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A Supramolecular Protecting Group Strategy Introduced to the Organic Solid State: Enhanced Reactivity through Molecular Pedal Motion**

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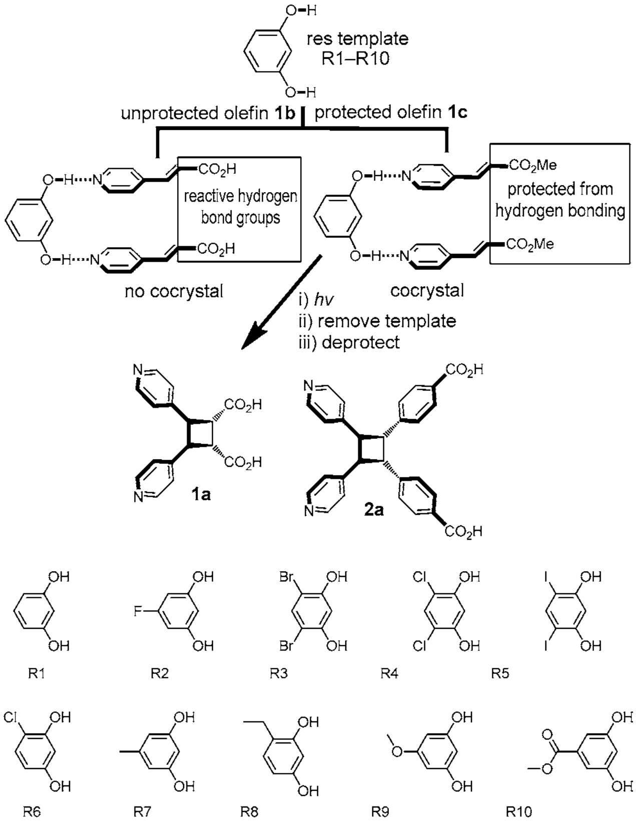
A major impediment when planning reactions in the organic solid state[1,2] is unpredictable structure effects of crystal packing. For bimolecular reactions, reactive centers must generally lie in proximity, being separated by distances on the order of 4 Å.[3] To achieve this goal, chemists often functionalize reactants with groups that participate in molecular recognition processes that drive the solid-state assembly process to a prerequisite geometry.[4] The idea is to identify supramolecular synthons,[2] akin to molecular synthons, that are able to overcome effects of crystal packing and, ultimately, enable molecular synthesis by design.

In this context, the use of protecting groups is a functionalization strategy replete in solution-phase synthetic organic chemistry.[5] A protecting group involves temporarily derivatizing a reactant so as to mask an organic group and to hinder it from participating in a chemical reaction and forming an unwanted covalent bond. In principle, the concept of a protecting group can be applied to an organic group that is likely to participate in an unwanted noncovalent bond.[6] In such a setting, it may be necessary to mask an organic group from participating in an intermolecular force that disrupts an assembly process aimed to afford a covalent-bond-forming supramolecular structure.[6] The field of metal–organic frameworks (MOFs) has recently benefited from protecting group strategies that involve noncovalent bonds whereby organic groups are removed in a postsynthetic step to generate MOFs of controlled dimensionalities.[6] Efforts to understand and exploit such interplay between noncovalent and covalent bonds, however, remain in a stage of infancy, yet can equip chemists with powerful tools for molecular and supramolecular design. Developing such interplay is especially important in the organic solid state where structural effects of noncovalent bonds are accentuated in the closely packed environment.[2]

Herein, we introduce the concept of a protecting group strategy applied to molecular syntheses in the organic solid state (Scheme 1). The strategy employs principles of supramolecular chemistry to achieve the targeted hydrogen-bond-mediated formation of carbon–carbon single (C−C) bonds and concomitant installation of carboxylic acid (-CO_2H) groups.



Scheme 1. Solid-state supramolecular protecting group strategy.

