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The Norrish Type II Reaction in the Crystalline State: Toward a Better Understanding of the Geometric Requirements for γ-Hydrogen Atom Abstraction

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Abstract: By correlating the success or failure of the Norrish type II reaction for a series of compounds in the crystalline state with geometric data derived from X-ray crystallography (the so-called Crystal Structure-Solid State Reactivity Method), the distance and angular requirements for photochemical γ-hydrogen atom abstraction have been established. These studies indicate that abstractions are preferred when the $C{=}O\ldots H_\gamma$ distance is close to the sum of the van der Waals radii of hydrogen and oxygen (2.72 Å), and that the γ-hydrogen atom can deviate by as much as 50-60° from the plane containing the oxygen n-orbital responsible for abstraction. Because molecular conformations and interatomic distances and angles can be calculated readily by using empirical force field methods, such data permit predictions to be made concerning the outcome of hypothetical Norrish type II processes.

INTRODUCTION

The Crystal Structure-Solid State Reactivity Correlation Method

Chemical reactions that take place in the crystalline state occur with a minimum of atomic and molecular motion. This simple yet profound concept, first formulated by Kohlschütter in 1918,[1a] placed on a firm experimental basis by the work of Schmidt and co-workers with cinnamic acid,[1b] and subsequently elaborated by Cohen[2] and most recently by Weiss et al.,[3] lies at the heart of the field of solid state organic chemistry and has come to be known as the topochemical postulate. The topochemical postulate derives from the fact that molecules in crystals are densely packed with large overall packing potential energies—the result being that the motions of any given molecule in the lattice are resisted by the presence of its neighbors.

Because of these physical restraints to motion, chemical reactions in crystals frequently differ from those occurring in fluid media, where the reactants are free to explore alternative conformations and react *via* geometries of approach that are inaccessible in the solid state. Several books and review articles summarize the remarkable differences between solution phase and solid state chemical behavior that have been observed.[4] In addition to inducing changes in chemical behavior, the crystalline state can be used to investigate structure-reactivity

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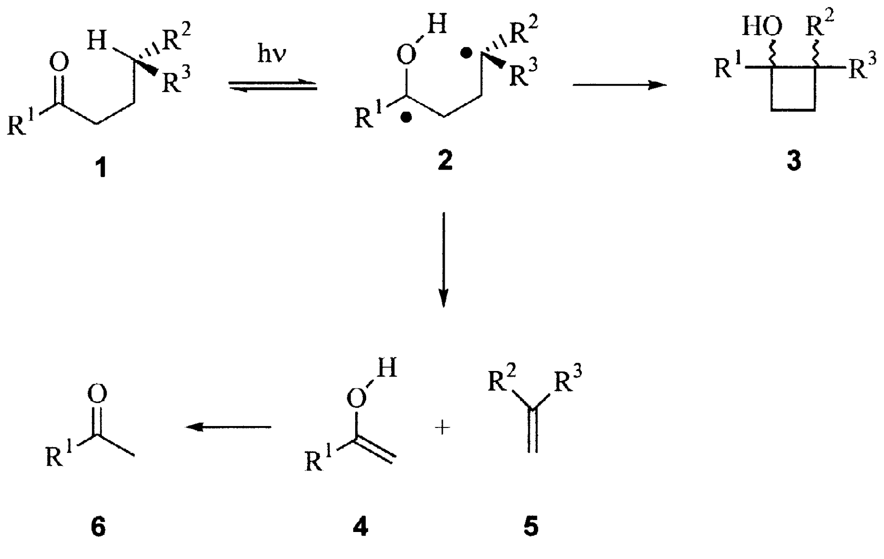
relationships in organic and inorganic chemistry. This stems from the fact that, when working with crystals, one has access to several extremely powerful techniques for determining chemical structure, the most important being X-ray crystallography and ^{13}C CPMAS NMR spectroscopy. These techniques give the investigator an intimate picture of the reactant molecules and their surroundings immediately prior to the chemical activation process, and because the molecules are constrained to least motion pathways, insights into the corresponding transition state and intermediate structures may be obtained as well. By correlating such structural data with observed solid state reactivity for a series of closely related compounds (the Crystal Structure-Solid State Reactivity Correlation Method), it is possible to deduce the geometric requirements for general classes of organic reactions—one well known example being the [2+2] photocycloaddition reaction of alkenes studied in the solid state by Schmidt and co-workers[1b] as well as subsequently by others.[5] In this chapter, we wish to report on the insights that we and others have obtained in the last several years using the Crystal Structure-Solid State Reactivity Correlation Method to elucidate the geometric requirements for the Norrish type II photochemical reaction.

The Norrish Type II Reaction

The Norrish type II reaction is among the most thoroughly investigated of all photoreactions and has been reviewed a number of times.[6] In the course of this reaction, an excited ketone **1** abstracts a γ-hydrogen atom to give a 1,4-hydroxybiradical intermediate **2** (Scheme 1), which has been detected by laser flash photolysis and



Scheme 1

trapped by S-deuterated thiols or oxygen.[7a,b] This biradical can either cyclize to the corresponding cyclobutanol **3** (Yang photocyclization[7c]) or, upon fragmentation, form alkene **5** and enol **4**, which subsequently tautomerizes to ketone **6**. Furthermore, in a reverse reaction, the hydrogen atom of biradical **2** can be returned to the γ-carbon to yield the starting ketone **1**.

Geometric Parameters

The hydrogen atom abstraction process that initiates the type II reaction occurs *via* a six-membered transition state, and at the time we began this project, there was relatively little experimental evidence in the literature concerning the most favorable geometric relationship between the abstracting carbonyl group and the abstracted γ-hydrogen atom.[8] It was this question that we set out to answer by studying the reaction by the Crystal Structure-Solid State Reactivity Correlation Method. Knowledge of the geometric parameters that favor abstraction would allow the design of new photoreactive systems as well as permit predictions of regioselectivity in molecules containing two or more abstractable hydrogen atoms.

For discussion purposes, it is useful to define four geometric parameters associated with the abstraction process (Figure 1). The first of these is **d**, the distance between the carbonyl oxygen and the γ-hydrogen. It seems reasonable to suggest that the optimum value of **d** should be close to the sum of the van der Waals radii for oxygen and hydrogen, which is 2.72 Å. The second parameter is given the symbol Δ, and is defined as the C=O...H angle. The optimum value of Δ should lie between 90-120°, depending on the hybridization of the orbitals containing the non-bonding electrons on oxygen (the orbitals generally agreed to be involved in the abstraction process). The third parameter is θ, defined as the C-H...O angle, which according to theory,[9] should have an optimum value of 180°, and the fourth parameter is ω, the angle by which the γ-hydrogen atom lies outside the mean plane of the carbonyl group. Since the n-orbitals on oxygen lie in this plane, the ideal value of ω is expected to be 0°.

