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Dewar Benzene as a Protecting Group? Demonstration of Photolithographic Crystallization

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ABSTRACT

The concept of Dewar benzene as a supramolecular protecting group for solid-state aryl–aryl interactions is reported. Photoisomerization of 1,4,5,6-tetramethyl-bicyclo[2.2.0]hexa-2,5-diene-2,3-dicarboxylic acid dimethyl ester (1) to the corresponding benzene isomer proceeds with rapid crystal formation. Herein this property is applied to the photolithographic patterning of crystal domains on a surface.

Although protecting groups play a crucial role in covalent synthetic chemistry,[1,2] their role in supramolecular chemistry is practically nonexistent. In theory, supramolecular protecting groups could contribute significantly to fields such as crystal engineering,[3,4] providing a means to diminish specific, noncovalent, intermolecular interactions, thus biasing self-assembly by design. With regard to crystal engineering, such protecting groups must be the epitome of atom economy.[5] Specifically, deprotection must not require or produce any unwanted chemical species, as they would ultimately constitute impurities within the crystal lattice. Such restrictions are significant and limit the use of most common protecting groups. Herein we propose Dewar benzene as a supramolecular protecting group for aryl−aryl supramolecular interactions and exemplify its use by demonstrating photolithographic patterning of crystal domains on a surface.

The ideal supramolecular protecting group is subject to several requirements. As stated, it cannot require or produce unwanted chemical species. Furthermore, conversions must be quantitative and irreversible. Finally, the protecting group must be capable of masking all intrinsic properties of the parent synthon that would otherwise lead to noncovalent interactions (hence its denotation as a protecting group). To test this concept, we have employed the photochemical conversion of Dewar benzene to benzene. Our choice was based, in part, on the ability of the Dewar isomer to completely destroy all aspects of aromaticity, hence muting the ubiquitous supramolecular aryl−aryl interaction.

During the course of investigating a series of Dewar benzenes, we recognized that the known Dewar benzene, compound **1**,[6] underwent a photoisomerization and commensurate phase change, converting from an oil (compound **1**) to a crystalline solid (compound **2**). We recognized that this observation may serve as a highly visual litmus test of the aforementioned concept, Dewar benzene as a protecting group. Substantiation of such a claim would require not only meeting the aforementioned requirements but also clear demonstration of aryl−aryl interactions in the X-ray crystal structure of compound **2**.

The Koster procedure was implemented for the synthesis of Dewar benzene **1** (Scheme 1)[6] By streamlining the

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[1] Green, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1980.

[2] Wuts, P. G. M.; Green, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991; Vol. 2.

[3] Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: New York, 1989; Vol. 54.

[4] Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311−2327.

[5] Trost, B. M. *Science* **1991**, *254*, 1471.

[6] Koster, J. B.; Timmermans, G. J.; van Bekkum, H. *Synthesis* **1971**, 139−140.

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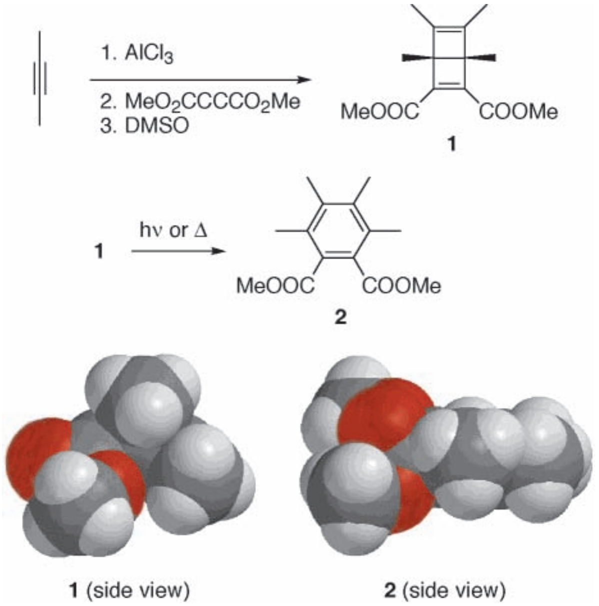
Scheme 1



reported workup, we were able to increase isolated yields of compound **1** from 27% to 44%. Regardless, partial isomerization of reactive **1** typically takes place during the course of the reaction and/or workup, thus contaminating isolated product with trace amounts of compound **2**. Fortunately, this mixture can be readily separated by addition of pentane and subsequent filtration, as the two isomers have dramatically different solubilities. Indeed, contamination of **1** by **2** is detected by the presence of a heterogeneous mixture of needle-shaped crystals (**2**) and oil (**1**). Note that the neat mixture does not prevent crystallization of the minor component. Isolated crystals of compound **2** exhibit a melting point of 128 °C. The latter two facts illustrate that the strong crystal packing forces present in compound **2** are muted in isomer **1**.