Our interests lie in developing cocrystals based on resorcinol (res) to direct [2+2] photodimerizations in solids.[4] Res acts as a ditopic hydrogen bond donor template that assembles and stacks olefins lined with acceptor pyridyl groups for photoreaction. During studies to use res templates to direct the [2+2] cycloaddition, we developed an interest to generate head-to-head **1a** (Scheme 1).[7] The diacid is attractive as a building block for MOFs and related porous solids.[4,8] Moreover, the presence of the 4-pyridyl groups suggested that **1a** could be generated from a photodimerization of the acrylic acid **1b**, wherein a res assembles **1b** by O−H···N hydrogen bonds in a head-to-head geometry for photoreaction. To be realized, the O−H groups of a res

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would be required to participate in O–H···N interactions and, thereby, successfully compete[9] with the O–H acid group of the olefin that directs the self-assembly of pyridine-carboxylic acids such as **1b** in solids.[10] We reveal how an inability to utilize res templates involving R1–R10 to assemble **1b** to form **1a** can be overcome by using a supramolecular protecting group strategy. The strategy involves masking the acid group[5] of **1b** as an ester in **1c**[11] that remains dormant in the assembly process and can be easily removed post synthesis to generate the acid groups of **1a.** The protecting strategy enables res templates to afford **1a**, and a lengthened congener **2a**, stereospecifically and in quantitative yield. In addition to the solid state, we are unaware of a supramolecular protecting group strategy having been applied to related hydrogen-bond-mediated syntheses developed in solution.[12] We also show how integrating a stilbene unit into a lengthened protected olefin results in strikingly enhanced reactivity that enables the generation of lengthened cyclobutane **2a**, which we attribute to often overlooked pedal motion[13] in stilbene-based solids.

In our initial studies to synthesize the target **1a**, we attempted to achieve a reactive hydrogen-bonded assembly involving **1b** and a res. The olefin **1b** was insoluble in most organic solvents, which is attributed to **1b** participating in intermolecular O–H(acid)···N(pyridyl) hydrogen bonds in the pure solid.[10] For a res template, we employed our cocrystal screening strategy termed "template switching."[14] The strategy involves screening a pyridine-based olefin with res derivatives by solvent precipitation and by exposing the resulting cocrystals to UV irradiation. The method allows us to assemble the same olefin into similar yet different packing environments to improve the probability of obtaining a photoreactive solid.[14] From our studies, the application of template switching to **1b** using R1–R10 in organic solvents (e.g. EtOH, DMF) afforded pure **1b** alone as a precipitate, as evidenced by powder X-ray diffraction (PXRD) analyses (Figure S-25). We attribute the inability of each res to form a cocrystal with **1b** to the marked insolubility of the olefin and, corresponding, intermolecular hydrogen bonds present in the pure solid.

To achieve a reactive cocrystal that furnishes **1a**, we designed a protecting group strategy.[5,11] In particular, we expected that the hydrogen bond donor abilities of the acid group of **1b** could be effectively rendered inactive by converting the acid group into the corresponding methyl ester **1c** that masks the proton. Conversion of **1b** into **1c** was expected to result in increased solubility and, at the same time, enable a res to form O-H···N hydrogen bonds to the alkene (Scheme 1). Although the sp^2-hybridized O atom of an ester can act as a hydrogen bond acceptor group, the basicity of a pyridine ($pK_a = 5.2$) versus an ester ($pK_a = -6$) suggested that the pyridyl group would selectively participate in a hydrogen bond with a res.[15] Upon photoreaction, the resulting diester **1d** would be deprotected by hydrolysis to generate **1a**.

The methyl ester **1c** was, thus, prepared.[16] Our template switching method was applied to screen for reactive cocrystals of **1c** and R1–R10. Cocrystals were generated by mixing **1c** and each res (0.5 equiv) in MeCN and allowing the solution to stand. Within two days, all samples contained a precipitate that was dried and subjected to UV irradiation. In contrast to the acid **1b**, an examination of PXRD patterns revealed a new solid phase in each case, which supported cocrystal formation. ^{1}H NMR analysis showed each solid to consist of **1c** and a res (2:1 ratio).

