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Anion-Controlled Stereoselective Synthesis of Cyclobutane Derivatives by Solid-State [2 + 2] Cycloaddition Reaction of the Salts of *trans*-3-(4-Pyridyl) Acrylic Acid

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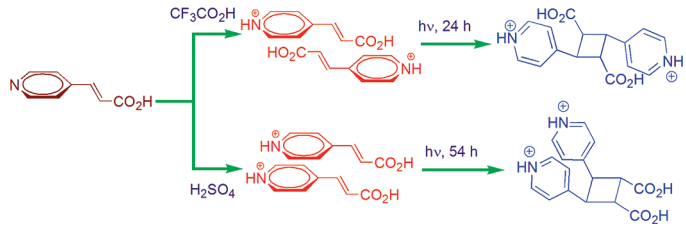
ABSTRACT



Two stereoisomers of cyclobutane derivatives with pyridyl and carboxylic acid functionalities have been stereoselectively synthesized by a solid-state photochemical [2 + 2] cycloaddition reaction in quantitative yields. The *head-to-head* and *head-to-tail* parallel orientations of the monomers, required to obtain these two isomers, have been controlled by the anions present in the salts. The photoinert behavior of these salts in solution signifies the importance of the solid-state synthesis of these cyclobutane derivatives.

The ability to control the regio- and stereoselectivities during the photocycloaddition reactions of olefins has drawn considerable attention of researchers in synthetic organic photochemistry.[1] Various organized media and supramolecular entities such as cyclodextrines,[2] zeolites,[3] clays,[4] biomolecules,[5] micelles,[6] hydrogen-bonded cocrystals,[7] molecular salts,[8] coordination polymers,[9] self-assembled cages,[10] and hosts[11] have been designed and successfully synthesized for this purpose. Although the geometric criteria for the photocycloaddition reactions in the solid state have been established by Schmidt,[12] the parallel orientation of the photoreactive C═C bonds satisfying this postulate in the solid

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state still remains a challenge. The thirst to synthesize strained cyclobutane derivatives with desired functionalities in the solid state by a [2 + 2] cycloaddition route still persists as a result of its high efficiency and distinguished selectivity.[1] In addition, the solid-state synthesis has environmental impact, being a solvent-free route, and enables the products to adopt geometries inaccessible in the solution phase.[13]

Solid-state photodimerization of cinnamic acid analogues is well-explored in the literature.[14] The polymorph α-*trans*-cinnamic acid with the olefins aligned in *head-to-tail* fashion results in α-truxillic acid upon irradiation under UV light, whereas *β*-truxinic acid can be obtained from another polymorph *β*-*trans*-cinnamic acid with olefins aligned in *head-to-head* fashion. The same for *trans*-3-(3-pyridyl) acrylic acid (3-PA) was reported by Lahav and Schmidt,[15] but the detailed crystallographic characterizations were later presented by Briceño.[16] In this study we have employed *trans*-3-(4-pyridyl) acrylic acid (4-PA) to allocate hetero-functionality in the cyclobutane derivatives. Furthermore, different cyclobutane ring compounds can be synthesized depending upon the orientation of 4-PA in the solid state controlled by various supramolecular interactions. To our surprise 4-PA is photostable, unlike 3-PA, and thus requires engineering in the solid state to achieve a parallel orientation prior to irradiation under UV light. Although the role of cation−*π* interactions on the solid-state photodimerization has been explored by Yamada,[17] the role of the anions in such interactions is relatively unexplored. In this contribution, we report on how an anion can influence the orientation of the parallel alignment of cations containing photoreactive double bonds (4-PAH$^+$) so as to direct the regio- and sterocontrolled synthesis of two different cyclobutane derivatives.

4-PA reacted with CF_3CO_2H and H_2SO_4 to form molecular salts in aqueous media, and the resulting salts were employed for photodimerization experiments. 4-PA

