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Solid-State Diphotocyclization of Iso- and Terephthalaldehydes via Dihalogen Substitution

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The supramolecular nonbonded C—H···X interactions between formyl hydrogens and ortho-halogen atoms (Br/Cl) have been exploited to achieve conformational control in the solid state of dimethyl-substituted iso- and terephthaladehydes (**1−3**) for unprecedented diphotocyclization. It is shown that the dihalogen substitution also contributes to the stability of the benzocyclobutenols relative to their precursor photoenols, so that the solid-state photolysis of dialdehydes **2b**, **2c**, and **3b** leads to diphotocyclization to afford respectable yields of bis-benzocyclobutenols.

Introduction

Crystal engineering is concerned with the design and synthesis of materials with predetermined physical and/or chemical properties.[1] With regard to the chemical reactivity in the solid state, various approaches for steering molecules into reactive orientations for bi- and polymolecular [2 + 2] photocycloadditions have been elegantly demonstrated.[2] Interestingly, rational strategies for engineering the molecules into their "reactive conformations" for unimolecular photoreactions are rather limited despite a vast amount of literature.[3] Photocyclization of *o*-alkyl ketones is one of various unimolecular reactions that has been extensively investigated;[4] both solution and solid-state photolyses lead invariably to photocyclization yielding synthetically very important intermediates, namely, benzocyclobutenols.[5] In contrast, there exists only scant literature on the solution and solid-state photoreactivity of *o*-alkyl aromatic aldehydes;[6] the solution-state photochemistry is frustrated by the formation of a variety of products, while their solid-state photochemistry is marked by intriguing photochromism due to enolization,[7] cyclization, and polymerization. Our recent mechanistic investigations have shown that the benzocyclobutenols, the products of photocyclization, derive from the precursor photoenols by a thermal conrotatory closure (vide infra, Scheme 1); consequently, the relative energies of the photoenols and the benzocyclobutenols determine the observation of photochromism (photoenolization) or formation of the latter.[6] Given this scenario, a rational execution of photocyclization of *o*-alkyl aromatic aldehydes in the solid state necessitates the need to take into account not only the appropriate conformation of the formyl group for H-abstraction but also the relative energies of the E-photoenol and the benzocyclobutenol. Herein, we demonstrate how the dihalogen substitution may be exploited to achieve not only the conformational control via weaker C—H···X interactions but also the promotion of the reactivity of the enols of iso- and terephthalaldehydes (**1−3**, Chart 1) to undergo unprecedented solid-state diphotocyclization to bis-benzocyclobutenols.

Our rationale for selection of the aldehydes **1−3** was the following. The Cambridge Structural Database analysis by Koppenhoefer has revealed that the carbonyl oxygen points toward the halogen atom in all of the *o*-bromoaroyl compounds (ketones, carboxylic acids, esters, etc.) with the exception of *o*-haloaldehydes.[8] In the latter, an entirely opposite scenario, i.e., the carbonyl oxygen pointed away from the *o*-halogen atom, has been found to result as a consequence of stabilization through