The difference in propensity for the two isomers to crystallize stems, in part, from their topological differences. Scheme 1 shows the side-on view of the two isomers (space filling models; minimized at the PM3 level of theory[7]). Note, however, that topology is not the only factor driving aryl−aryl interactions.[3,4,8] As stated, a protecting group for aryl−aryl interactions must eradicate *all* intrinsic properties of the aryl moiety, hence our choice of Dewar benzene.

When neat samples of **1** are irradiated with 365 nm light, photoisomerization is followed by rapid crystal formation. The efficiency of this process is remarkable and led us to believe that the conversion from **1** to **2** takes place with the absence of byproducts. Monitoring this process by ^{1}H NMR confirmed that the photoisomerization was indeed quantitative.[9] In contrast to this result, it should be noted that examples of product mixtures resulting from the photoirradiation of Dewar benzenes have been reported.[10]

Given the aforementioned results, Dewar benzene **1** is an ideal example of a supramolecular protecting group for synthon **2**. Specifically, the protecting group eradicates the aryl moiety, thus inhibiting intermolecular aryl−aryl interactions that would otherwise promote crystallization. Deprotection via photoisomerization is quantitative, irreversible, and without byproduct, and subsequent crystal formation takes place spontaneously. Furthermore, the thermal stability of compound **1** at room temperature is excellent (complete thermal isomerization requires heating in refluxing toluene for ca. 2 h).[11] Last, the X-ray crystal structure of compound **2** reveals a face-to-face packing motif exhibiting a neighboring aromatic ring C···C spacing of 3.780 Å (Figure 1).[12] Such a packing motif is characteristic of the aryl−aryl supramolecular synthon.[3,4,8]

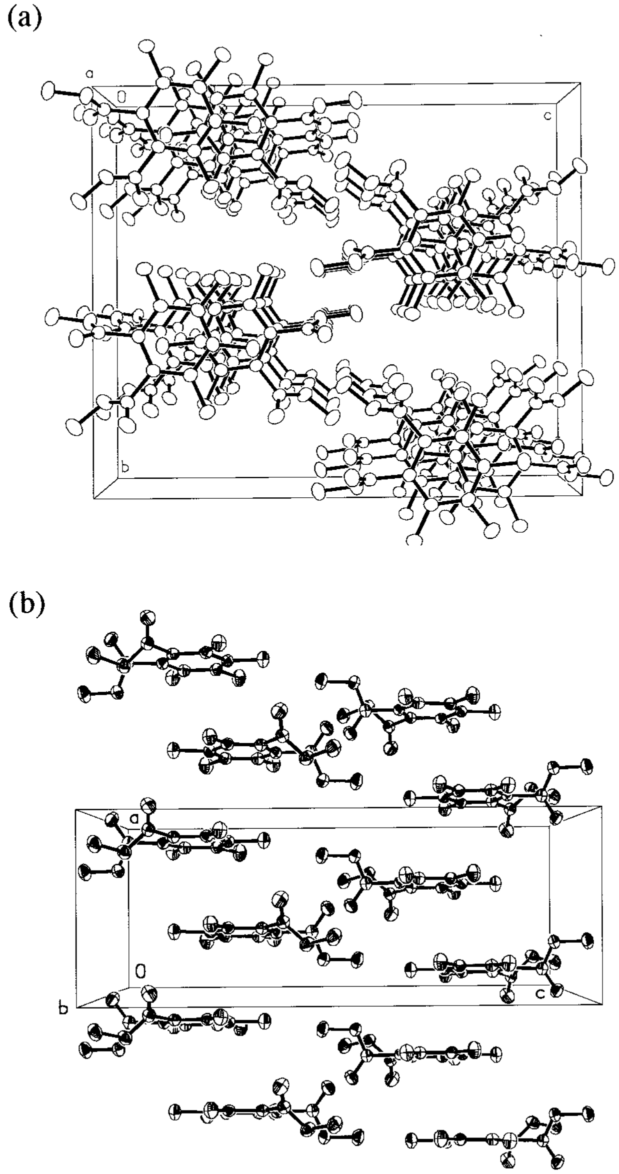


Figure 1. ORTEP representations of compound **2** viewed (a) down and (b) along the face-to-face stacks. The closest C···C aromatic ring distance in this face-to-face packing motif is 3.780 Å.