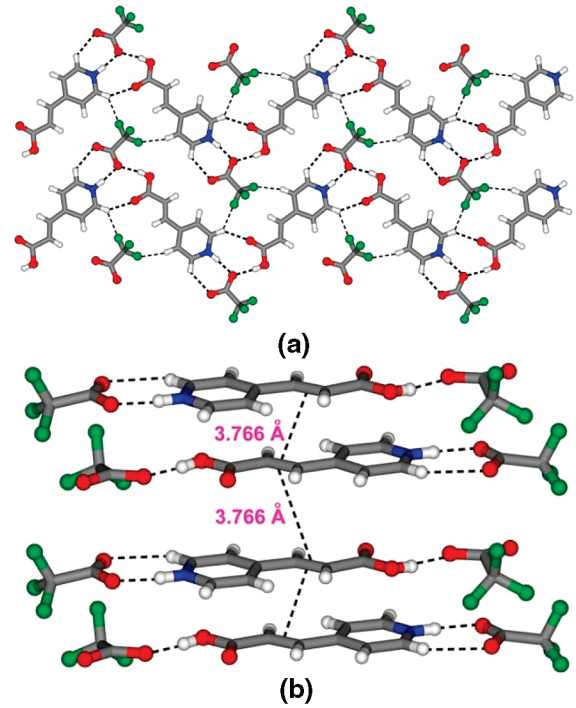

Figure 1. (a) A portion of two-dimensional sheets in the *ab* plane; (b) *head-to-tail* stacking of 4-PAH$^+$ cations in **1**.

with CF_3CO_2H forms the 1:1 salt $C_{10}H_8F_3NO_4$ **1**,[18] which crystallized in the orthorhombic $Pca2_1$ space group where 4-PAH$^+$ cations were found in infinite parallel orientation in *head-to-tail* fashion with a distance of separation 3.766 Å. Various kinds of C−H···O, N−H···O, and C−H···F hydrogen bonding interactions furnish two-dimensional sheets in the *ab* plane (Figure 1).

UV irradiation of a powdered crystalline sample of **1** placed between two glass plates produced a quantitative photodimerization to yield the $CF_3CO_2^-$ salt of 2,4-bis(4-pyridyl)-cyclobutane-1,3-dicarboxylic acid (*head-to-tail*, HT-BPCD) after a period of 24 h, as determined by 300 MHz ^{1}H NMR spectroscopy in DMSO-d_6 by the disappearance of olefinic protons at δ 7.65 (1H, d) and 6.94 (1H, d) ppm and the appearance of cyclobutane protons at δ 4.52 (2H, dd) and 4.1 (2H, dd) ppm, as well as a 297.3 *m*/*z* peak in the ESI-MS [M]$^-$ (Supporting Information). The stereochemistry of HT-BPCD and its $CF_3CO_2^-$ salt was confirmed by X-ray crystallography[19] (Supporting Information) as shown in Figure 2.

The powder X-ray diffraction pattern of the finely ground powder of **1** does not match with the simulated patterns generated from the single crystal data (Supporting Information) which seems to imply a change in the crystalline phase of **1** during grinding. However, there is no significant

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(18) Crystal data for **1**: $C_{10}H_8F_3NO_4$, M = 263.17, orthorhombic, space group $Pca2_1$, a = 18.015(2) Å, b = 8.9617(10) Å, c = 6.7552(8) Å, V = 1090.6(2) Å^3, Z = 4, D_{calcd} = 1.603 g cm^{-3} (Mo Kα, λ = 0.71073 Å), T = 223 K. $R1$ = 0.0595 and $wR2$ = 0.1616 for 2071 unique reflections >2σ(I) and GOF = 1.060. Elemental analysis calcd for $C_{10}H_8F_3NO_4$: C, 45.64; H, 3.06; N, 5.32. Found; C, 45.58; H, 3.19; N, 5.36.

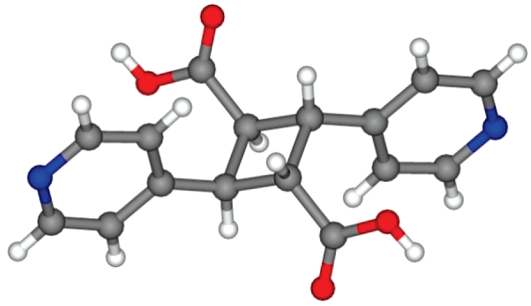

Figure 2. Molecular structure of HT-BPCD.

difference noted between the reactivities of the single crystals and powdered samples both of which furnished 100% HT-BPCD in 30 and 24 h respectively under similar experimental conditions. It appears that the orientation of the 4-PAH$^+$ cation was not changed due to grinding. The slightly increased reactivity for the ground powder may be attributed to increased surface area exposed to the UV light.