Of the 10 res R1–R10 screened with **1c**, to our surprise, only the cocrystal 2(**1c**)·(R2) was photoactive. A single-crystal-structure analysis revealed a discrete, three-component hydrogen-bonded assembly sustained by two O–H···N hydrogen bonds (O···N distances [Å]: O1···N1 2.763(2), O2···N2 2.741(2); Figure 1a). The stacked C=C bonds were ordered, organized in parallel, and separated by 3.73 Å, geometries that conform to the criteria for photoreaction.[3] Olefins between nearest-neighbor assemblies were antiparallel and separated by 4.87 Å (Figure 1b).

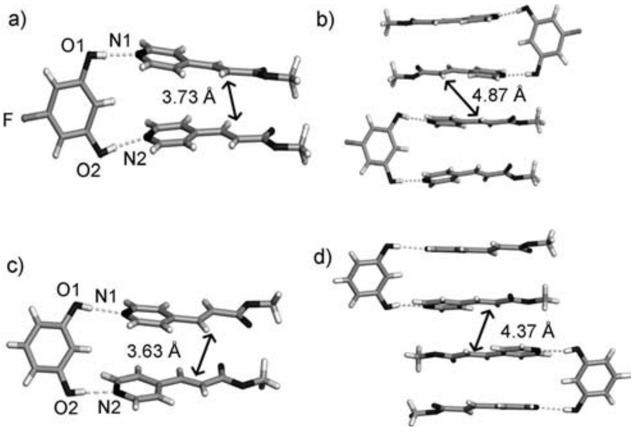


Figure 1. Top: X-ray structure of reactive 2(**1c**)·(R2): a) assembly with parallel C=C bonds and b) antiparallel packing. Bottom: X-ray structure of unreactive 2(**1c**)·(R1): c) assembly with criss-crossed C=C bonds and d) antiparallel packing.

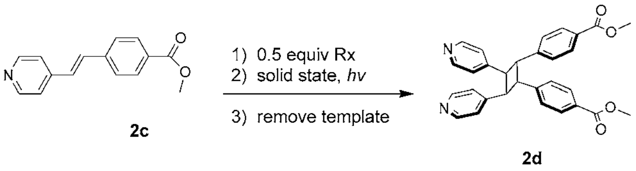
UV irradiation of a powdered sample of 2(**1c**)·(R2) revealed **1c** to react quantitatively to give **1d**, as evidenced by ^{1}H NMR spectroscopy. The product was characterized by the disappearance of the olefinic signals at 7.65 and 6.95 ppm and the appearance of cyclobutane signals at 4.38 and 4.15 ppm. Basic extraction and a subsequent hydrolysis afforded the unmasked diacid **1a**, as confirmed by ^{1}H NMR spectroscopy (95% yield).[7]

To gain insight into the photostabilities of the remaining solids, single crystals of 2(**1c**)·(R1) were obtained after slow solvent evaporation from MeCN.[17] An X-ray analysis revealed, similar to 2(**1c**)·(R2), a discrete assembly sustained by two O–H···N hydrogen bonds (O···N distances [Å]: O1···N1 2.787(3), O2···N2 2.800(3)). The C=C bonds were determined to be ordered and separated by 3.63 Å but, in contrast to 2(**1c**)·(R2), adopted a criss-cross conformation (Figure 1c,d).[13] The photostability of the cocrystal 2(**1c**)·(R1) can likely be attributed to the criss-cross arrangement of the stacked C=C bonds in the solid state.[13]