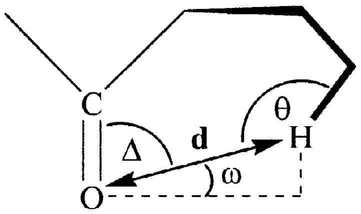
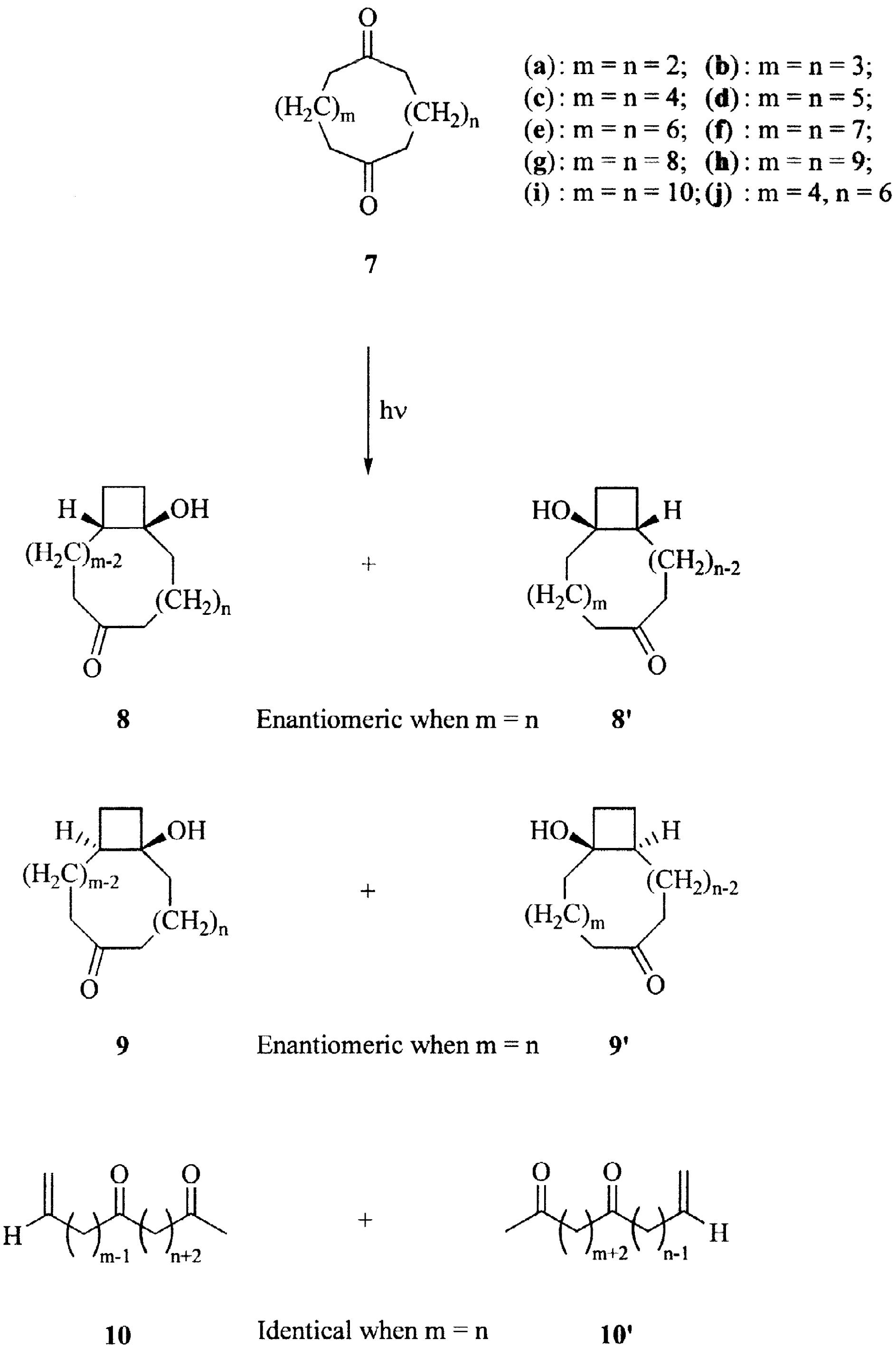


Figure 1. Definition of geometric parameters **d**, Δ, θ and ω for γ-hydrogen atom abstraction

RESULTS AND DISCUSSION



Scheme 2

Macrocyclic Diketones

We begin this review with a discussion of our recent work on the Norrish type II reaction of macrocyclic diketones.[10] Consider, for example, 1,10-cyclooctadecanedione (**7e**, Scheme 2), a "diametric" diketone that adopts a conformation in the crystalline state in which each oxygen comes close to a γ-hydrogen atom with a separation of 2.78 Å (Figure 2). This distance is close to the 2.72 Å sum of the van der Waals radii for oxygen and hydrogen, which led us to believe that this compound should undergo a Norrish type II reaction in the solid state. In fact, irradiation of diketone **7e** in the crystalline state led to the formation of the corresponding *trans*-cyclobutanol **9e** as the main product, with lesser amounts of *cis*-cyclobutanol **8e** and the cleavage product **10e** being formed as well (Scheme 2, Table 1). This result differed from that observed in solution. When compound **7e** was photolyzed in n-hexane, photoproducts **9e** and **10e** were formed in a 1:1 ratio, and cyclobutanol **8e** was a minor product.