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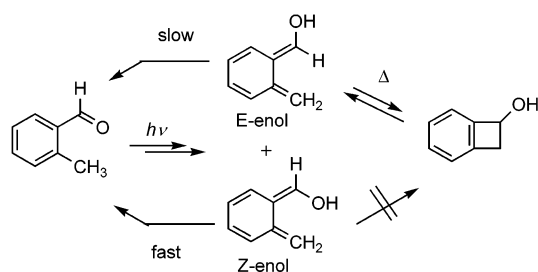(7) (a) Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P. *Org. Lett.* **2001**, *3*, 1579. (b) Sarkar, T. K.; Ghosh, S. K.; Moorthy, J. N.; Fang, J.-M.; Nandi, S. K.; Sathyamurthy, N.; Chakraborty, D. *Tetrahedron Lett.* **2000**, *41*, 6909.
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CHART 1
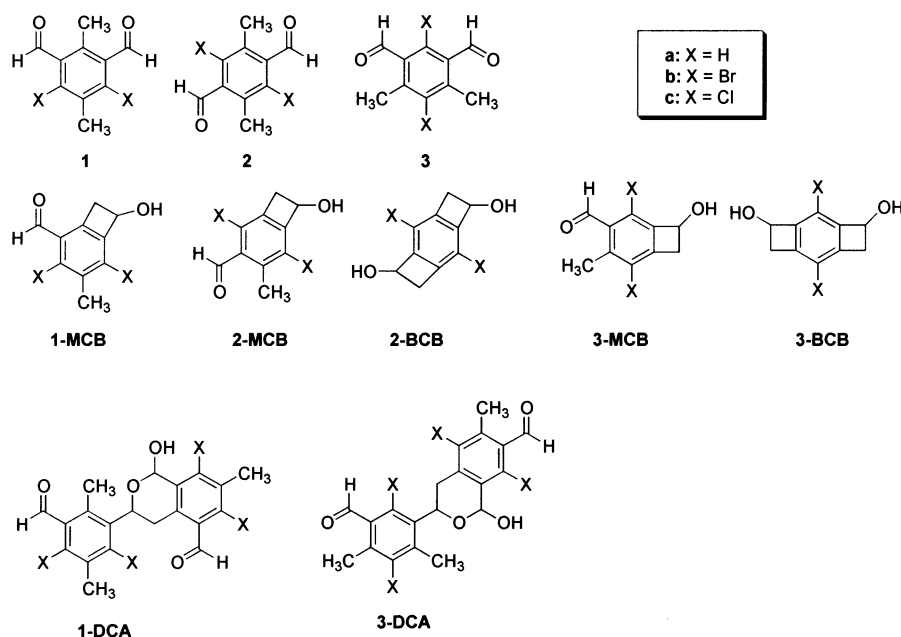
SCHEME 1

intramolecular C−H···X interaction.[9,10] Thus, we reasoned that the unpredictability as to the orientations of the formyl groups in **1a**, **2a**, and **3a** and hence their photoreactivity could be completely eliminated by a dihalogen substitution as in **1b**, **2b,c**, **3b**, and **3c**. In these compounds, the C−H···X interaction between the formyl hydrogens and the halogen atoms could ensure the orientation of the formyl groups for γ-hydrogen abstraction[11] from the methyl groups after photoexcitation. Further, we wished to explore the influence of dihalogen substitution on the relative energies of the photoenols and the cyclobutenols, for it is the energy difference between the two that determines the formation of the cyclobutenols (cf. Scheme 1).

Results and Discussion

The aldehydes **1−3** were synthesized from 2,6-dicyano-*p*-xylene and durene following a sequence of synthetic transformations and fully characterized (IR, ^{1}H, ^{13}C, MS, and combustion analyses; see Supporting Information). The solid-state photobehavior of isophthaladehyde **1a** has already been reported by Kumar et al.;[12] while its photochromic behavior was correlated with the X-ray crystal structure, no attention was paid to the analysis of photoproducts. We subjected all the aldehydes **1−3** to solid-state photolysis in a photoreactor (λ ca. 350 nm) equipped with a turntable by dispersing the gently ground crystals in Pyrex test tubes under a N_2 gas

atmosphere. With the exception of **2a**, all other aldehydes **1−3** exhibited photochromism in that a perceptible color change was observed upon brief exposure to UV irradiation (Table 1), which could be reverted thermally on standing in the dark or by heating; the observed color change is readily attributed to the formation of E-photoenols (Scheme 1). For product studies, the irradiation was typically carried out for 24 h, during which time the samples were shaken periodically to ensure uniform exposure. The dialdehyde **1a** turned red initially, and the color faded to yellow upon continued irradiation. From the preparative photolysis employing ca. 100 mg of the substrate, only a Diels−Alder cycloadduct (**1a**-DCA) could be isolated in 15% yield (entry 1, Table 1). The remainder was found to be a highly intractable polymeric material. In contrast, a similar photolysis of the dibromo-derivative **1b** led to monocyclobutenol with low mass balance (entry 2). The remainder was a polymeric material as in the case of **1a**. While the ^{1}H NMR analysis of the photolyzed sample of **2a** indicated no product formation suggesting its photostability, the aldehyde **3a** turned orange-yellow upon photolysis; the Diels−Alder cycloadduct was isolated as in the case of **1a** (entry 8). The dibromo-substituted dialdehydes **2b** and **3b** turned yellow upon exposure to the UV radiation. From preparative photolyses, a mixture of monocyclobutenol (MCB) and bicyclobutenol (BCB) was isolated in both cases with no evidence for the formation of Diels−Alder cycloadducts (entries 4 and 9). An excellent mass balance and high yields of BCBs are noteworthy at low conversions (entries 5 and 10). The preparative photolysis led to the formation of MCB and BCB in the case of **2c**, while the bicy-