Given that organization of molecules in solids is extremely sensitive to subtle changes to the molecular structure, we investigated the generality of the protecting group strategy to generate the extended cyclobutane congener **2a**. As for **1b**, each attempt to screen **2b** for a cocrystal involving R1–R10 afforded the pure solid olefin, as confirmed by PXRD analyses (Figure S-26). The corresponding protected lengthened phenyl ester **2c** was, thus, prepared by using a modified procedure.[18]

In contrast to **1c**, the application of template switching to **2c**, remarkably, afforded a photoactive solid in each case (Table 1). As for **1c**, each solid was formed by mixing **2c** and a res (0.5 equiv) in EtOH and allowing the solution to stand. Within two days, each sample contained a solid that was dried and subjected to UV irradiation. PXRD and ^{1}H NMR analyses supported cocrystal formation. Of the 10 reactive solids, four (res = R3, R5, R6, R7) afforded **2d** stereospecifically and in quantitative yield.

Table 1: Template switching applied to **2c**.



Entry	Res Rx	*t* [h]	Conv. [%]	Yield of **2d** [%]
1	R1	175	66	44[a]
2	R2	175	85	55[a]
3	R3	175	100	100
4	R4	75	90	90
5	R5	175	100	100
6	R6	75	100	100
7	R7	130	100	100
8	R8	175	52	52
9	R9	175	96	64[a]
10	R10	175	75	75

[a] Mixture of **2d** and unidentified minor product.

Single-crystal X-ray diffraction was employed to study the enhanced solid-state reactivity of **2c** versus **1c**.[17] Moreover, a structure analysis of each solid that afforded **2d** in 100 % yield in 2(**2c**)·(res) (where: res = R3, R5, R6, R7) revealed the components, similar to 2(**1c**)·(R2), to form discrete assemblies sustained by two O–H···N hydrogen bonds (O···N distances [Å]: 2(**2c**)·(R3) O1···N1 2.750(3), O2···N2 2.706(4); 2(**2c**)·(R5) O1···N1 2.698(4), O2···N2 2.707(3); 2(**2c**)·(R6) O1···N1 2.713(4), O2···N2 2.725(5); 2(**2c**)·(R7) O1···N1 2.737(4), O2···N2 2.760(5)) (Figures 2a–h). In contrast to 2(**1c**)·(R2), however, the C=C bonds in three stacked stilbene pairs were disordered (2(**2c**)·(R5): 0.51/0.49 and 0.91/0.09; 2(**2c**)·(R6): 0.53/0.47 and 0.50/0.50; 2(**2c**)·(R7): 0.71/0.29 and 0.66/0.34.), with the C=C bonds being separated by 3.94, 3.94, and 3.96 Å, respectively. Olefins between the stacked assemblies were either parallel (R5) or antiparallel (R6 and R7), being separated by 5.42, 5.11, and 4.01 Å, respectively (Figures 2d,f,h). For 2(**2c**)·(R3), the C=C bonds were ordered and separated by 4.10 Å, with adjacent assemblies adopting an antiparallel arrangement (Figures 2a,b). The C=C bonds between adjacent assemblies were also parallel and separated by 4.01 Å. UV irradiation of (**2c**)·(res) (where: res = R3, R5, R6, R7) revealed **2c** to react stereospecifically and quantitatively in each cocrystal. The generation of the cyclobutane photoproduct was evidenced by the disappearance of the signals at 7.65 and 7.43 ppm and the appearance of signals at 4.75 and 4.69 ppm.