4-PA reacted with H_2SO_4 in water to form the salt $(C_8H_8NO_2)_3(SO_4)(HSO_4)(H_2O)$ **2**.[20] The presence of both the sulfate and bisulphate anions and a water molecule make the orientation of 4-PAH$^+$ cations interesting as it is found that all of them orient infinitely in *head-to-head* fashion. The possible cation - cation repulsion in *head-to-head* orientation is balanced and stabilized by cation - anion interactions of bisulphate and sulfate anions. Among the three 4-PAH$^+$ cations in the asymmetric unit, the two 4-PAH$^+$ cations A and C shown in Figure 3 are parallel to the other counterparts

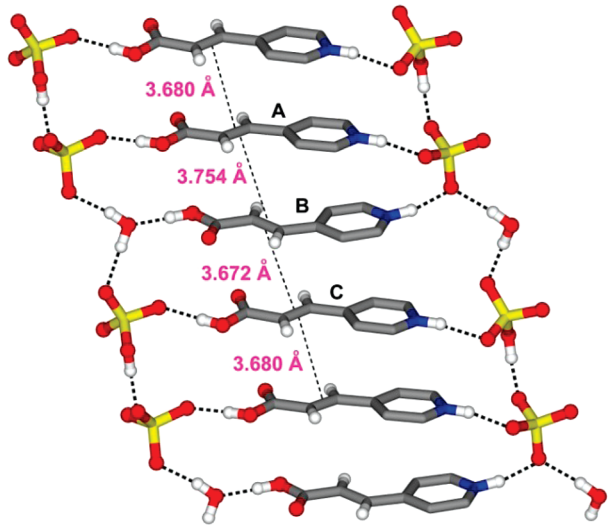

Figure 3. Infinite *head-to-head* arrangement of 4-PAH$^+$ cations in **2**, where B is criss-crossed to both A and C.

keeping a center-to-center distance of 3.68 Å; while the middle one (B), which is directly connected to a water

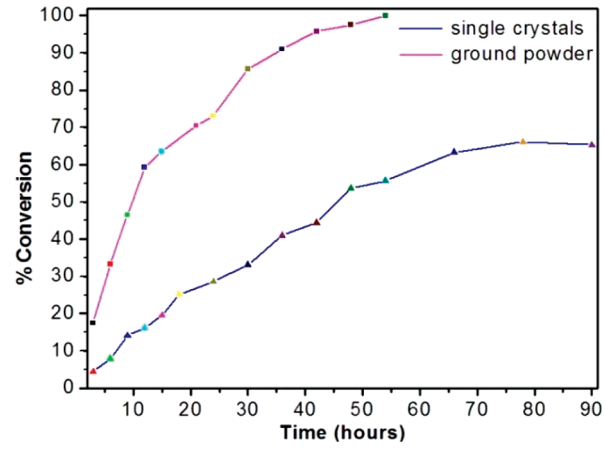

Figure 4. Percentage conversion versus time plots for single crystals and ground powder of **2**.

molecule, is criss-crossed with both A and C, but keeping center-to-center distances between the adjacent C═C bonds of 3.672 Å and 3.754 Å.

Although these two distances are well within the Schmidt criteria and further the [2 + 2] cycloaddition reaction of C═C bonds aligned in criss-cross positions are known to take place as a result of pedal motion.[21] In this regard, the cationic monomer (B) in **2** has been found not to furnish 100% dimerized product. Upon irradiation of single crystals of **2** under UV light, only 66% dimerization was observed as monitored by ^{1}H NMR spectroscopy, which indicated that only the cations A and C underwent dimerization, having a more favorable condition. Surprisingly, when the single crystals were ground into powder, the crystalline powder sample was found to undergo 100% dimerization in 54 h. The formation of *syn-head-to-head*-dimer, namely, 3,4-bis(4-pyridyl)-cyclobutane-1,2-dicarboxylic acid (HH-BPCD), was confirmed by two doublet peaks at δ 4.51 and 4.04 ppm for the cyclobutane protons in the 300 MHz ^{1}H NMR spectrum in DMSO-d_6 (Supporting Information), and the percentage conversion versus time plot is shown in Figure 4.

(19) Crystal data of recrystallized $CF_3CO_2^-$ salt: $C_{20}H_{16}F_6N_2O_8$, M = 526.34, monoclinic, space group $P2_1/c$, a = 12.3692 (7) Å, b = 8.2108 (5) Å, c = 10.8302 (6) Å, β = 94.956(1)°, V = 1095.89(11) Å^3, Z = 2, D_{calcd} = 1.595 g cm^{-3} (Mo Kα, λ = 0.71073 Å), T = 223 K. $R1$ = 0.0451 and $wR2$ = 0.1203 for 2317 unique reflections >2$\sigma(I)$ and GOF = 1.041. Elemental analysis calcd for $C_{20}H_{16}F_6N_2O_8$: C, 45.64; H, 3.06; N, 5.32. Found: C, 45.43; H, 3.03; N, 5.36. Crystal data for neutral HT-BPCD compound: $C_{16}H_{14}N_2O_4$, M = 298.293, monoclinic, space group $P2_1/c$, a = 5.9012(7) Å, b = 6.9480(8) Å, c = 16.0585(19) Å, β = 99.931(2)°, V = 648.56(13) Å^3, Z = 2, D_{calcd} = 1.527 g cm^{-3} (Mo Kα, λ = 0.71073 Å), T = 223 K. $R1$ = 0.0493 and $wR2$ = 0.1510 for 1376 unique reflections >2$\sigma(I)$ and GOF = 1.131. Elemental analysis calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.77; N, 9.28.

