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Hammett Analysis of Photodecarbonylation in Crystalline 1,3-Diarylacetones

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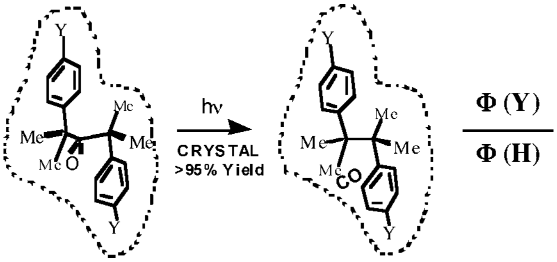
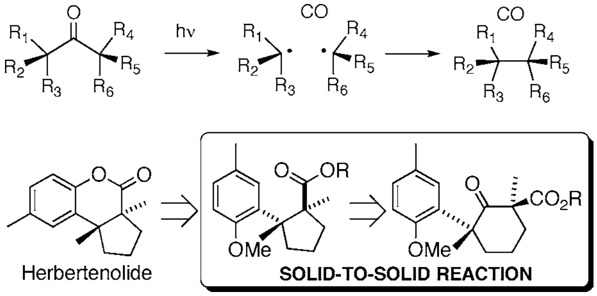
ABSTRACT



The relative quantum yields and chemical efficiencies of crystalline *p,p′*-disubstituted 1,3-diphenyl-2-propanones with 4-MeO, 4-Me, 4-F, 4-CF$_3$, and 3,4-diMeO groups were determined by parallel irradiation of polycrystalline samples. Variations in quantum yields that span a factor of 4 are analyzed in terms of the effects of substituents on the stability of the benzylic radical. All solid-state reactions proceeded with 100% chemoselectivity and in >95% chemical yield.

It has been suggested that the intrinsic reactivity of organic molecules may be less important than packing effects when reactions in crystals are concerned.[1] However, recent work has shown that some reactions may be reliably predicted from well-known trends in reactive intermediates.[2] In particular, rapidly accumulating evidence shows that the photodecarbonylation of crystalline ketones depends on the energy content of the triplet state and the bond dissociation energies of the α-bonds,[3] as long as they have no intramolecular quenching interactions.[4] Remarkably, whereas reaction feasibility relies on the intrinsic reactivity of the excited ketone, the selectivity and specificity of the solid-state reaction are determined by the rigidity and homogeneity of the crystalline medium. In fact, we have shown the synthetic potential of the reaction in the preparation of optically pure compounds with adjacent quaternary stereogenic centers[5] and in the total synthesis of the natural product herbertenolide (Scheme 1).[6] However, for the reaction to be considered a robust synthetic method, it is important to show that is amenable to structure−

Scheme 1



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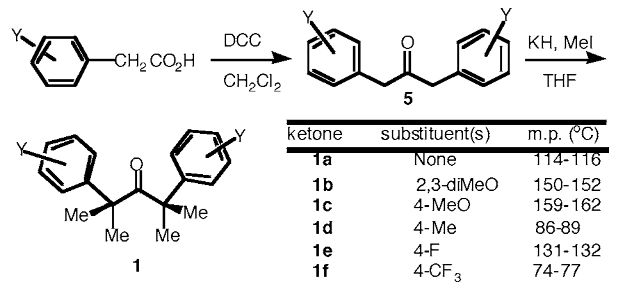
reactivity correlations analogous to those commonly carried out for a wide variety of reactions in solution.