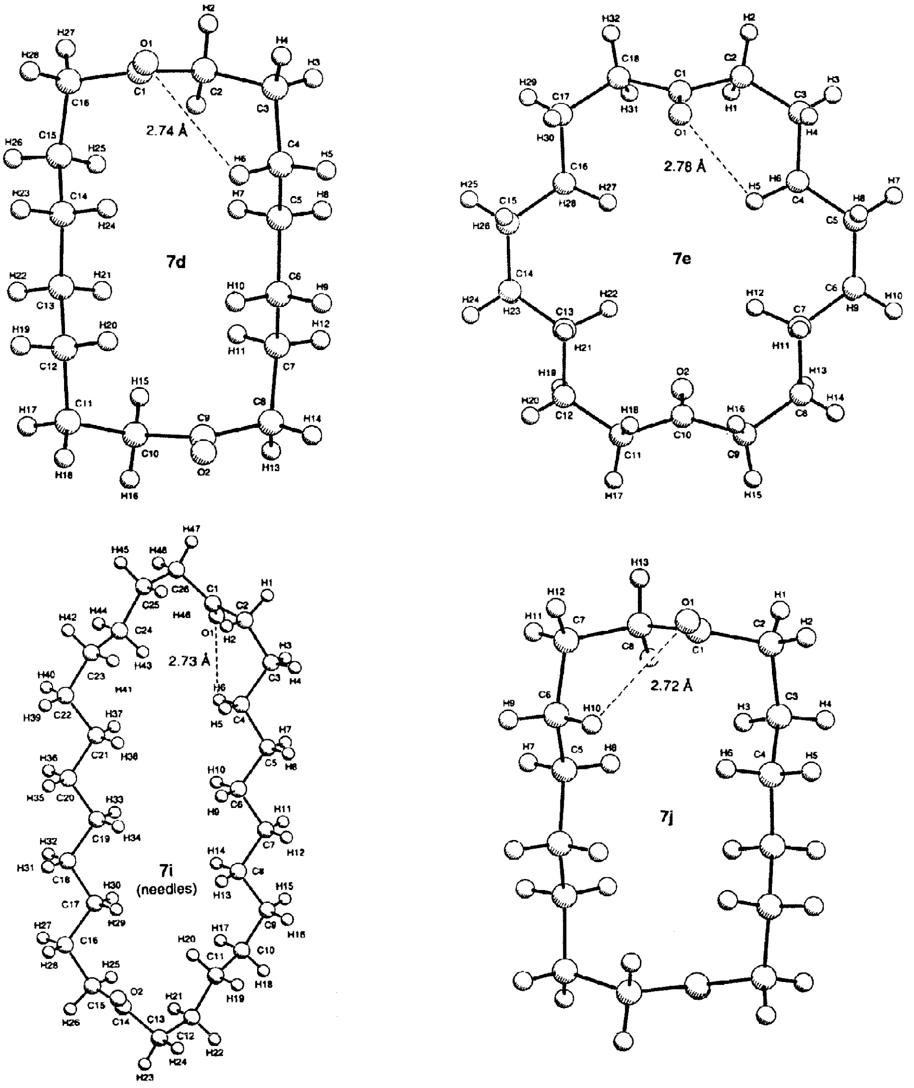


Figure 2. Solid state conformations of diketones **7d**, **7e**, **7i** (needles) and **7j**.
Closest γ-hydrogen atom contacts are shown by the dotted lines.

The observation that the type II photoreaction of diketone **7e** proceeds well in the crystalline state and shows a high selectivity for the formation of *trans*-cyclobutanol prompted an investigation of the photochemistry of homologues of this compound.[10] The macrocyclic diketones **7a-j** (Scheme 2), ranging in ring size from 10- to 26-membered (all known compounds), were readily available *via* classical organic synthesis. All of them are crystalline with reasonably high melting points, which makes them well suited for studies in the solid state. The X-ray crystal structures of diketones **7e** and **7h** were known when this work began; the crystal structures of all other diketones (with the exception of compound **7b**, crystals of which were not suitable for X-ray diffraction) were determined at UBC. As a bonus, diketone **7i** could be crystallized in two different polymorphic forms (needles and plates), and crystal structures of both were successfully obtained.[10] Figure 2 shows the molecular conformations of diketones **7d**, **7e**, **7i** (needles) and **7j** as determined by X-ray crystallography; crystal structures of the remaining diketones may be found in reference 10.

The results of photolyzing diketones **7a-j** to low conversions in n-hexane solution and in the crystalline state are summarized in Table 1. With the exception of 1,6-cyclodecanedione (**7a**), which did not react either in solution or the solid state, every diketone underwent smooth type II photochemistry. Compared to the results in solution, there is a strong preference for the formation of cyclobutanols in the solid state, and in every case, one of the two possible cyclobutanols was formed in much higher yield than the other.

Table 1. Results of photolyzing macrocyclic diketones **7a-7j** in solution and the solid state.

	Hexane			Solid State		
Diketone	**8** (%)	**9** (%)	**10** (%)	**8** (%)	**9** (%)	**10** (%)
7a	No Reaction			No Reaction		
7b	84	0	16	99	0	1
7c	65	25	10	58	29	13
7d	22	35	43	89	10	1
7e	17	42	41	3	84	13
7f	10	23	67	90	4	6
7g	10	34	56	4	91	5
7h	15	27	58	98	1	1
7i (needles)	14	33	53	9	91	0
7I (plates)	14	33	53	97	3	0
7j	**8/8'**	**9+9'**	**10+10'**	**8/8'**	**9+9'**	**10+10'**
	13/13	35	39	100/0	0	0

Having the solid state photochemical results in hand along with the corresponding X-ray crystallographic data, we are in a position to correlate the two. Let us first discuss the case of the 18-membered ring diketone **7e**. Here, owing to the high symmetry of the molecule in the crystalline state (Figure 2), only two types of γ-hydrogen atoms need to be considered: the "inner" hydrogens (e.g., H5) at a distance of 2.78 Å from the nearest oxygen atom, and the "axial" hydrogens (e.g., H21), for which **d** = 3.87 Å. It seems almost certain that it is one of the inner hydrogens that is abstracted in this case, not only because of the shorter abstraction distance, but because this can also explain the predominant formation of *trans*-cyclobutanol **9e** in the solid state. Following abstraction of H5, the OH group at C1 and the remaining hydrogen on C4 (H6) are *anti* to one another, and least motion closure with "retention of configuration" at C1 and C4 leads naturally to cyclobutanol **9e**. This is shown more clearly in Figure 3, which depicts the abstraction geometry from a different perspective. We note in passing that the 6-atom geometry in this case (and indeed, in all but one of the diametric diketones) is boat-like rather than chair-like. Early ideas concerning the transition state geometry of the type II reaction had assumed that a chair-like arrangement would be favored.[8]

The situation in the case of the 16-membered ring diketone **7d** is more complex. Here, because the molecule lacks symmetry in the solid state (Fig. 2), four γ-hydrogens lie within a reasonable distance for abstraction: H6 (**d** = 2.74 Å), H10 (**d** = 2.92 Å), H20 (**d** = 2.79 Å) and H24 (**d** = 2.92 Å). For this compound it is difficult to say with certainty which of the four hydrogen atoms is abstracted preferentially, since abstraction of any one of them followed by least motion closure is predicted to lead to *cis*-cyclobutanol **8d**, the major product formed in the solid state (Table 1). A partial structure depicting the formation of the pre-*cis* biradical for diketone **7d** is shown in Figure 3.

