alternative auxiliary to control solid-state reaction, see: Kane, J. J.; Liao, R.-F.; Lauher, J. W.; Fowler, F. W. Preparation of Layered Diacetylenes as a Demonstration of Strategies for Supramolecular Synthesis. *J. Am. Chem. Soc.* **1995**, *117*, 12003.
- 4-Chlorostilbazole was prepared by an aldol-type reaction involving 4-picoline with 4-chlorobenzaldehyde.
- Crystal data for (res)·2(4-Cl-sbz): crystal size 0.20 × 0.25 × 0.40 mm, triclinic, space group *P1*, *a* = 9.926(1) Å, *b* = 10.203(1) Å, *c* = 13.865(1) Å, α = 105.433(1)°, β = 97.863(1)°, γ = 92.481(1)°, *U* = 1336.0(1) Å³, 2θ = 45°, Mo K α radiation (λ = 0.71070 Å) for *Z* = 2 and *R* = 0.028.
- The Cl···Cl separations are relatively long compared to those found in crystalline Cl₂. See: Sarma, J. A. R. P.; Desiraju, G. R. The Role of Cl···Cl and C–H···O Interactions in the Crystal Engineering of 4-Å Short-Axis Structures. *Acc. Chem. Res.* **1986**, *19*, 222.

(18) An examination of the X-ray data reveals that electron density associated with a conformer that corresponds to parallel alignment of the olefins is not present.

(19) Crystal data for (res)·(4-Cl-dpcb): crystal size $0.25 \times 0.25 \times 0.30$ mm, monoclinic, space group $C2/c$, $a = 38.240(4)$ Å, $b = 9.463(1)$ Å, $c = 14.971(1)$ Å, $\beta = 98.193(3)^\circ$, $U = 5362.3(9)$ Å³, $2\theta = 45^\circ$, Mo K α radiation ($\lambda = 0.71070$ Å) for $Z = 2$ and $R = 0.060$.

(20) The 4, 5, or 6 position places the substituent in a location away from the active site of the template.

(21) Desiraju, G. R. Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311.

(22) Crystal data for (4-Et-res)·2(4-Cl-sbz): crystal size $0.25 \times 0.25 \times 0.40$ mm, monoclinic, space group $P2_1/n$, $a = 8.572(1)$ Å, $b = 36.722(2)$ Å, $c = 9.739(1)$ Å, $\beta = 108.457(1)^\circ$, $U = 2908.1(3)$ Å³, $2\theta = 45^\circ$, Mo K α radiation ($\lambda = 0.71070$ Å) for $Z = 2$ and $R = 0.056$.

(23) (a) Dol, G. C.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. Synthesis of 5-Substituted Resorcinol Derivatives via Cross-Coupling Reactions. *Eur. J. Org. Chem.* **1998**, *359*, 9. (b) Fürstner, A.; Seidel, G. Shortcut Syntheses of Naturally Occurring 5-Alkylresorcinols with DNA-Cleaving Properties. *J. Org. Chem.* **1997**, *62*, 2332. (c) Thomsen, I.; Torssell, K. B. G. Iodination of Resorcinol, 5-Methoxyresorcinol, Phloroglucinol, and Resorcylic Acid. *Acta Chem. Scan.* **1991**, *45*, 539.

(24) Lehn, J.-M. *Supramolecular Chemistry*; Wiley-VCH: Weinheim, Germany, 1995.

(25) The significance of this observation in the context of targeted solid-state synthesis has not been discussed.

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