Knowing that aliphatic ketones with aryl substituents at their two α-positions display an efficient reaction in the solid state,[7] we decided to test the effect of substituents in several 2,2,4,4-tetramethyl-1,3-diphenylacetones (Scheme 2). Compounds **1a**−**1f**, prepared in two steps as illustrated in Scheme 2, were crystalline solids with melting points shown to be conveniently high for all solid-state reactions to be carried out at ambient temperature without melting.[8]

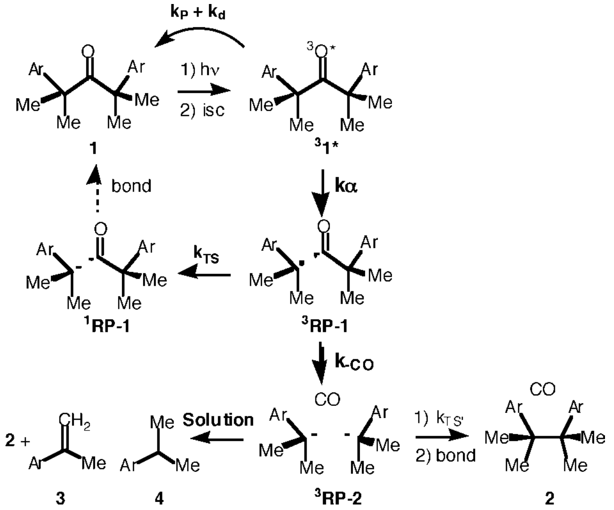
Scheme 2



ketone	substituent(s)	m.p. (°C)
1a	None	114-116
1b	2,3-diMeO	150-152
1c	4-MeO	159-162
1d	4-Me	86-89
1e	4-F	131-132
1f	4-CF$_3$	74-77

Photochemical reactions of **1a**−**1f** carried out as control experiments in ca. 0.1 M benzene with $\lambda > 300$ nm produced the expected diphenylethanes (**2a**−**2f**), styrenes (**3a**−**3f**), and isopropyl benzenes (**4a**−**4f**). As indicated in Scheme 3, the reaction is known to start by α-cleavage from the triplet excited state to give an acyl-alkyl radical pair (**RP1**).[9,10] Free from the constraints of the σ bond, the fragments separate and the free acyl radical loses CO. Free radical encounters in solution lead to the second radical pair (**RP2**), which forms diphenylethane **2** by bond formation and products **3** and **4** by disproportionation. Quantum yields of reactant consumption determined in C_6H_6 solutions using diphenylacetone ($\Phi \approx 0.6 \pm 0.05$)[9] as a chemical actinometer were essentially identical for all tetramethyl-substituted compounds ($\Phi \approx 0.8 \pm 0.1$).

Scheme 3



Reactions in crystals proceeded with ideal chemoselectivity, giving the diphenylethanes **2a**−**2f** in >95% yield. To determine the effects of the substituents on the quantum yields of reaction, competition experiments were set up by mechanically mixing 15 mg of independently powdered samples of each ketone, irradiating the powder mixture at 298 K with a medium-pressure Hg arc Hanovia lamp using a $\lambda > 300$ nm cutoff filter, and analyzing the extent of reaction by gas chromatography as a function of conversion every 5 min for 1−2 h (e.g., Figure 1).

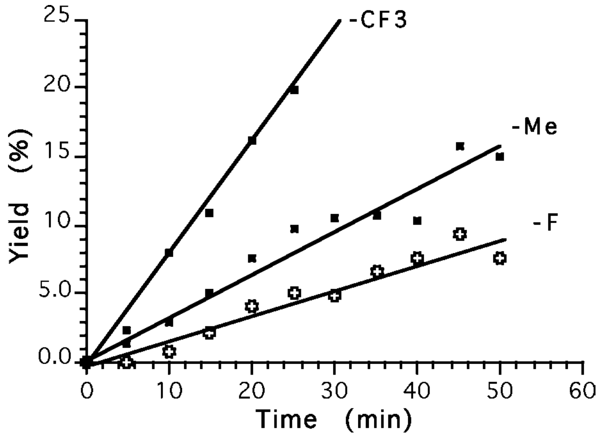


Figure 1. Representative plot of reaction progress with crystals of 1,3-diphenylacetones **1d** (4-Me), **1e** (4-CF$_3$), and **1f** (4-F).