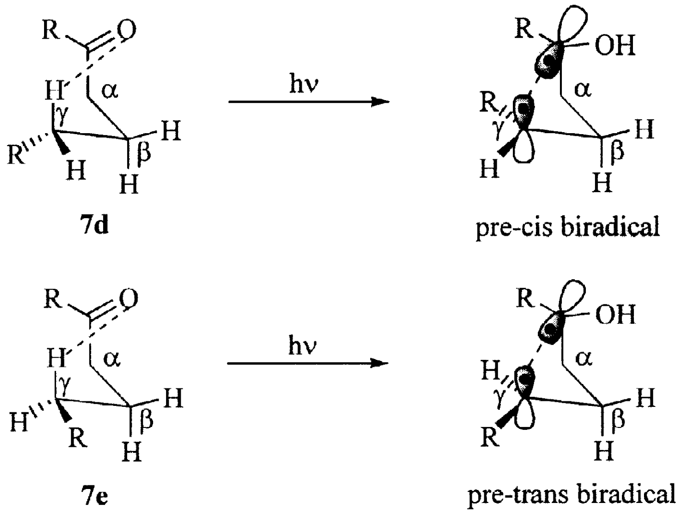


Figure 3. Partial conformations of diketones **7d** and **7e** leading to pre-*cis* and pre-*trans* 1,4-biradicals.

The corresponding non-diametric 16-membered ring diketone **7j** was expected to resolve some of these ambiguities, since in this case, abstraction of a γ-hydrogen from the longer methylene chain would lead to products structurally different from those formed by abstraction from the shorter chain (Scheme 2). The X-ray crystal structure of diketone **7j** (Figure 2) revealed that H10 on the 8-carbon chain is better situated for abstraction (**d** = 2.72 Å) than H6 on the 6-carbon chain, for which **d** = 2.99 Å. Experimentally, irradiation of diketone **7j** in the crystalline state afforded only cyclobutanol **8j**, the result of abstraction of the closer hydrogen H10. From this we conclude that it is also quite likely that the closer hydrogens in diketone **7d** are preferentially abstracted in the solid state.

A similar conclusion is reached based on the crystal structure-solid state reactivity correlation for the needle dimorph of diketone **7i** (Figure 2). Here too, one potentially abstractable hydrogen (H6, **d** = 2.73 Å) is better situated than the other (H20, **d** = 3.26 Å); thus, the expected result would be that the *trans*-cyclobutanol **9i** would be formed in preference to the *cis*-isomer resulting from abstraction of H20. Again, the experiment confirms the prediction, and *trans*-cyclobutanol **9i** is formed as the major product (91%) in the solid state.

In fact, for all the diketones studied, the solid state photochemical results are consistent with abstraction of the closest γ-hydrogen atom. For those interested, reference 10 provides a full discussion of each case along with the relevant crystal structures. Of course, distance is not the only factor contributing to γ-hydrogen abstractability; the angles ω, Δ and θ (Figure 1) must be considered as well. Table 2 summarizes the crystallographic values of **d**, ω, Δ and θ for diketones **7a** - **7j**. Perusal of this table reveals that, *for all of the diketones, the γ-hydrogens that have the most favorable* **d** *values also have more nearly ideal values of the angular parameters ω, Δ and θ.* Consider, for example, the needle dimorph of the 26-membered ring diketone **7i.** In this case, the closer hydrogen atom H6, for which **d** = 2.73 Å, has values for ω, Δ and θ of 49°, 85° and 115°, whereas the more distant hydrogen H20 (**d** = 3.26 Å) has values for the same parameters of 57°, 58° and 100°. Compared with the "ideal" values for ω, Δ and θ of 0°, 90-120° and 180°, it is apparent that the former group of numbers is closer to the ideal than the latter. By averaging the data for each of the "best" γ-hydrogens, we arrive at the numbers shown at the bottom of Table 2. It is interesting to note that, whereas the average experimental value for **d** is very close to the theoretical ideal of 2.72 Å, the values of the angular parameters are quite far off, especially those for ω and θ. As we shall see, this feature is common to other type II systems that have been studied by the X-ray crystal structure-solid state reactivity method.

Table 2. Crystallographically derived C=O...H_γ abstraction geometries for **d** ≤ 3.50 Å for diketones **7a** - **7j**.

