Engineering reactions in crystals: suppression of photodecarbonylation by intramolecular β-phenyl quenching

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Abstract—The photochemical reactivity of *cis*- and *trans*-2-(*p*-carboxybenzyl)-2,6-diphenyl-6-vinylcyclohexanone, *cis*-**1** and *trans*-**1**, was investigated in solution and in the crystalline solid state. Photochemical decarbonylation in solution proceeded in excellent yields to give *cis*- and *trans*-1-(*p*-carboxybenzyl)-1,2-diphenyl-2-vinylcyclopentanes *cis*-**2** and *trans*-**2** along with 3-(*p*-carboxybenzyl)-1,3-diphenylcycloheptene **3**. Reactions in crystals were suppressed by a stereospecific quenching interaction between the benzyl substituent and the carbonyl oxygen in the crystalline ketone. © 2001 Elsevier Science Ltd. All rights reserved.

We have recently embarked on a systematic effort to test whether the rational design and planning of reactions in crystals is a feasible enterprise. We have explored unimolecular reactions determined by steric and electronic factors that are given by the structure of the reactant, and we have generally avoided reactions that require specific packing arrangements.[1] Given that reactions in crystals require bond-breaking and bond-making processes under conditions of minimal kinetic energy, we take advantage of symmetry-allowed reactions involving high (potential) energy species such as carbenes,[2] biradicals, and radical pairs.[3] For instance, based on a well known relation between heats of reaction and activation energies for bond-breaking processes,[4] we have proposed that the photodecarbonylation of ketones in crystals may proceed in high yields when the two bond-breaking processes are exothermic with respect to the energy of the excited state (Scheme 1).[5]

We have shown that 2,6-disubstituted cyclohexanones with α-phenyl substituents undergo stepwise α-cleavage (Norrish type-I)[6] and decarbonylation reactions to yield the corresponding cyclopentanes in highly stereospecific solid-to-solid reactions (Scheme 1).[7] We have extended our analysis to other radical stabilizing substituents and our thermochemical model has been remarkably reliable.[5] However, complications not considered by a thermochemical model may come from alternative decay pathways for the excited state. In this regard, it is known that ketones with β-phenyl groups are suscepti-

ble to conformation-dependent quenching by charge transfer interactions between the carbonyl n,π* excited state and the β-phenyl substituent (Scheme 2).[8–10] Scaiano et al. have shown that β-phenyl quenching may reduce triplet lifetime of crystalline propiophenones from 8 μs down to 0.7 and 0.4 μs, depending on the proximity of the β-phenyl to the carbonyl and packing differences in racemic and chiral crystals.[11]
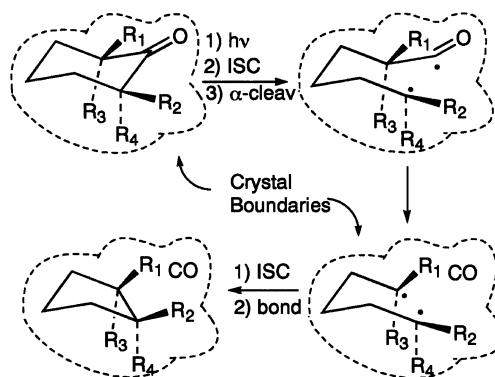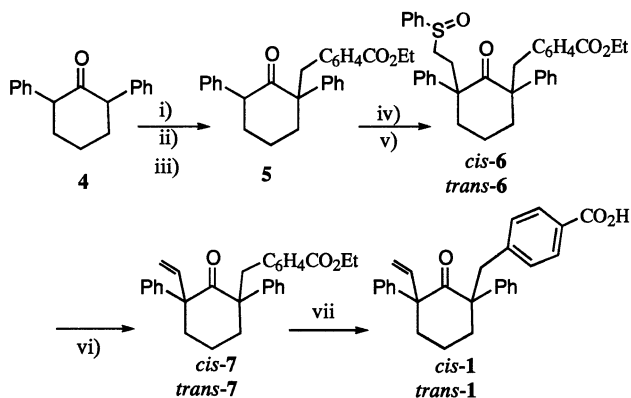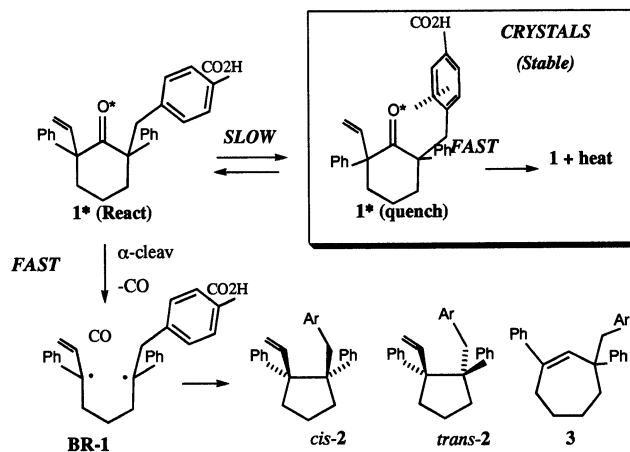