Given the excellent overlap in the UV spectra (Supporting Information) and assuming that absorption and scattering of the various powders are similar, the initial slopes of the plot in Figure 1 are proportional to the quantum yields (Φ) of reaction. As shown in Figure 1, conversion values varied by a factor of 4 between the most (**1b**, 4-CF$_3$) and least reactive (**1c**, 4-F) ketones. Internally consistent results from repeated experiments suggest that the ca. 5% difference observed between compounds **1a** (H) and **1f** (4-Me) are reliable. Relative quantum yields [Φ(Y)/Φ(H)] are summarized in Table 1 along with the experimentally determined ratios of the solution rate constants of 1,3-diphenylacetones (please see below) and the differences in bond dissociation energies of the benzylic C−H bonds [BDE(Y) − BDE(H)] reported in the literature.[11−13]

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Table 1. Relative Quantum Yields in the Solid State with Relative Rates Constants for α-Cleavage and Decarbonylation and with Differences in Bond Dissociation Energies for Substituted Diphenylacetones

Y	$\Phi(Y)/\Phi(H)$	$k_\alpha(Y)/k_\alpha(H)$	$k_{-CO}(Y)/k_{-CO}(H)$	BDE(Y) − BDE(H)
3,4-MeO	1.08	n.a.	n.a.	−1.1[a]
4-MeO	1.65	3.18	1.55	−0.7[b]
4-Me	1.05	1.53	1.14	−0.5[b]
4-F	0.54	1.05	n.a.	0.1[c]
H	1.0	1.0	1.0	0
4-CF_3	2.18	n.a.	1.06	0.3[b]

[a] Reference 13. [b] Reference 11. [c] Reference 12

Knowing that the effects of substituents on radical reactions are generally small, the results in Figure 1 and Table 1 are reassuring, as large variations due to undetermined "packing effects" would undermine our hypothesis. As discussed below, the relatively poor correlation with substituent constants is consistent with observations in solution. The quantum yields of reaction for compounds **1a**−**1f** [Φ(Y)] depend on several consecutive steps (eq 1), and the mechanism in Scheme 3 illustrates the intermediates to consider in going from ketones **1** to diphenyl ethanes **2**.

$$\Phi(Y) = \Phi_T(Y)\cdot\Phi_\alpha(Y)\cdot\Phi_{-CO}(Y) \qquad (1)$$

Assuming that photons are absorbed at the same rate by all solids and that the loss of CO is irreversible, the Φ(Y) values will depend on the effects of substituents on the yields of triplet formation [$\Phi_T(Y)$], α-cleavage [$\Phi_\alpha(Y)$], and the loss of CO [$\Phi_{-CO}(Y)$].

Although the α-cleavage reaction may proceed in solution from singlet and triplet manifolds, singlet radical pairs in the solid state are likely to retrace their trajectory back to the original σ bond rather than going on to products. Fortunately, $\Phi_T(Y)$ values for ketones are generally high [e.g., $\Phi_T(Y) \approx 0.5-1.0$].[10a] After reaching ^{3}**1***, the quantum efficiency of product formation depends on the quantum yield of α-cleavage [$\Phi_\alpha(Y)$], which is given by the rate of α-cleavage (k_α) as compared to the rate of return to the ground state by phosphorescence (k_P) and radiationless decay (k_d) as indicated in eq 2.

$$\Phi_\alpha(Y) = \frac{k_\alpha}{k_\alpha + k_P + k_d} \qquad (2)$$

Notably, while efficient α-cleavage reactions in solution lead to the products thanks to the rapid separation of ^{3}**RP1** to form free radicals, the same is not true in the solid state. Unable to separate much beyond the sum of their van der Waals radii, a rapid spin flip (k_{TS}) to form ^{1}**RP1** makes it possible to form the σ bond and go back to ground-state starting material (dashed arrow in Scheme 3). However, if the rate of decarbonylation (k_{-CO}) is substantially greater than the rate of intersystem crossing (k_{TS}), the yield of decarbonylation will be high (eq 3).

$$\Phi_{-CO}(Y) = \frac{k_{-CO}}{k_{-CO} + k_{TS}} \qquad (3)$$

Local diffusion of CO should render decarbonylation irreversible so that formation of ^{3}**RP2** should determine product formation. If this assumption is correct, substituent effect in the following steps ($k_{TS'}$ and k_{bond}) should not affect the observed quantum efficiency.