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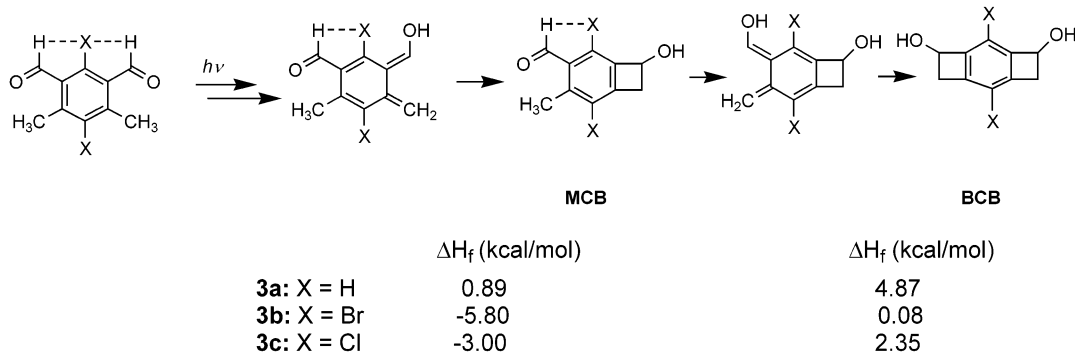(11) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168.
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TABLE 1. Results of Solid-State Photolysis of the Dialdehydes 1-3

entry	substrate	color[b]	conv[c]	mb[d] (%)	product composn[e] (%)		
					MCB	BCB	DCA
1	**1a**	red	96	15			100
2	**1b**	bright yellow	87	33	100		
3	**2a**[f]	colorless					
4	**2b**	bright yellow	96	53	16	84	
5			68[g]	91	25	75	
6	**2c**	bright yellow	90	23	43	57	
7			41[g]	77	100		
8	**3a**	orange-yellow	67	22			100
9	**3b**	bright yellow	84	50	10	90	
10			67[g]	91	23	77	
11	**3c**	pale orange	79[h]	19	>90		<10

[a] All the solid-state photolyses were carried out in a photoreactor fitted with $\lambda = 350$ nm lamps for 24 h under a N_2 gas. [b] Color of the crystals upon exposure to UV−vis radiation. [c] Based on recovered starting compound in preparative photolysis employing ca. 100−150 mg of the dialdehyde. [d] Mass balance is based on isolated yields of the products. [e] Relative ratios normalized to 100. [f] Unreactive. [g] The photolysis was carried out on a sample of 300 mg. [h] The Diels−Alder adduct formed in low yields was inseparable from the cyclobutenol (see Supporting Information).

SCHEME 2. AM1 Enthalpy Changes (ΔH_f) for *E*-Enol to Cycobutenol Conversions

	ΔH_f (kcal/mol) MCB	ΔH_f (kcal/mol) BCB
3a: X = H	0.89	4.87
3b: X = Br	-5.80	0.08
3c: X = Cl	-3.00	2.35

clobutenol was not formed at all in the case of **3c** (entries 6 and 11). At low conversions, only monocyclobutenol was isolated in the case of **2c**. In **3c**, the MCB was invariably associated with a highly inseparable <10% of the Diels−Alder cycloadduct. A perusal of the results in Table 1 suggests that the mass balance in all the cases with the exception of **2b** and **3b** is poor, unless the photolyses are limited to low conversions. The photoproducts were invariably accompanied by the formation of an intractable polymeric material at high conversions.