Scheme 1.
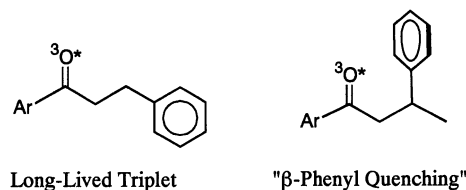
Scheme 2.

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While studying the photodecarbonylation of several crystalline ketones, we became interested in testing whether β-phenyl substituents could quench the reaction in the solid state. Since time constants of α-cleavage and decarbonylation for diphenyl ketones in solution fall within 2–200 ns,[12] a competition between β-phenyl quenching and solid state reactivity may shed light on the stereoelectronic demands of the latter. As a test, we have analyzed samples of *cis*- and *trans*-2-(*p*-carboxybenzyl)-2,6-diphenyl-6-vinylcyclohexanone (*cis*-1 and *trans*-1).

Isomers *cis*-1 and *trans*-1 were obtained from commercial 2,6-diphenylcyclohexanone by the sequence of reactions shown in Scheme 3.[13] Separation of the *cis*- and *trans*-stereoisomers by column chromatography was readily achieved in the case of sulfoxides 6, after which the preparation of *cis*-1 and *trans*-1 was carried out in a stereospecific manner. The structures and purities of all compounds in Scheme 3 were established by standard spectroscopic and chromatographic methods. Their relative stereochemistries were established by chemical correlation with respect to those of acids of *cis*-1 and *trans*-1, which had their structures solved by single crystal X-ray diffraction.

Photochemical experiments were carried out in dilute benzene solution and in the solid state. Irradiation of deoxygenated 2.5 mM benzene solutions of *cis*-1 and *trans*-1 with λ >300 nm (Pyrex filter) resulted in the efficient formation of *cis*- and *trans*-diphenyl cyclopentanes 2 and cycloheptene 3 (Scheme 4). A very clean reaction giving a 10:5:1 ratio of *trans*-2:*cis*-2:3 (see Scheme 4) after >95% conversion was observed. Product analyses were carried out by ^{1}H NMR and by gas chromatography after the acid group had been esterified with diazomethane. The exclusive formation of cyclopentanes 2 and cycloheptene 3 indicates that α-cleavage is followed by a very fast decarbonylation reaction. The regioselectivity of bond formation towards five- rather than seven-membered ring formation probably reflects the more favorable entropy of the
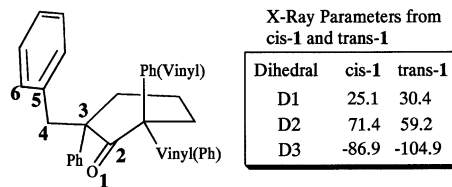

Scheme 4.

former and a greater spin density at the benzylic center of the delocalized allyl radical in **BR-1** (Scheme 4). In stark contrast to the results obtained in solution, photolysis of *cis*-1 and *trans*-1 in the crystalline solid state gave only traces of cyclopentanes 2 after 12 h of irradiation. We established that experimental factors related to differences in the photolysis of solutions and crystals were not responsible for their differences in reactivity. Similar experiments with dilute solutions and crystalline samples of the tetrasubstituted *cis*-2,6-diphenyl-2,6-dimethylcyclohexanone resulted in nearly complete conversion in either reaction media after only 30 min of irradiation.[3b]