The lack of significant substituent effects on the solution quantum yields implies that the rate constants for the product-limiting steps are greater than those of other competing processes. It is known that fast separation of the acyl-alkyl radical pair (^{3}**RP1**) makes α-cleavage product formation limiting. In crystals, the fate of ^{3}**RP1** is determined by a competition between decarbonylation, which goes on to give products, and intersystem crossing to ^{1}**RP1**, which returns to the starting material and decreases the solid-state quantum yield.

The effects of light atom substituents on intersystem crossing rates are expected to be small. Similarly, Johnston et al. reported that the relative rates of α-cleavage in solution [$k_\alpha(Y)/k_\alpha(H)$, Table 1] span a factor of 3, with a reactivity ranking that includes *p*-MeO > *p*-Me > *p*-F ≈ H.[14] Finding a reasonable fit to the Hammet equation when the substituent σ^+ values were used,[15] the authors inferred a transition state stabilized by electron-donating substituents. The effects of substituents on the absolute rate constant of decarbonylation in several symmetric ketones (Y-$PhCH_2COCH_2Ph$-Y) were investigated by Nau using transient absorption methods.[16] The decarbonylation rate constants turned out to be remarkably insensitive to *p*-MeO, *p*-Me, *p*-Cl, and *p*-CF_3 substituents as indicated by $k_{-CO}(Y)/k_{-CO}(H) \approx 1$ values in Table 1.

At a first approximation, one may expect that variations in solid-state Φ values may correlate with k_α and $\sigma^+(Y)$. Alternatively, because a good correlation is expected between the height of the barrier and the heat of reaction (as suggested by the Hammond postulate),[10a,17] the results may reflect the effect of substituents on the bond dissociation energy [BDE] of the α bonds. In fact, there is a reasonable correlation between ΔBDE(Y) and $\sigma^+(Y)$. However, although results with 4-MeO, 4-Me, 4-H, and 4-F compounds would be as expected, the plot of Φ(Y)/Φ(H) vs ΔBDE(Y) in Figure 2 shows a poor correlation with the 3,4-diMeO- and CF_3-ketones deviating at the two ends of the plot.

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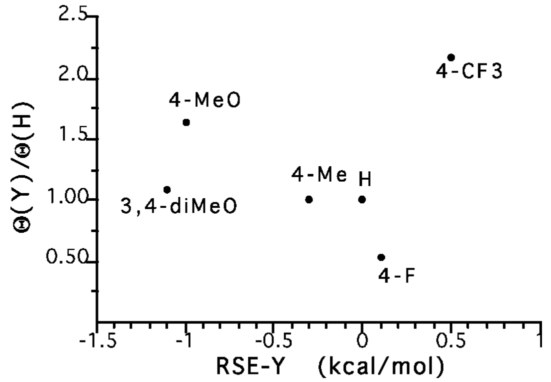
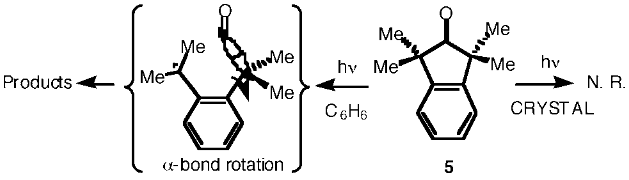


Figure 2. Relative quantum yields [log(ΦY/ΦH)] plotted against the difference in bond dissociation energies [ΔBDE(Y) = BDE(Y) − BDE(H)] of the substituent Y for several crystalline 1,3-diphenylacetones.

