

Molecular Control of Solid-State Reactivity and Biradical Formation from Crystalline Ketones

Thomas Choi, Krisztina Peterfy, Saeed I. Khan, and Miguel A. Garcia-Garibay*

Department of Chemistry and Biochemistry
University of California
Los Angeles, California 90024

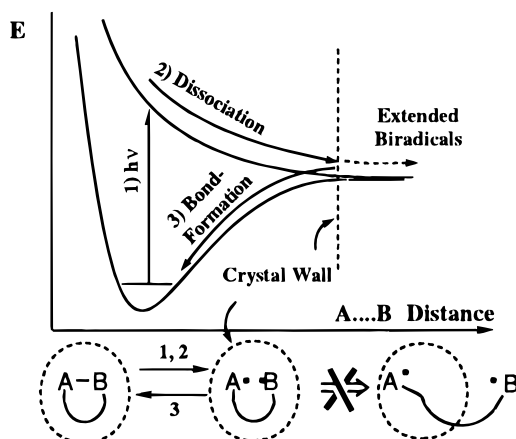
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A growing number of solid-state reactions with high selectivities and specificities have been reported in recent years.¹ As the potential of highly selective transformations where solvents can be omitted is increasingly appreciated, it has become desirable to search for reliable methods to carry out reactions in the crystalline solid state.² In this Communication, we analyze some of the factors that affect the photochemical reactivity of crystalline ketones capable of forming biradicals and radical pairs.³ Our interest in biradicals comes from the fact that they occur in a large number of organic reactions, and strategies for their generation may help develop protocols where selectivity and specificity may be achieved by means of crystal control.

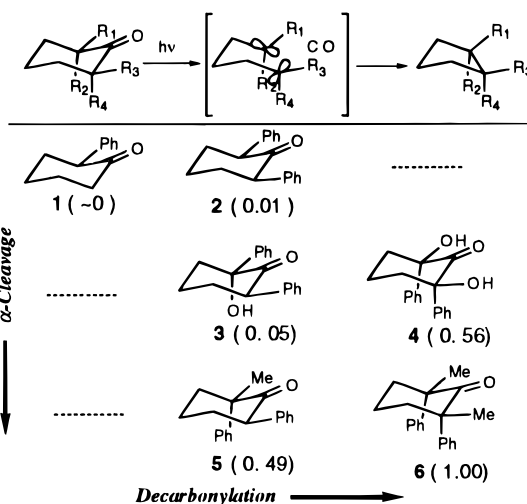
The main challenge in the preparation and use of biradicals in solid-state reactions comes from the fact that biradical formation requires cleavage of a σ bond under conditions where separation of the radical termini is essentially impossible (Scheme 1). It is known that photochemical excitation (step 1) to dissociative surfaces in solution and in the gas phase leads to separation of atoms A and B (step 2) to form extended biradicals that explore bimolecular reactions and unimolecular rearrangements.⁴ In contrast, the two radical centers in the solid state are held close together by their rigid environment, and the two termini are likely to collapse to remake the bond that was originally broken (step 3). For biradical products to form in the solid state, chemical reactions that are comparable to or faster than step 3 will be required. We suggest that proper conditions may be facilitated by molecular design. For instance, in the case of ketone precursors, we propose that dissociative triplet state surfaces and irreversible radical–radical reactions may be formulated with some certainty from known substituent effects.⁴ A triplet surface will slow down step 3, and a rapid decarbonylation reaction may make up for the lack of biradical separation in a sequence that should lead to products from dialkyl biradicals (Schemes 2 and 3).⁵

To test our hypothesis, we analyzed the solid-state reactivity of several known 2-phenyl- and 2,6-diphenylcyclohexanones with 2-hydroxy, 2-methyl, 2,6-dihydroxy, or 2,6-dimethyl substituents. The selection of compounds 1–6 (Scheme 2) was based on the expected photochemical effects of their α -substituents and on their abilities to form good crystals. We have elucidated all their X-ray structures.⁶ The positions of their α -substituents (axial/equatorial) are represented in the scheme.

Scheme 1



Scheme 2



The conformation about the phenyl groups is such that good benzylic stabilization is expected. If the orientation of the ring is maintained through the reaction, the p-orbitals of the aromatic systems should be kept in close alignment with the benzylic radical p-orbital (see Supporting Information).