The differences between solution and solid state photochemical reactivity in the cases of *cis*-1 and *trans*-1 can be explained by considering their X-ray structures and conformational dynamics in the two reaction media. It is known that the rate of β-phenyl quenching[8] is generally limited by conformational dynamics in solution and it occurs within sub-nanosecond time-scales. α-Cleavage for substituted ketones with radical-stabilizing α-phenyl groups in solution should be equally fast. Since it is expected that conformational equilibration in solution should be comparatively slow, we propose that the relatively high reaction efficiency reflects a large population of reactive conformers, and a slow conformational equilibration within the lifetime of the excited state (Scheme 4). This explanation is akin to observations involving kinetically distinguishable triplets from compounds having slowly interconverting quenching and non-quenching conformations.[9,11] With a remarkable suppression of the decarbonylation reaction, the solid state must have a very favorable β-phenyl quenching conformation. Although quenching of the singlet excited state is also possible,[8a] the observation of fluorescence emission from crystals of *cis*-1 and *trans*-1 shows that β-phenyl quenching does not dominate singlet decay in the same way that it dominates the decay of the triplet.

High quality crystals of *cis*-1 and *trans*-1 were grown by slow solvent evaporation from mixtures of ether and methyl cyclohexane. Melting points of 219–220 and

Scheme 3. *Reagents and conditions*: (i) KH (THF), BrCH₂C₆H₄CN; (ii) H₂SO₄, AcOH, H₂O; (iii) EtOH, H⁺; (iv) KH (toluene), H₂C=CH-SO-Ph; (v) separate isomers; (vi) 180°C; (vi) NaOH, MeOH.

200–202°C for *cis*-**1** and *trans*-**1**, respectively, prevented ample melting during the prolonged photochemical exposure. X-Ray analyses were carried out at ambient temperature by direct methods. Both carboxylic acids were found to form centro-symmetric dimers. Compounds *cis*-**1** and *trans*-**1** pack in the space groups $P2_1/c$ and $P\bar{1}$, respectively.[14] The lack of solid state reactivity can be understood by analysis of their molecular structures.

Compounds *cis*-**1** and *trans*-**1** adopt twist-boat conformations with the benzyl group in a pseudoequatorial position. (Fig. 1 and Scheme 5). The closest interaction between carbonyl and β-phenyl groups revealed by the X-ray structures involve the carbonyl oxygen and the edge of the aromatic ring. The precise orientation of the phenyl group can be described in terms of the following geometric parameters (Scheme 5). (a) The dihedral angle given by $D1 = O1–C2–C3–C4$, indicating whether the point of attachment of the β-phenyl group is pseudoaxial (~90°) or pseudoequatorial (~0°). (b) The dihedral $D2 = C2–C3–C4–C5$, which describes the orientation of the β-phenyl group with respect to the carbonyl C=O axis. When $D2 = 0°$, the β-phenyl group and the carbonyl are *syn*, and when $D2 = 180°$ they are *anti*. (c) The dihedral angle $D3 = C3–C4–C5–C6$ describes how the face of the β-phenyl group is oriented with respect to the carbonyl group. For $D1 \approx 0°$ and $D2 \approx 0°$, a value of $D3 = 90°$ would result in a face-on orientation. The values found in *cis*-**1** and *trans*-**1**, indicated in Scheme 5, position the β-phenyl groups within close distance of the carbonyl. While values of $D1$ and $D3$ near 0 and 90° describe an equatorial face-on relation, the values for $D2$ of 71.4 and 59.2° for *cis*-**1** and *trans*-**1**, respectively, give rise to conformations having the carbonyl bond and the axis along *ipso*

Dihedral	cis-**1**	trans-**1**
D1	25.1	30.4
D2	71.4	59.2
D3	-86.9	-104.9

X-Ray Parameters from cis-**1** and trans-**1**

Scheme 5.

and *para* carbons of the β-phenyl group nearly orthogonal to each other. This orientation prevents an interaction between the electron-rich carbonyl n-orbital and the center of the aromatic π-face, which should be electrostatically unfavorable. The closest distance between the carbonyl and the aromatic ring occurs between the oxygen atom and one of the *ortho*-carbons at the edge of the aromatic ring, i.e. O1···C6 in Scheme 5. The corresponding distances for *cis*-**1** and *trans*-**1** are 3.19 and 3.13 Å, which are slightly less than 3.2 Å, the sum of the van der Waals radii of carbon (2.7 Å) and oxygen (2.5 Å).[15] This relatively close contact interaction suggests that a carbonyl-oxygen to aromatic ring bonding interaction may be responsible for excited state deactivation. Although this interaction has been previously considered,[9] charge transfer quenching has been given preference in the literature.[9–11]