As mentioned at the outset, the orientations of the formyl groups in **1a**, **2a**, and **3a** cannot be predicted a priori. Thus, the observed photobehavior of **1a** and **3a** must result from a molecular structure in which one or both carbonyl groups are oriented toward the *o*-methyls for the primary photochemical event, namely, γ-hydrogen abstraction. Indeed, the reported X-ray crystal structure of **1a** shows that one of the carbonyl groups is oriented toward the *o*-methyl group. In contrast, the photostability of **2a** must be attributed to its carbonyl groups being not predestined for γ-hydrogen abstraction, for it is difficult otherwise to reconcile why it should not behave like **1a** and **3a**. The elegance of dihalo substitution in controlling the conformations of the formyl groups for γ-hydrogen abstraction is clearly borne out from the photochemical results of **2b** and **2c**. In both cases, one observes not only the monocyclization but also the diphotocyclization leading to MCBs and BCBs. That the dihalogen substitution plays a similar role in all other dialdehydes, viz., **1b**, **3b**, and **3c**, is obvious from their photochemical reactivity. Given that the reactions in solid state occur with mini-

mum displacement of atomic positions,[13] the observed photoproducts (MCBs and BCBs) from **2b,c** and **3b,c** can be reconciled only if the precursor aldehydes are predestined for γ-hydrogen abstraction (cf. Scheme 2) to afford respective photoenols, which undergo thermal conrotatory closure to benzocyclobutenols (Scheme 1). To verify the conformational preferences of the formyl oxygens (toward the *o*-methyl groups for γ-hydrogen abstraction) enforced by halogen atoms, we have determined the X-ray crystal structures of the aldehydes **2c** and **3b** as representative cases. The molecular structures shown in Figure 1 unambiguously establish the conformational preferences of the formyl groups, which could also be implicated from the photochemical results. The intramolecular H···X distances, i.e., $d_{H···Cl}$(**2c**) = 2.69 Å and $d_{H···Br}$(**3b**) = 2.75 and 2.80 Å, in both of the aldehydes are significantly shorter than the sum of their van der Waals radii (H···Cl = 2.95 Å and H···Br = 3.05 Å) and suggest strong interaction.[9,14] Furthermore, the Scheffer's geometrical parameters,[3c] which describe the feasibility of abstraction of the closest γ-hydrogens by the carbonyl oxygens, calculated for the aldehydes **2c** and **3b** nicely permit the γ-hydrogen abstraction, the primary photochemical event, to occur readily after photoexcitation.

Scheme 1 typically exemplifies the consequences of photoexcitation of *o*-alkyl aromatic aldehydes.[6] The *Z*-enols are short-lived and undergo rapid reversion to the

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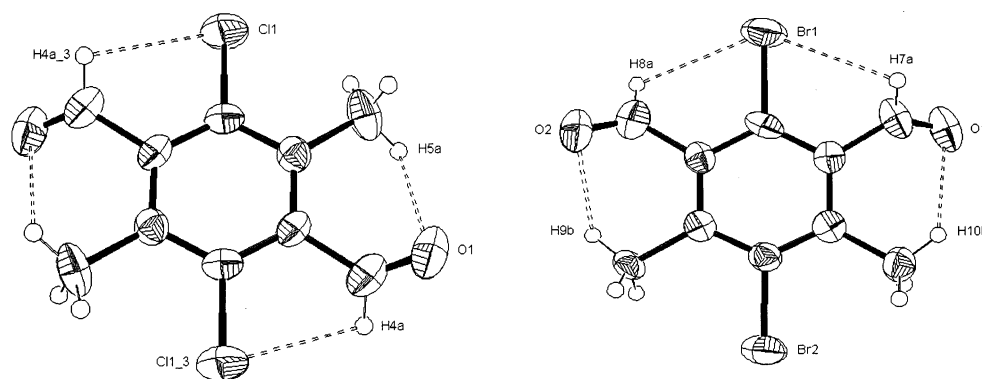
FIGURE 1. Ortep drawings of the molecular structures of **2c** and **3b**. The geometrical parameters for C−H···X interactions in **2c** and **3b** are as follows: $d_{\text{H}\cdots\text{Cl}}$(**2c**) = 2.69 Å; $\theta_{\text{C−H}\cdots\text{Cl}}$(**2c**) = 97.2°; $d_{\text{H}\cdots\text{Br}}$(**3b**) = 2.75 and 2.80 Å; $\theta_{\text{C−H}\cdots\text{Br}}$(**3b**) = 100.6 and 98.1°.