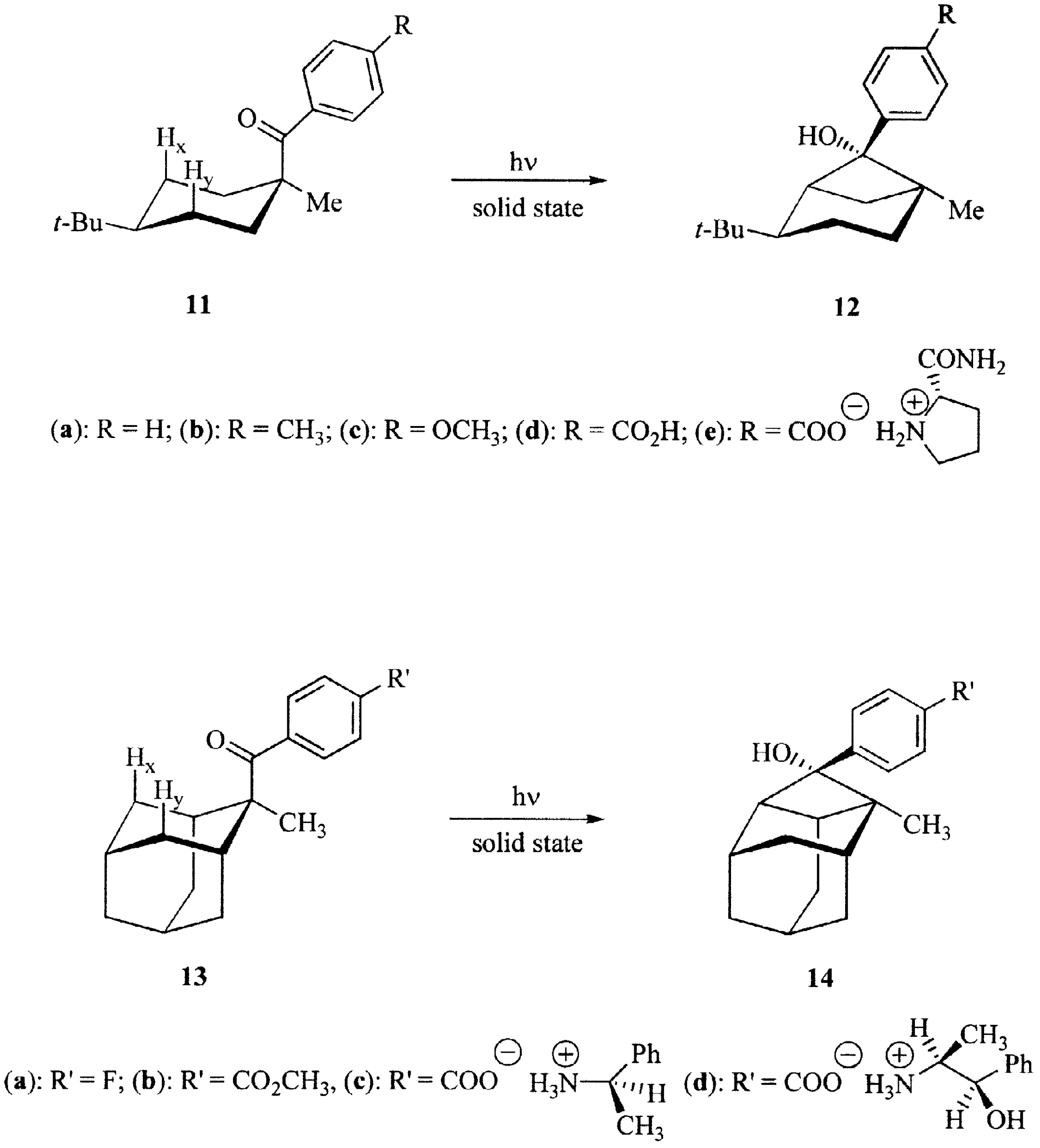
Ketone	γ-Hydrogen	**d** (Å)	ω (°)	Δ (°)	θ (°)
7a	H3	2.74	52	91	113
7b[a]	H6 by O1	2.80	66	74	117
	H6 by O2	2.73	64	78	113
7c	H6	2.71	53	83	116
7d	H6	2.74	53	82	115
	H10	2.92	60	66	118
	H20	2.79	53	82	111
	H24	2.92	60	66	116
7e	H5	2.78	53	82	114
7f	H5	2.70	52	83	115
	H13	3.00	59	63	114
	H23	2.70	52	84	115
	H31	2.99	60	64	115
7g	H16	2.82	52	81	111
	H26	3.10	57	59	114
	H35	2.71	44	88	114
7h	H5	3.12	56	59	115
	H17	2.69	50	84	116
	H27	3.17	55	57	116
	H39	2.67	50	83	118
7i (needles)	H6	2.73	49	85	115
	H20	3.26	57	58	100
7i (plates)	H5	3.30	52	53	115
	H20	2.76	52	82	113
7j	H6	2.99	59	66	117
	H10	2.72	53	81	116
Average for Diketones 7a-7j[b]	"Best" γ-Hydrogen	2.73 ± 0.03	52 ± 5	83 ± 4	115 ± 2
Hypothetical	Ideal[c]	2.72	0	90-120	180

[a]Data for diketone **7b** are MM2-derived. [b]With standard deviation. [c]See text for discussion.

Cyclohexyl and 2-Adamantyl Aryl Ketone Derivatives

Cyclohexyl aryl ketones of general structure **11** and 2-adamantyl aryl ketones of general structure **13** (Scheme 3) both undergo smooth Yang photocyclization[7c] in the solid state as well as in solution,[11] and in this section we discuss our studies of these compounds by the X-ray crystal structure-solid state reactivity correlation method. Irradiation of ketones **11a-e** in the crystalline state leads to exclusive formation of cyclobutanols **12a-e**;

similarly, photolysis of adamantyl ketones **13a-d** affords cyclobutanols **14a-d** as the only products (in the case of photoproducts **12d**,e and **14c,d**, diazomethane workup afforded the corresponding methyl esters). Cyclobutanols of general structure **12** and **14** are the major photoproducts in solution as well, but are usually accompanied by small amounts of the corresponding diastereomers in which the configuration of the hydroxyl-bearing carbon atom is reversed.



Scheme 3

The X-ray crystal structures of ketones **11a-e** and **13a-d** reveal that these compounds adopt similar conformations in the solid state in which the mean plane of the carbonyl group is roughly orthogonal to the plane bisecting the cyclohexane ring. Figure 4 shows a typical example, that of ketone **13c**. In this conformation, the carbonyl oxygen is much closer to one of the abstractable γ-hydrogen atoms than to the other, and in the case of ketone **13c**, the relevant abstraction distances are **d** = 2.60 Å for H_x and **d** = 3.59 Å for H_y. Table 3 summarizes the values of **d** for ketones **11a-e** and **13a-d**, along with the values of the angular parameters ω, Δ and θ.

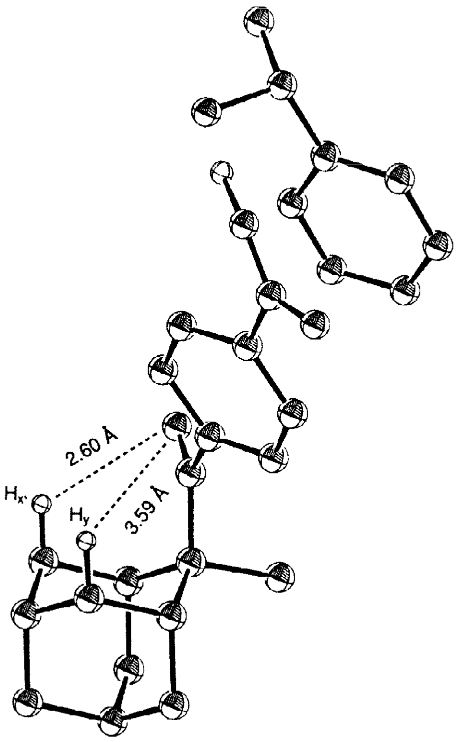


Figure 4. Solid state conformation of ketone **13c**, showing abstractable γ-hydrogen atoms H_x and H_y.

Table 3. Crystallographically derived C=O...H_γ abstraction geometries (**d** ≤ 3.50 Å) **for ketones 11a-e** and **13a-d**.