In conclusion, compounds *cis*-**1** and *trans*-**1** undergo a very efficient decarbonylation reaction in solution, but their chemical reactivity is completely quenched in the solid state. Considering the high rates of α-cleavage and decarbonylation that one should expect from ketones with α-phenyl and α-vinyl groups, the quenching efficiency of the β-phenyl group in the solid state is
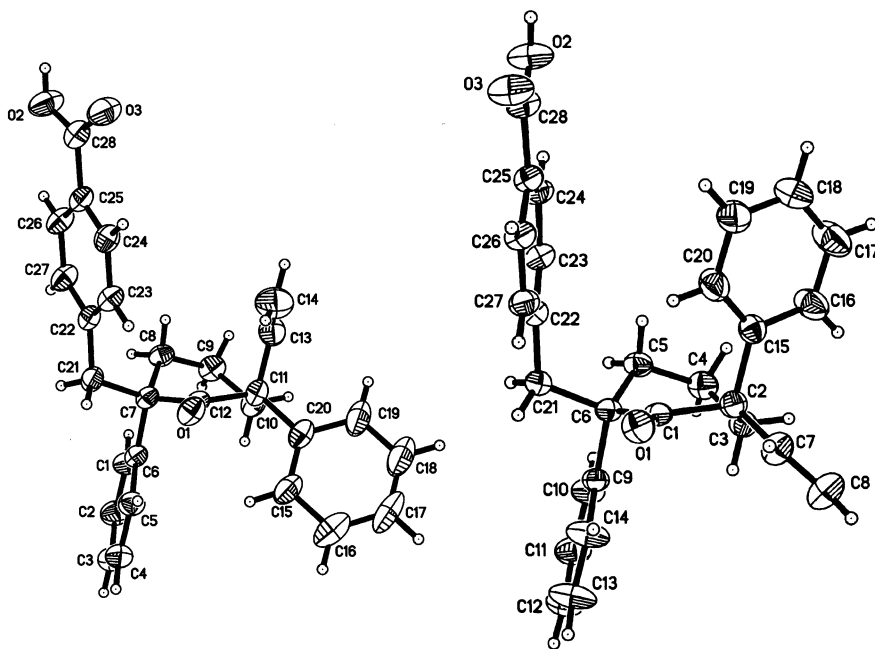

Figure 1. ORTEP views of compounds *cis*-**1** (left) and *trans*-**1** (right) illustrating their twist-boat conformations and the disposition of the benzyl group with respect to the ketone carbonyl.

remarkable. Further studies with compounds having β-aryl groups with different geometries will help us document the detailed stereoelectronic nature of this interaction. *Most importantly, results from this study support the premise that reactions in crystals can be engineered with knowledge acquired from solution studies.* If desired, β-phenyl groups in the proper conformation may be used as excellent quenchers for ketone reactions in crystalline solids.

Acknowledgements

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13. All the compounds used for this study were properly characterized by spectroscopic methods. Detailed experimental details will be published elsewhere.

14. *cis*-**1**: $C_{28}H_{26}O_3$, $M_W = 410.49$, monoclinic, space group $P2_1/c$, $a = 9.306(3)$, $b = 17.649(2)$, $c = 13.501(2)$ Å, $\alpha = 90$, $\beta = 95.28(2)$, $\gamma = 90°$, $V = 2207.9(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.235$ Mg/m^3, $F(000) = 872$, $\lambda = 1.54180$ Å, $T = 293(2)$ K, crystal size = 0.4×0.3×0.3 mm^3, of the 3525 reflections collected ($4.13 \leq \theta \leq 60.23°$), 3300 [$R_{int} = 0.0273$] were independent reflections; $R_1 = 0.0562$ ($I > 2\sigma(I)$) and $wR_2 = 0.1526$. *trans*-**1**: $C_{28}H_{26}O_3$, $M_W = 410.49$, monoclinic, space group P_1-bar, $a = 8.802(2)$, $b = 16.299(4)$, $c = 8.271(2)$ Å, $\alpha = 102.25(2)$, $\beta = 97.79(2)$, $\gamma = 104.49(2)°$, $V = 1100.1(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.239$ Mg/m^3, $F(000) = 436$, $\lambda = 1.54180$ Å, $T = 293(2)$ K, crystal size = 0.4×0.3×0.1 mm^3, of the 3530 reflections collected ($2.90 \leq \theta \leq 60.06°$), 3282 [$R_{int} = 0.0176$] were independent reflections; $R_1 = 0.0479$ ($I > 2\sigma(I)$) and $wR_2 = 0.1314$.

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