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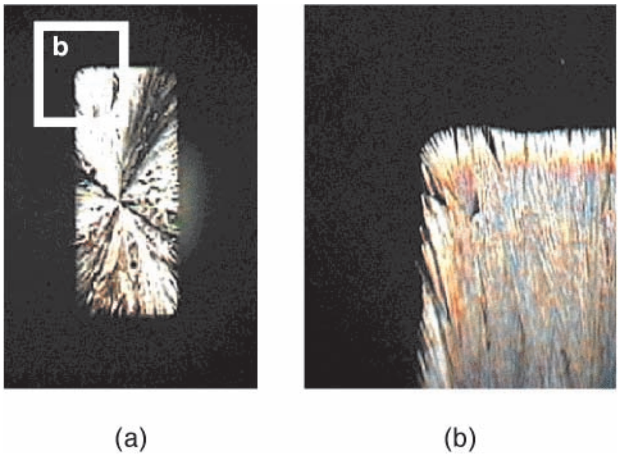
[7] Calculations reported herein were performed using Titan software, Schrödinger, Inc., 1500 SW First Avenue, Suite 1180, Portland, OR 97201.

[8] Desiraju, G. R.; Gavezzotti, A. *J. Chem. Soc., Chem. Commun.* **1989**, 621−623.

In an effort to provide a visual litmus test of this concept, we focused on the application of photolithographic patterning of crystal domains on a surface. In theory, such an application may add a significant *processing* tool to the field of crystal engineering. The following conditions represent our initial (unoptimized) efforts to perform photolithographic crystallization using compound **1**.

A neat sample (ca. 10 μL) of compound **1** (oil) was sandwiched between two 1” × 3” standard microscope slides. A shadow mask was prepared by ink-jet printing a design onto a transparency film and was subsequently affixed to the exterior surface of the top microscope slide. The sample was irradiated for 15−20 min at 25 °C (365 nm @ 7 mW/cm^2). If crystals were not immediately apparent, the sample was cooled to 0° until the formation of colorless crystals within the unmasked area was detected by the naked eye. This latter process took place rapidly. To best assess the match between mask design and crystal domain, the sample was examined under a cross-polarizing microscope. Under these viewing conditions, regions of amorphous **1** appear dark (denoting the protected region), while crystals of **2** are readily visible (denoting that deprotection has occurred; see Figure 2). As a litmus test for our proposed concept, it is visually apparent from Figures 1 and 2 that aryl−aryl interactions are, as expected, activated (deprotected) by photoisomerization. Furthermore, given the simplicity of the unoptimized photolithographic conditions, the match between mask and crystal domain is excellent (Figure 2; both mask and crystal domains have dimensions of 1.05 cm × 0.45 cm).



(a) (b)

Figure 2. (a) Photograph showing the patterned crystal domain of compound **2** surrounded by amorphous compound **1** (light and dark areas, respectively, as viewed under cross polarizers). (b) Magnified view of the top left corner of patterned crystal domain shown in (a).

Aryl−aryl interactions are a ubiquitous supramolecular synthon, playing a dominant role in many self-assembly processes. Herein, we have proposed Dewar benzene as the corresponding supramolecular protecting group and highlighted such an application by demonstrating a process we have termed “photolithographic crystallization.” In an effort to further test the scope of this supramolecular protecting group, we are currently investigating synthetic methodology aimed at facilitating the covalent incorporation of Dewar benzene moieties onto a wide range of molecular scaffolds.

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Supporting Information Available: Details of X-ray determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Characterization of compounds **1**and **2** are consistent with literature values. Compound **1**: see ref 6. Compound **2**, see: McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666−1668.

[10] Gleiter, R.; Treptow, B. *J. Org. Chem.* **1993**, *58*, 7740−7750.

[11] Gleiter, R.; Ohlbach, F.; Oeser, T.; Irngartinger, H. *Liebigs Ann.* **1996**, 785−790.

[12] Crystallographic data has been deposited in the Cambridge Crystallographic Data Centre Database.