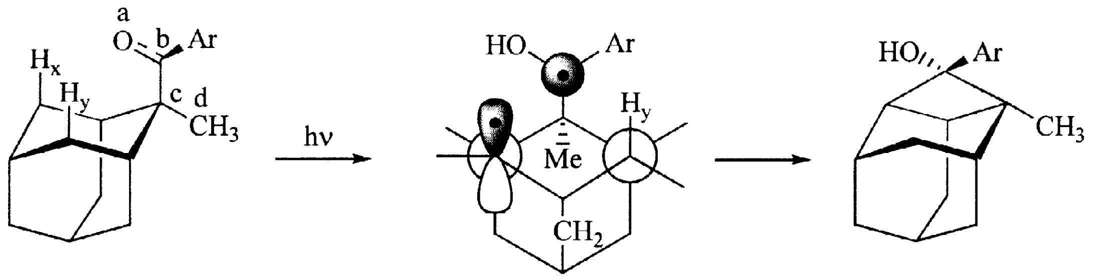
Ketone	γ-Hydrogen	**d** (Å)	ω (°)	Δ (°)	**θ** (°)
11a	H_x	2.70	57	81	114
11b	H_x	2.69	57	83	112
11c	H_x	2.63	56	85	113
	H_y	3.49	45	46	108
11d[a]	H_x	2.65	55	85	113
	H_y	3.50	45	46	108
	$H_{x'}$	2.61	52	88	114
	$H_{y'}$	3.44	48	49	108
11e	H_x	2.75	60	77	112
13a	H_x	2.54	61	80	116
	H_y	3.47	41	41	109
13b	H_x	2.58	61	79	115
13c	H_x	2.60	62	75	114
13d	H_x	2.55	60	80	116
	H_y	3.47	42	41	109
Average[b] **for H_x**	H_x	2.63 ± 0.06	58 ± 3	81 ± 4	114 ± 1

[a]Two independent molecules in the asymmetric unit. [b]With standard deviation.

In every case, the crystallographic data reveal that abstraction of H_x should be favored over abstraction of H_y. Not only is the abstraction distance for H_x much more favorable than that for H_y, but the values of Δ and θ are better as well. The fact that the value of ω is slightly more favorable for H_y than H_x does not alter this conclusion. Experimental evidence that H_x is preferentially abstracted comes from photolysis of ketone **13c** in the solid state.[11c] The photoreaction in this case was found to be topotactic, that is, X-ray quality single crystals of ketone **13c** were smoothly and continuously transformed into X-ray quality single crystals of cyclobutanol **14c**. This allowed X-ray diffraction studies to be carried out *on the same crystal* at the beginning, midpoint and final stages of reaction. The beauty of this is that it allows us to state with complete certainty that the carbon atom to which H_x was attached in ketone **13c** is in fact part of the newly formed four-membered ring of photoproduct **14c**, that is, abstraction of H_x leads to the observed product. In view of the similarity in the geometric data, it seems certain that this is true of the other ketones as well, although in these cases the reactions were not topotactic. Finally we note that (as for the diametric diketones discussed earlier) boat-like rather than chair-like six atom abstraction geometries are preferred.

Stereo- and Enantioselectivity of Cyclobutanol Formation

Preferential abstraction of H_x in ketones **11a-e** and **13a-d** is also consistent with the observed stereochemistry of cyclobutanol formation. As illustrated in Scheme 4 for ketones of type **13** (and applicable to ketones of type **11** as well), abstraction of H_x with maintenance of overall conformation leads to 1,4-hydroxybiradical **15** in which the aryl group is *syn* with respect to H_y. This species is poorly aligned for cleavage, and its direct closure affords the observed *endo*-arylcyclobutanol **14**. In contrast, formation of the *exo*-arylcyclobutanol would require a 180° rotation about the b-c bond of biradical **15**, a motion that would surely be resisted by the highly congested crystal lattice environment, and one that is also evidently slow relative to closure in liquid media.



13 **15** **14**

Scheme 4

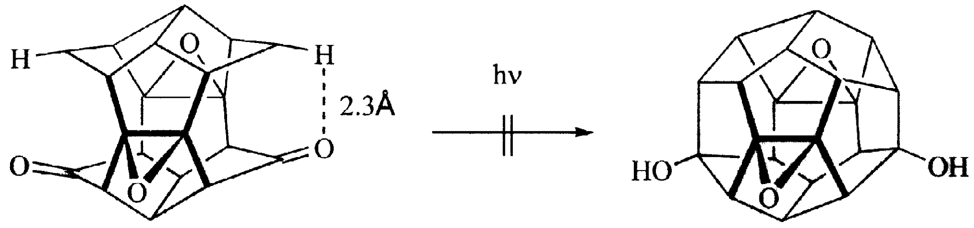
Given the difference in abstractability between γ-hydrogen atoms H_x and H_y, and the fact that these hydrogens are enantiotopic, it follows that if photolysis is conducted in an asymmetric environment, it should be possible to generate cyclobutanols **12** and **14** in optically active form. It is now well established from our work and that of others[12] that compounds crystallizing in chiral space groups provide excellent asymmetric environments in which to carry out enantioselective chemical reactions. Thus, in attempting to apply this methodology to the photochemistry of ketones **11** and **13**, the question was, how do we force compounds of this type to crystallize in chiral space groups? To solve this problem, we introduced the concept of the ionic chiral auxiliary.[13] The ketone under investigation is provided with a carboxylic acid functionality, and by linking a chiral, enantiomerically pure amine to this ketone *via* simple salt formation, we obtain an optically active salt which necessarily crystallizes in a chiral space group, examples being compounds **11e**, **13c** and **13d** (Scheme 3). As hoped, irradiation of these salts in the crystalline state (followed by diazomethane workup to afford the corresponding methyl esters) did in fact lead to enantiomerically enriched cyclobutanols. In each case, enantiomeric excesses of nearly 90% were obtained at low conversions. At higher conversions, the *ee*s diminished significantly for salts **11e** and **13d**, but, in the case of salt **13c**, the *ee* remained high (>80%) even at conversions of over 80% as a result of the aforementioned single crystal-to-single crystal nature of the photoreaction.[11c]

Comparison of the Geometric Data for Macrocyclic Diketones and Aryl Ketone Derivatives

A comparison of the average values of **d**, ω, Δ and θ for macrocyclic diketones **7a-7j** (Table 2) with those for aryl ketones **11a-11e** and **13a-13d** (Table 3) reveals that they are essentially identical. *The fact that two completely different classes of ketone—one aliphatic, the other aromatic—exhibit such similar solid state geometries argues very strongly that these data may be taken as being generally indicative of successful γ-hydrogen atom abstraction.* Thus, our notion going into this work, that abstraction distances should be close to the sum of the van der Waals radii for oxygen and hydrogen (2.72 Å), is clearly borne out; the data for both the macrocyclic diketones ($\mathbf{d}_{Av}$ = 2.73 ± 0.03 Å) and the aryl ketones ($\mathbf{d}_{Av}$ = 2.63 ± 0.06 Å) agree on this point.