Several reports on the solution photochemistry of most of the compounds in Scheme 2 are available.⁷ Although all the compounds in the scheme have high and very similar reaction yields in solution ($\Phi > 0.6$), variations in their solid-state reactivity are very large. Crystals of 1 are photostable. Relative yields of solid-state reaction for the other compounds are shown in parentheses in Scheme 2. These were determined in side-

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(6) 2-Phenylcyclohexanone (1), colorless needles from ethanol, mp = 56–59 °C, space group *P21/a*, *Z* = 8, *a* = 14.221(4) Å, *b* = 5.545(2) Å, *c* = 125.659(6) Å, β = 118.27(1)°, *V* = 1948.4(9) Å³, *R* = 0.057, *R_w* = 0.066. *cis*-2,6-Diphenylcyclohexanone (2), colorless prisms from hexane, mp = 124 °C, space group *C2/c*, *Z* = 8, *a* = 28.904(6) Å, *b* = 5.902(1) Å, *c* = 18.608(4) Å, β = 118.27(1)°, *V* = 2795(1) Å³, *R* = 0.054, *R_w* = 0.066. *cis*-2,6-Diphenyl-2-hydroxycyclohexanone (3), colorless prisms from hexane, mp = 104–105 °C, space group *P21/c*, *Z* = 4, *a* = 10.903(5) Å, *b* = 11.269(5) Å, *c* = 12.179(6) Å, β = 106.138(6)°, *V* = 1437.1(1) Å³, *R* = 0.060, *R_w* = 0.064. *cis*-2,6-Diphenyl-2,6-dihydroxycyclohexanone (4), see ref 19. *trans*-2,6-Diphenyl-2-methylcyclohexanone (5), colorless prisms from hexane, mp = 58–62 °C, space group *Fdd2*, *Z* = 32, *a* = 31.52(2) Å, *b* = 38.44(3) Å, *c* = 10.148(8) Å, *V* = 12294(12) Å³, *R* = 0.038, *R_w* = 0.043; *cis*-2,6-Diphenyl-2,6-dimethylcyclohexanone (6), colorless crystals from hexane, mp = 97 °C, space group *P21/c*, *Z* = 8, *a* = 12.552(8) Å, *b* = 15.46(1) Å, *c* = 15.878(8) Å, β = 91.71(2)°, *V* = 3079(3) Å³, *R* = 0.049, *R_w* = 0.054.

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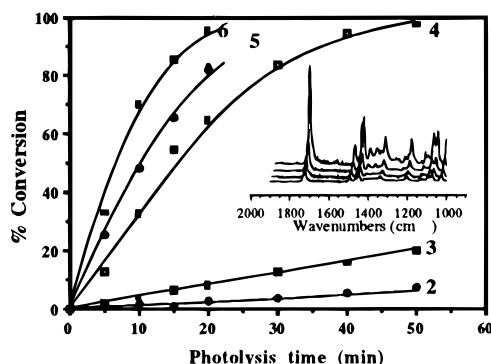
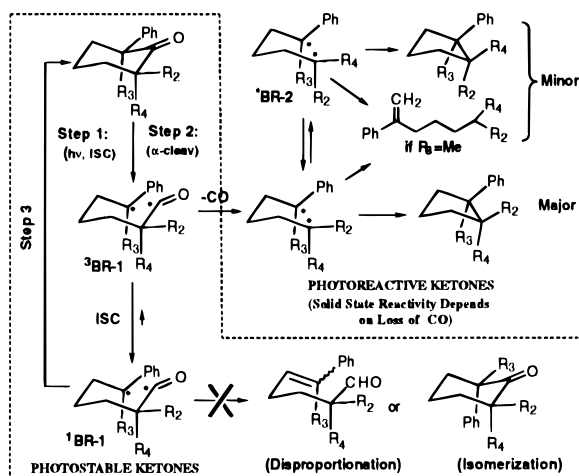


Figure 1. Normalized conversion vs irradiation time of microcrystals of cyclohexanones **2–6** dispersed in KBr matrices.⁸ Inset: representative FT-IR data from compound **5**.

Scheme 3



by-side irradiations carried out in microcrystals of each ketone dispersed in KBr with exposure to monochromatic UV-light at $\lambda = 350$ nm.⁸ The extent of reaction was conveniently determined by FT-IR at various intervals by measuring changes in the absorbance of the CO stretch as a function of irradiation time to construct plots such as those shown in Figure 1. Although absolute values varied from experiment to experiment, the relative yields of reaction between any two ketones could be reproduced within *ca.* 5% suggesting this method to be experimentally reliable. A good agreement was also obtained in experiments carried out by GLC analysis of larger powdered samples.