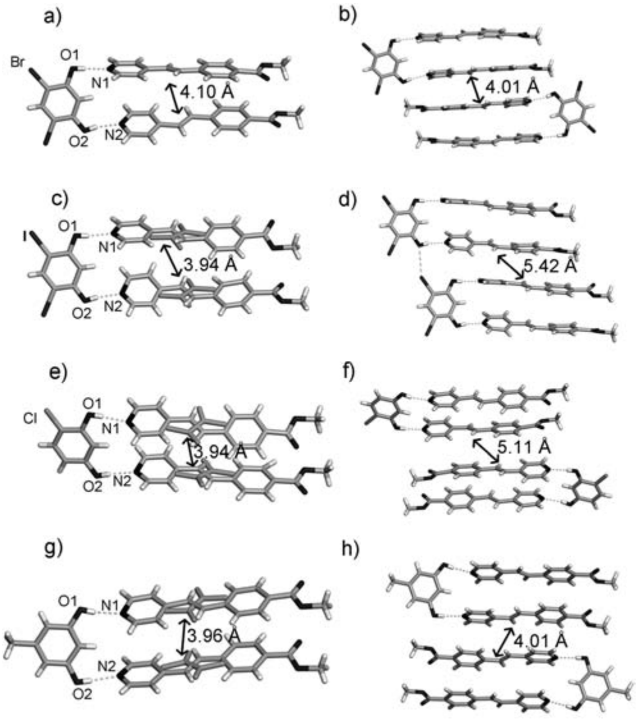


Figure 2. X-ray structures of reactive (**2c**)·(res): 2(**2c**)·(R3): a) antiparallel C=C bonds and b) packing, 2(**2c**)·(R5): c) parallel C=C bonds and d) packing, 2(**2c**)·(R6): e) parallel C=C bonds and f) packing, and 2(**2c**)·(R7): g) antiparallel C=C bonds and h) packing. Lower occupancies of each C=C bond in full gray.

The photoproduct **2d** was isolated from the res template by liquid-phase extraction using $CHCl_3$ and NaOH. Deprotection of **2d** was achieved through basic hydrolysis with aqueous NaOH. A subsequent neutralization with aqueous HCl afforded the target cyclobutane **2a**, as revealed by ^{1}H NMR spectroscopy (97 % yield). Moreover, the stereochemistry of **2a** was confirmed by an X-ray analysis of a deprotected intermediate in the form of the sodium salt $[Na_4(\mu_2\text{-}OH_2)_8(C_{28}H_{20}N_2O_4)_2(OH_2)_6(OH_2)]\cdot H_2O$ (Figure 3).

The markedly enhanced reactivity of cocrystals of **2c** compared to **1c** with R1–R10 can be attributed to the C=C units undergoing pedal, or crankshaft, motion in each solid.[13] Stilbenes such as **2c** exhibit dynamic motion in the crystalline state that can interconvert[13] C=C bonds from a criss-cross to a parallel conformation suitable for a photodimerization

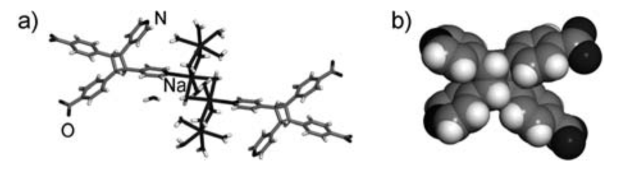
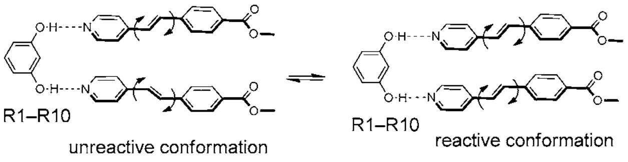


Figure 3. X-ray structure of the sodium carboxylate salt of **2a**: a) wireframe and b) space-filling model of the dianion of **2a**.

(Scheme 2).[19,20] Herein, the pedal motion of the stilbene acts to our advantage, compared to the acrylate **1c**, to achieve reactivity within a series of res-based solids. Given that our goal is to expand the synthetic versatility of reactivity in organic solids, these observations are important since the enhanced reactivities suggest that stilbene units and protecting groups, when applied in combination, can provide a route to highly reactive olefins for the directed formation of C–C bonds in solids.



Scheme 2. Enhanced reactivity of protected olefin in a cocrystal of res achieved through pedal motion.