In contrast, the prediction that the γ-hydrogen should lie in the same plane as the oxygen n-orbital (ω = 0°) is clearly *not* consistent with the experimental data, which uniformly indicate ω angles in the range of 50-60°. How can we reconcile this difference? Wagner has suggested that the rate of type II hydrogen atom abstraction should show a $\cos^2\omega$ dependence.[14] If this is correct (and he has supplied experimental evidence to show that it is[15]), then ω can be quite large, yet still lead to respectable rates of abstraction. For example, when ω = 60°, $\cos^2 60 = 0.25$, and abstraction is predicted to occur at 25% of its maximum rate—more than enough for observable solid state reactivity. Of course, when ω = 90°—i.e., when the target hydrogen atom lies in the carbonyl π-plane—abstraction should cease ($\cos^2 90 = 0$), and such situations are known. For example, it was hoped that the cage molecule **16**, synthesized by Prinzbach and co-workers,[16] would undergo photochemical double δ-hydrogen atom abstraction/cyclization to afford the corresponding dodecahedrane derivative **17** (Scheme 5). Estimates of the abstraction distance **d** indicated a very favorable value of 2.3 Å, but, despite this, diketone **16** proved to be photochemically inert, a circumstance that can be reasonably attributed to the strict ω = 90° hydrogen abstraction geometry enforced by the rigid cage structure.[17]

With respect to the geometric parameter Δ (the C=O...H angle), there is once again reasonably good agreement between the experimental data in Tables 2 and 3 and the hypothetical ideal of 90-120°. The fact that the average experimental values of Δ (83° and 81°) are closer to 90° than 120° could be taken as evidence for



16 **17**

Scheme 5

involvement of a non-bonding orbital on oxygen that is largely 2p-like in character (Kasha model[18]), but this is far from certain, since substantial deviations from an ideal "rabbit-ear" model ($\Delta = 120°$) may be tolerated. In line with this picture, a*b initio* calculations by Wiberg and co-workers indicate that, for typical carbonyl compounds, the charge density distribution about oxygen does not show any obvious directionality of the lone pairs.[19] Interestingly, however, Griesbeck *et al.* have recently reported that the singlet state Norrish type II photochemistry of phthalimides is critically dependent on the angle Δ.[20] Reactive substrates had MM2 and PM3-calculated Δ values of 100 ± 5°, whereas unreactive compounds had values of 82 ± 5°. Finally, with regard to the C-H...O angle θ, the widespread occurrence of the Norrish type II photoreaction in systems where θ cannot possibly approach the ideal value of 180° indicates that large deviations may be expected in this parameter as well. The data in Tables 2 and 3 ($\theta_{Av} \cong 115°$) bear this out.

Ground State versus Excited State Abstraction Geometries

There is an inherent problem with the structure-reactivity relationships outlined above, and that is that they correlate *ground state* structure with *excited state* reactivity. For example, it is well known that excitation lengthens carbonyl bonds by about 0.1 Å.[21] A second factor that makes the crystal structure—reactivity relationships less than exact is the fact that crystallographically-determined C—H bond lengths are consistently underestimated by approximately 0.1 Å. This is due to the fact that, in the case of hydrogen atoms, the X-rays are diffracted primarily by the electrons in the C—H bonds. The overall effect of these changes is not very significant, however, since keeping Δ and θ at their typical values of 82° and 115°, and applying a correction of +0.1 Å to both the C=O and C—H distances, decreases the abstraction distance **d** by a negligible amount (about 0.03 Å). More important for geometric considerations is the possibility that the ketone carbonyl groups may become pyramidalized in their reactive n,π* excited states. This is probably not a factor for aromatic ketones such as **11a-11e** and **13a-13d**,[22] but there seems to be general agreement that there *is* significant excited state pyramidalization in the case of aliphatic ketones (such as **7a-7j**).[23] This, of course, refers to the situation in fluid phases, and it is interesting to speculate that the crystalline environment may limit pyramidalization to a large extent. This notion is supported by the facts that both sets of ketones have essentially identical abstraction parameters, and that both react efficiently in the crystalline state.

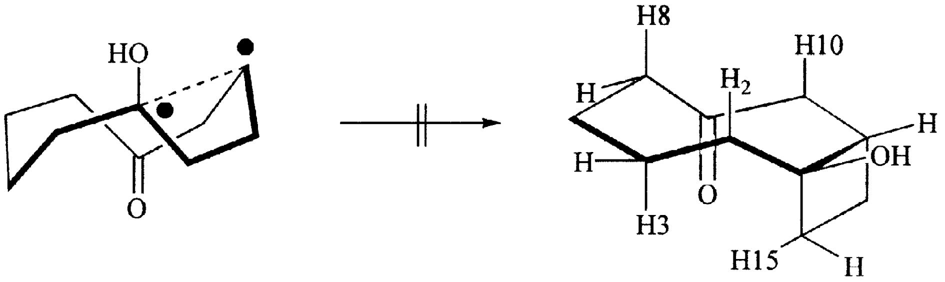
Thus, while the abstraction parameters measured by X-ray crystallography obviously do not provide exact information on the situation in the excited state, there is every reason to believe that the structure-reactivity relationships developed above are approximately correct and can now be used in a predictive sense. These days it is a relatively simple matter to calculate the values of **d**, ω, Δ and θ for a given ketone through the use of molecular force field programs, which means that it is now possible to estimate the probable success or failure of an unknown Norrish type II reaction and even—in favorable cases where reverse hydrogen transfer is not product-determining (see below)—predict its regioselectivity. Such work is underway in our laboratory at the present time. A final point is that, while the present results indicate that there is complete selectivity in the crystalline state for preferential abstraction of hydrogens near the sum of the van der Waals radii (2.72 Å versus 2.99 Å, ketone **7j**), this does not mean that hydrogen abstraction is *limited* to such distances. We have shown that values of **d** as great as 3.10 Å can be tolerated,[24] and this remains our best current estimate of the approximate upper limit to intramolecular hydrogen atom abstraction by ketone oxygen.