Quantum yields of reaction (Φ_R) reflect biradical yields (Φ_{BR-1}) and the probability (P_P) that the biradical will lead to product, i.e., $\Phi_R = \Phi_{BR-1} \cdot P_P$. In solution, products may come from the acylalkyl biradical BR-1, or from the dialkyl biradical BR-2 formed by loss of CO (Scheme 3).⁵ Disproportionation of BR-1 may give aldehydes (and ketenes), while bond rotation and biradical collapse may give rise to ketone stereoisomers. Reactions of BR-2 include the formation of cyclopentanes and alkenes (Scheme 3).

High quantum yields of reaction in fluid solution are accounted for by reactions of ¹BR-1 in the case of compound **1** and by extensive decarbonylation in the case of ketones **2–6**. We propose that the solid-state photostability of **1** and variations in reaction yields that span *ca.* 100-fold (e.g., **2** vs **6**) can be understood in terms of variations in P_P . Electronic excitation and intersystem crossing followed by cleavage of the α -bond to generate the most stable biradical (³BR-1) accounts for Φ_{BR-1} (steps 1 and 2, Scheme 3). While the termini of the acylalkyl biradical should remain within van der Waals distance, their multiplicity renders them unable to form a bond until enough singlet character is acquired by intersystem crossing (ISC). We propose that the value of P_P is determined by the fraction of

³BR-1 that loses CO relative to that undergoing ISC and leading back to starting ketone [$P_P = k_{-CO} / (k_{-CO} + k_{ISC})^{-1}$]. Although the possibility of spin-state equilibration in the acyl-alkyl biradical cannot be ruled out, it is likely that bond formation in ¹BR-1 (step 3) may be very rapid at ambient temperatures. The lack of products from BR-1 in the solid state suggests that bond rotation is slower than biradical collapse so that ketones with efficient ISC are likely to be photostable. It is known that ISC of related biradicals in solution occurs within a few to several hundred nanoseconds depending mainly on the average separation of the radical termini.⁹ While ISC rates of biradicals in solids are not known, decarbonylation is a spin-conserving reaction with rates that extend over 8–10 orders of magnitude depending on substituents. *In principle, one may use decarbonylation as a controllable solid-state reactivity "switch".*

As suggested by our model, there is a remarkable correlation between solid state reactivity and rates of decarbonylation taken from model compounds in solution (k_{-CO}).^{10,11} For instance, with propionyl as a model, acylalkyl biradicals from compound **1** are expected to have $k_{-CO} \sim 10^2\text{--}10^3$ s⁻¹ (Scheme 3, R₂ = R₄ = H). This rate is probably too slow to compete with ISC so that bond formation and regeneration of the ketone effectively maintain compound **1** photostable. The decarbonylation rates of **2**, **3**, and **5** (R₂ = Ph, R₄ = H) may be approximated to that of α -phenylpropionyl (4.9×10^7 s⁻¹), which seems to be large enough to compete with intersystem crossing. The relative reaction yields of **2**, **3**, and **5** reach values of 0.01, 0.05, and 0.49, respectively. These may reflect changes in k_{-CO} or k_{ISC} or an increase in the yields of α -cleavage. As expected, the highest solid-state reactivities were observed in compounds **4** and **6** which possess the most radical stabilizing and rate accelerating substituents of the set. Thus, based on the solution rate of α -methyl- α -phenylpropionyl, the decarbonylation rate of **6** may be as large as 1.5×10^8 s⁻¹.

We recently reported the phase separation mechanism accompanying the reaction of **4** and its high solid-state selectivity in reactions carried out in gram scale photolysis. A detailed account of the other compounds will be presented elsewhere. However, product analysis shows that reactions in solids **2–6** are more selective and specific than their solution counterparts. The main solid-state products come from stereospecific closure of the dialkyl biradical (cyclopentanes), although small amounts of alkenes were observed in compounds **5** and **6**. While there are questions that remain to be answered, the correlation between solid-state reactivity and substituent effects seems strong, and we intend to test its generality while trying to detect the postulated intermediates.

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Supporting Information Available: X-ray conformational parameters relevant to benzylic stabilization and Ortep drawings of compounds **1–6** from (4 pages). See any current masthead page for ordering and Internet access information.

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(8) Changes in the amount of reactant as a function of time in optically dense samples give reaction velocities that are proportional to the intensity of the irradiating light and to the quantum yield of reaction (see: Wagner, P. J. In *CRC Handbook of Organic Photochemistry*; Scaiano, J. C., Ed.; CRC Press: Boca Raton, FL, 1993; p 251. The linear portion of the plots were used to calculate relative yields. It is assumed that scattering and reflection are minimized in the optically clear samples. It is also assumed that side-by-side irradiations result in very similar UV exposure.

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