precursor aldehydes. On the contrary, the *E*-enols, which are longer-lived, either undergo slow reversion to the precursor aldehydes or collapse to the benzocyclobutenols; which of these two processes is operative depends on the relative energies. The lack of cyclization in the case of **1a** and **3a** may reflect relatively higher stability of the *E*-enols formed prior to cyclization (cf. Scheme 1). Indeed, the formation of Diels−Alder cycloadducts in these two cases clearly suggests the persistence of *E*-enols. The origin of Diels−Alder cycloadducts appears to be the lattice disruptions (defects) brought about by the formation of persistent *E*-enols. Presumably, the disruptions arising from the build up of the *E*-enols on continued irradiation increase the proximity of the carbonyl groups with the neighboring *E*-enols to undergo cycloaddition. The intractable polymeric material in all the cases should also be explicable from similar defect sites, at which the polymerization of enolic moieties is presumably propagated. In the case of the dialdehyde **1b**, the formation of mono-cyclobutenol is in line with the expectation. The poor diphotocyclization in the case of **2c** and lack of it in **3c** should be traceable to the relative energetics of the *E*-enols and bis-benzocyclobutenols. By comparison, the superior influence of dibromo substitution is evident from the photochemical results of **2b** and **3b**, which afford comparable yields of the bis-benzocyclobutenols.

To gain better insights into the influence of dibromo and dichloro substitution on the relative energies of the enols and benzocyclobutenols, we performed AM1 calculations, which have thus far offered proven predictability as applied to the photoreaction in consideration.[15] The results of the calculations (QCMP 137, MOPAC/PC)[16] typically carried out for the dialdehydes **3a−c** are given in Scheme 2. Accordingly, one finds a striking stabilization of the benzocyclobutenol relative to its precursor photoenol when the substituents are changed from hydrogens to chloro to bromo groups. A similar trend is witnessed for the formation of bis-benzocyclobutenol from its precursor photoenol as well. Thus, the dibromo substitution emerges superior to that of the dichloro variant in terms of enhancing the stabilization of cyclobutenols relative to their precursor *E*-enols. Whether or not the results of gas-phase calculations applicable to

the present condensed-phase experimental results is questionable. Otherwise, it is tempting to believe that a similar, if not exact, trend in the energy differences between the photoenols and the corresponding cyclobutenols applies in the solid state. Presumably, the higher stability of the cyclobutenols relative to the precursor *E*-enols in the case of dibromo−dialdehydes (see ΔH_{f}, Scheme 2) causes the latter to undergo cyclization, so that the bis-benzocyclobutenols are formed in respectable yields from **2b** and **3b**. Relatively weaker influence of dichloro substitution (Scheme 2) as in **2c** and **3c** should presumably increase the persistence of enols, thereby permitting the competing polymerizations or other processes (e.g. oxygenation reactions) to operate.

In summary, we have shown that the supramolecular C−H···X interactions can be exploited to achieve conformational control in the solid state for unprecedented diphotocyclization; the bis-benzocyclobutenols can be isolated in excellent yields from the dibromo-substituted dialdehydes **2b** and **3b**. Thus, the promise of weaker interactions for decisive and predictive application in solid-state photochemical reactions is convincingly demonstrated. While the solid-state photolysis of dialdehydes **1a** and **3a** leads to Diels−Alder cycloadducts (DCAs), **2a** remains photostable. The dibromo substitution in **2a** leads to photoreactivity and all the dibromo−dialdehydes, i.e., **1b**, **2b**, and **3b**, undergo expected mono- and diphotocyclizations. The absence or poor cyclization in the case of dichloro-substituted aldehydes can be reconciled from AM1 calculations; the AM1 results suggest that the contribution from dichloro substitution to the stabilization of cyclobutenols (relative to *E*-enols) is not comparable to that of the dibromo substitution. As a result, the persistent *E*-enols appear to undergo polymerization leading to highly intractable material.

Supporting Information Available: The synthetic procedures and characterization data for the aldehydes **1−3**, the photolysis procedure, the data for all the photoproducts, the crystallographic data for the aldehydes **2c** and **3b**, and output.arc files of AM1 calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026055W

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