In conclusion, we have introduced a protecting group strategy to the organic solid state used to direct the formation of C–C bonds mediated by principles of supramolecular chemistry. An ester masks a carboxylic acid to generate head-to-head photodimers with restored acid groups from organic solids. We have also shown how the solid-state reactivity is enhanced using stilbenes as protected functionalities. We anticipate the protecting strategy to be amenable to other protecting group strategies developed in the liquid phase and applicable to other reactions mediated by templates (e.g. hydrogen bond acceptors) in both the solid state and in solution.

Experimental Section

Syntheses of ester-based cocrystals: Cocrystals of 2(**1c**)·(res) were obtained by slow solvent evaporation. **1c** (50 mg) and a res (R1–R10, 0.5 mol eq) were dissolved in MeCN (5 mL). The solution was heated to reflux and was cooled slowly to ambient temperature. Within 48 h, single crystals suitable for X-ray analysis were obtained. The cocrystals were isolated by vacuum filtration and were air dried. Cocrystals of 2(**2c**)·(res) were obtained in the same manner described above, using EtOH as the solvent.

Single-crystal X-ray diffraction: Single-crystal diffraction data were collected on a Nonius Kappa CCD single-crystal X-ray diffractometer at both room and low temperatures using $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Data collection, cell refinement, and data reduction were performed using Collect[21] and HKL Scalepack/Denzo,[22] respectively. Structure solution and refinement were accomplished using SHELXS-97 and SHELXL-97,[23] respectively. The structures were solved by direct methods. All nonhydrogen atoms were identified from the difference Fourier map within several refinement steps. All nonhydrogen atoms were refined anisotropically. Hydrogen atoms associated with carbon atoms were refined in geometrically constrained positions with isotropic thermal parameters $U_{iso}(H) = 1.5\,U_{eq}(C_{CH3})$ and $U_{iso}(H) = 1.2\,U_{eq}(C_{CH})$. Hydrogen atoms belonging to phenolic OH groups were refined using a riding model with isotropic thermal parameters $U_{iso}(H) = 1.5\,U_{eq}(O_{hydroxy})$. Hydrogen atoms belonging to water molecules were identified from the difference Fourier map and were refined with isotropic thermal parameters $U_{iso}(H) = 1.5\,U_{eq}(O_{water})$. Details of the structural analyses are summarized in Table S-1. CCDC 798921 2(**1c**)·(R1), 823833 2(**1c**)·(R2), 798920 2(**2c**)·(R3), 836620 2(**2c**)·(R5), 823834 2(**2c**)·(R6), 823835 2(**2c**)·(R7), 798922 **2a** Na^+ salt contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Photoreactions: Photoreactions were conducted using UV irradiation from a 500 W medium-pressure mercury lamp in an ACE Glass photochemistry cabinet. The cocrystals were finely ground using a mortar and pestle and were placed between a pair of pyrex glass plates. The samples were irradiated in 10 h increments and were mixed between consecutive irradiations. Product formation was monitored using ^{1}H NMR spectroscopy. Upon completion of photoreaction, products were isolated using basic extraction with $CHCl_3$.

Deprotections of photoproducts: Cyclobutanes **1d** and **2d** were stirred in 2 M NaOH for 2 h. 10 % HCl was added until the solutions tested neutral by pH paper and the solutions were allowed to stir overnight. Evaporation gave the product and sodium chloride. Trituration of the solid with 2:1 $CH_3OH/CHCl_3$ solution, followed by evaporation, afforded diacids **1a** and **2a**. ^{1}H NMR (**1a**, 300 MHz, [D$_6$]DMSO): $\delta = 3.89$ (d, 2H), 4.26 (d, 2H), 7.08 (dd, 4H), 8.36 ppm (dd, 4H). ^{1}H NMR (**2a**, 400 MHz, [D$_6$]DMSO): $\delta = 4.62$ (d, 4H), 7.12 (d, 4H), 7.28 (dd, 4H), 7.66 (d, 4H), 8.36 ppm (dd, 4H).

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