Comparison of the Present Geometric Data with Those for Other Type II Systems

The present article amplifies and reinforces the conclusions we came to in our initial work on the geometric requirements for intramolecular hydrogen atom abstraction.[8] There, too, in studies of 17 variously substituted compounds having the basic α-cycloalkylacetophenone structure, a preference for abstraction over distances near the sum of the van der Waals radii was observed (**d** = 2.74 ± 0.16 Å) , coupled with a predilection for ω angles in the range of 30-50° (ω = 43 ± 9°) and Δ angles around 90° (Δ = 84 ± 8°) (θ was not calculated). Thus, in three separate systems studied by the Crystal Structure-Solid State Reactivity Correlation Method (α-cycloalkylacetophenones,[8] macrocyclic diketones[10] and cyclohexyl/adamantyl aryl ketone derivatives[11]), similar structure—reactivity relationships have been seen. In addition, since we began this work over 15 years ago, there have been several one-of-a-kind reports in which individual compounds have been shown to undergo the type II reaction in the crystalline state through geometries very similar to those described above. Since these studies reinforce rather than contradict the overall picture developed above, we forego their description here in the interests of brevity, and the interested reader is referred to the original literature, which includes (in a by no means comprehensive list) reports from our laboratory,[25] as well as the laboratories of P.J. Wagner,[26] F. Toda,[27] M Sakamoto[28] and M.A. Garcia-Garibay.[29]

The Reversibility of Hydrogen Atom Transfer

The sum total of the evidence presented above makes a very convincing case for Norrish type II photochemical hydrogen atom abstraction reactions that favor geometries in which **d**, the C=O...H_γ abstraction distance, is close to the sum of the van der Waals radii (2.72 Å), and in which the angles ω, Δ and θ are approximately 50°, 80° and 115°, respectively. Although we can now confidently state that such geometries virtually guarantee successful hydrogen atom transfer, they do not always lead to observable photoproduct formation. The reason for this is that hydrogen transfer is reversible,[6] and if reverse hydrogen transfer is faster than cyclization or cleavage of the intermediate 1,4-hydroxybiradical, no type II photoproducts will be formed. An illustrative case of such behavior in the crystalline state is provided by 1,6-cyclodecanedione (**7a**). Here, despite the fact that the molecule adopts a conformation in the solid state that is nearly ideal for hydrogen atom abstraction (**d** = 2.74 Å, ω = 52°, Δ = 91° and θ = 113°), prolonged irradiation of crystals leads to no net product formation. A detailed analysis[30] reveals that the failure of diketone **7a** to form cyclobutanol(s) is very likely associated with the difficulty in forming an 8-membered ring. Enthalpies of activation for the formation of 8-membered rings are known to be particularly high owing to transannular interactions between hydrogen atoms.[31] In the particular case of diketone **7a**, hydrogen abstraction would lead to a biradical (structure **18**, Scheme 6) in which the rate of closure to *cis*-cyclobutanol **19** (i.e., **8a**) is retarded by severe transannular repulsions between H2 and H8 on the 8-membered ring, as well as by unfavorable interannular contacts between H3 and H15. With closure thus retarded, and cleavage made difficult by poor orbital alignment, the biradical reverts to starting material and the diketone appears to be photochemically inert in the solid state. For a discussion of the reasons for the failure of diketone **7a** to react in solution, see references 10 and 30.



18 **19**

Scheme 6

The reversibility of hydrogen atom transfer also raises the possibility that, in cases where two different hydrogens can be abstracted, the final product ratios may reflect the relative rates of the *reverse* process rather than of the forward one. While this has been demonstrated clearly in solution,[32] it does not seem to be a problem in the crystalline state, where abstraction of the stereoelectronically favored hydrogen atom invariably leads to the observed product. A good example of this is the previously discussed non-diametric diketone **7j**, which in the solid state, leads to products arising exclusively from abstraction of H10 (**d** = 2.72 Å, ω = 53°) rather than H6 (**d** = 2.99 Å, ω = 59°). Thus, in crystals, product ratios *do* reflect relative hydrogen abstractability, and the structure-reactivity relationships developed above are secure.

Summary

The Crystal Structure-Solid State Reactivity Correlation Method works well for the elucidation of the preferred geometry of intramolecular hydrogen atom abstraction in the Norrish type II reaction. As in the pioneering work of G.M.J. Schmidt and his co-workers on the geometric requirements for [2+2] photocycloaddition in crystalline cinnamic acids,[1b] distance and angular requirements for reaction have been established, and the structure and stereochemistry of the products have been shown to be simply and directly related to molecular structure as it exists in the bulk crystal. It is important to emphasize that such structure-reactivity relationships are only approximate, as they correlate *ground state* structure with *excited state* reactivity. Nevertheless, because the ground and excited states of aromatic ketones have very similar structures, the correlation works well and can be used predictively. Even for aliphatic ketones, in which the carbonyl carbon is expected to be partially pyramidalized in the excited state, the correlation seems to hold, since the pyramidalization may be restricted by the rigid crystal lattice. Looking to the future, an important extension of the Crystal Structure-Solid State Reactivity Method would be to correlate the *rate* of hydrogen atom abstraction in the crystal with the C=O...H geometry. It would be particularly interesting, for example, to test the validity of the predicted[14] dependence of the hydrogen atom abstraction rate constant on $\cos^2\omega$. These are not simple experiments, but steps in this direction are being taken in the laboratory of Professor M.A. Garcia-Garibay at UCLA.

From the triplet excited state, the Norrish type II reaction is a two step process—hydrogen atom abstraction followed by cyclization and/or cleavage of the resulting biradical. Owing to space limitations, this review has dealt only with the first step of the reaction—hydrogen abstraction. Given the likelihood that the structure of the Norrish type II biradical is very similar to that of its ketonic precursor in the crystalline state, the Crystal Structure-Solid State Reactivity Correlation Method can also be used to analyze the geometric requirements for biradical cyclization and cleavage, and in due course this will form the subject of another review.

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Biographical sketch

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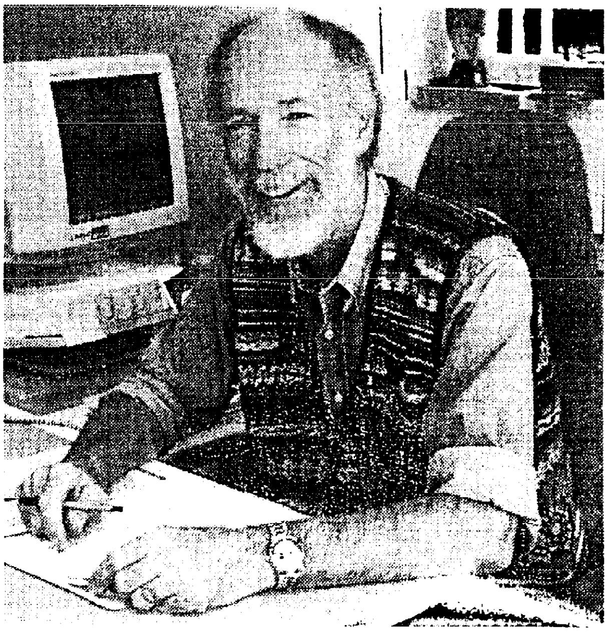

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