Although the ΔBDE(Y) values differ by only 1.5 kcal/mol and the variation in Φ(Y)/Φ(H) is only a factor of 4, we decided to see whether the unexpected behavior of **1f** as compared to **1a** may be explained by differences in the conformation of the aryl groups in their respective crystals. As aryl rotation in crystals should be limited, the prospective radicals may not enjoy the same extent of benzylic delocalization. In fact, experiments[18] and calculations[19] indicate that the difference in energy between benzyl radical conformations with parallel and orthogonal *p*-π-orbital alignment is ca. 12.5 kcal/mol. Recent results from our group with 1,1,3,3-tetramethyl-2-indanone **5** (Scheme 4) are particularly relevant in this context.[20] Closely related to the 1,3-diphenyl acetones studied here, tetramethyl indanone **5** reacts efficiently in solution where bond rotations allow benzylic stabilization to take place, but it is completely stable in the solid state.

Scheme 4



Knowing that interaction energies have an angular dependence $E(\Theta) = E_{max} \cos^2 \Theta$, where Θ is the angle between the two orbital systems and E_{max} is the maximum stabilization energy when $\Theta = 0$, we decided to investigate the X-ray structures of **1a** (Y = 4-H) and **1f** (Y = CF$_3$).

As illustrated in Figure 3, the conformations of **1a** and **1f** are quite similar. They have two α-methyl groups eclipsed with the C=O bond, as expected by a dipole−induced dipole interaction,[21] and their two α-phenyl groups are anti to each other. The dihedral angles made by the plane of each phenyl group and the α-bond in **1a** are $D_1 = 50.6°$ and $D_2 = 50.3°$, respectively. The corresponding values in **1f** are $D_1 = D_2 = 46.3°$. Because the orientation of the π-system is orthogonal to the aromatic plane, the ideal benzylic stabilization would occur for $D = 90°$ (i.e., $\Theta = 90° - D$). The resonance energy expected if Θ were to remain constant during the solid-state reaction would be $E(\mathbf{1a}) = 12.5[\cos^2(39.4°)] = 7.3$ kcal/mol and $E(\mathbf{1f}) = 12.5[\cos^2(43.7°)] = 6.5$ kcal/mol, respectively. This would predict **1f** to react less efficiently than **1a**, suggesting that small ground-state conformational differences in the crystal may not be playing a determining role. Other factors to consider include the effect of substituents on the "polarity" of the medium, which is known to affect the rates of decarbonylation in solution,[16] and differences in packing interactions leading to different steric barriers for the bond-cleavage processes.

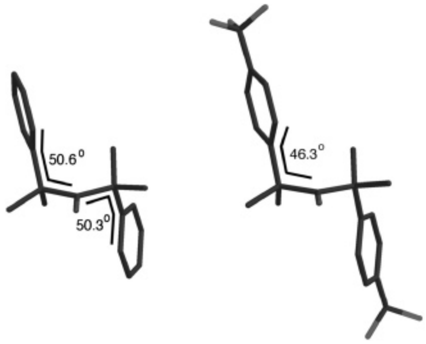


Figure 3. Molecular structures of **1a** and **1f** determined by X-ray. Only one of two disordered positions is shown for the CF$_3$ groups.

In conclusion, although the effect of aromatic substituents on the α-cleavage and decarbonylation reactions of 1,3-diarylacetones is relatively modest, it is important that reactions in crystals are as tractable and not much more complex than analogous reactions in solution. This gives support to our suggestion that reactions in crystals can be engineered from known molecular structure parameters.

Acknowledgment. Financial support by the National Science Foundation is gratefully acknowledged.

Supporting Information Available: Preparation and characterization of compounds **1a**−**1f**, **2a**−**2f**, and **5a**−**5f** and crystallographic data for compounds **1a** (tables) and **1f** (in CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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