(20) Crystal data for **2**: $C_{24}H_{27}N_3O_{15}S_2$, M = 661.612, monoclinic, space group $P2_1/n$, a = 11.0902(8) Å, b = 9.1024(7) Å, c = 27.822(2) Å, β = 94.389(1)°, V = 2800.4(4) Å^3, Z = 4, D_{calcd} = 1.569 g cm^{-3} (Mo Kα, λ = 0.71073 Å), T = 223 K. $R1$ = 0.0386 and $wR2$ = 0.1015 for 5906 unique reflections >2$\sigma(I)$ and GOF = 1.055. Elemental analysis calcd for $C_{24}H_{27}N_3O_{15}S_2$: C, 43.57; H, 4.11; N, 6.35. Found: C, 43.36; H, 4.50; N, 6.32.

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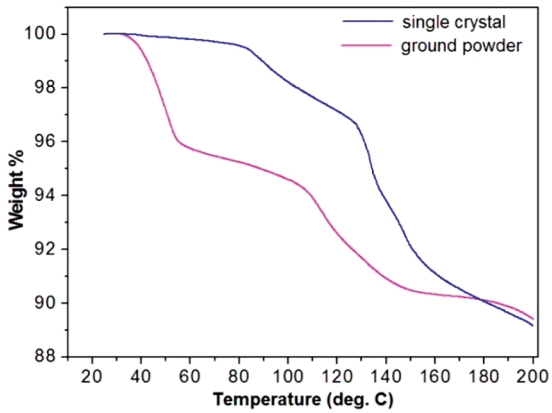

Figure 5. TGA plots for single crystals and ground powder of a sample of **2** show that the ground powder absorbs moisture during grinding. The water loss for single crystals: found, 2.8%; calcd for one H_2O, 2.7% from $(C_8H_8NO_2)_3(SO_4)(HSO_4)(H_2O)$. The water loss for the ground powder: found, 5.4%; calcd for $2H_2O$, 5.3% from $(C_8H_8NO_2)_3(SO_4)(HSO_4)(H_2O)_2$.

The TGA of the powdered sample of **2** is shown in Figure 5, which indicates that the sample has absorbed an extra water molecule in the crystal lattice after grinding. Further, the powder X-ray diffraction pattern of the ground sample does not match with the simulated pattern from single crystal data, confirming that this is a different crystalline material with a different packing arrangement. From the 100% photochemical product indicated by the ^{1}H NMR spectrum, it is expected that in the powdered sample, the 4-PAH$^+$ cations would be perfectly oriented as isolated pairs in *head-to-head* fashion. Thus the difference in the reactivity of single crystals and the powder sample is attributed to a different composition and hence a different molecular packing.

It has been observed previously that the removal of solvents from crystal lattices triggers structural transformations.[21] In this case, the grinding of single crystals into powder under the experimental conditions employed in the lab incorporates an additional water molecule, which in turn influences the molecular packing. In the powdered sample of **2**, all of the 4-PAH$^+$ cations are packed in *head-to-head* fashion with perfectly aligned isolated C═C bond pairs satisfying the Schmidt criteria for photoreactivity. Further, pedal motion of double bonds has also been found to take place during grinding.[21a]

Interestingly, both of these salts **1** and **2** were found to be photoinert and did not undergo the dimerization reaction under UV radiation in D_2O solution. This observation signifies the importance of solid-state photochemical routes to access these two cyclobutane derivatives, HT-BPCD and HH-BPCD, from these two salts. Further, the neutral monomer 4-PA is reluctant to dimerize both in solid and the solution phase under UV light (Supporting Information), and this highlights the importance of the salts in the synthesis of two different isomers of the cyclobutane derivative BPCD.

In summary, this approach illustrates a novel pathway in synthetic organic photochemistry to tune the orientations of the photoreactive monomeric cations by the anions for the regioselective synthesis of functional cyclobutane derivatives that are inaccessible otherwise in solution. It is proposed that during the grinding process the infinitely packed molecules in **2** rearrange to form isolated HH pairs, congenial to 100% [2 + 2] cycloaddition reactions, to account for the observed ^{1}H NMR spectral data. Work is in progress to synthesize functional coordination polymers from these cyclobutane derivatives for various potential applications.

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Supporting Information Available: NMR spectra and other characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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