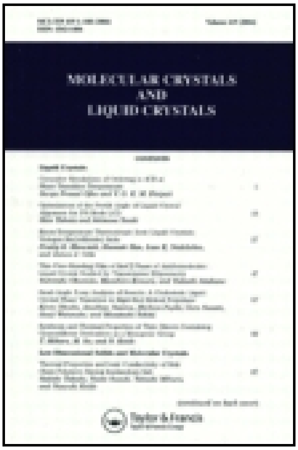

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CRYSTALLOGRAPHIC DETERMINATION OF THE PREFERRED GEOMETRY FOR INTRAMOLECULAR HYDROGEN ATOM ABSTRACTION IN 1,8-CYCLOHEXADECANEDIONE

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Abstract The two carbonyl groups in 1,8-cyclohexadecanedione (**1a**) are separated by eight methylene groups on one side and six on the other, thus giving rise to two nonequivalent γ-hydrogen atoms for abstraction *via* the Norrish type II reaction. X-ray crystallography reveals that, in the solid state, the γ-hydrogen atom on the longer methylene chain is more favorably situated for abstraction than that on the shorter chain, both in terms of abstraction distance (2.72 Å vs 2.99 Å) and angular relationship. In accord with this analysis, photolysis of diketone **1a** in the solid state leads exclusively to a single cyclobutanol diastereomer resulting from abstraction of the stereoelectronically favored hydrogen atom. In contrast, irradiation of compound **1a** in solution affords a complex mixture of all six possible type II cyclization and cleavage products resulting from non-selective abstraction of both γ-hydrogens. The solid state results are interpreted in terms of the crystallographically determined conformation of diketone **1a**, which favors stereoselective cyclization over cleavage.

Keywords: Solid state organic photochemistry, Crystal structure-reactivity relationships, Hydrogen abstraction geometry, Norrish type II reaction, Macrocyclic diketone

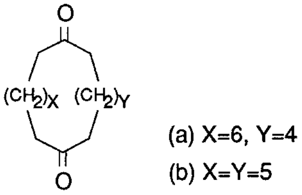
INTRODUCTION

There is much current interest in determining the preferred geometry for abstraction of a hydrogen atom by the oxygen atom of an excited state carbonyl compound. Intramolecular versions of this process that involve six-membered transition states are examples of the well known Norrish type II reaction, one of the most ubiquitous photochemical reactions known.[1] 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. In addition, such information would provide valuable insight into closely related ground state processes such as the McLafferty rearrangement[2] and the Barton reaction.[3]

Most studies of the Norrish type II reaction have been on conformationally mobile molecules in solution. In these systems, because of rapid equilibration among conformers, the exact disposition of the abstracted and abstracting atoms in the transition state can only be estimated. As a result, previous attempts at delineating preferred hydrogen abstraction geometries have been primarily theoretical in nature.[4-5]

Our approach has been an experimental one. By studying hydrogen abstraction reactions in the *crystalline* state, two advantages accrue. First, because of the relatively strong forces that hold crystals together, atomic and molecular motions are restricted, and chemical reactions in this medium tend to be least motion in character such that the transition states, intermediates and products closely resemble the reactants in shape and volume. This is the well known "topochemical principle" of Cohen and Schmidt.[6] Secondly, determination of the crystal and molecular structure of the reactant by X-ray diffraction methods provides a detailed, three-dimensional view of the reaction ensemble immediately prior to reaction. As a result, hydrogen abstraction distances and angles may be calculated and related to solid state behavior, and structure-reactivity correlations may be developed with the assurance that the reactive species in the solid state is closely related in structure to that determined crystallographically. A review article summarizing some of our earlier findings on hydrogen abstraction-initiated reactions in the solid state has appeared.[7]

In the present paper we report our work on the hydrogen abstraction reaction that takes place in crystalline 1,8-cyclohexadecanedione (**1a**, Scheme I). This is an extension of previous research from our laboratory on the solid state photochemistry of so-called "diametric" macrocyclic diketones.[8,9] An example of this class of compounds is diketone **1b**, in which the ketone moieties are separated by an equal number of methylene groups (seven) on each side of the ring. In contrast, diketone **1a** is non-diametric; its carbonyl groups are separated by six methylene groups on one side and eight on the other. The result of this structural difference is that there are two non-equivalent γ-positions for hydrogen atom abstraction in diketone **1a**, whereas all four γ-positions in compound **1b** are identical. It was anticipated that the regioselectivity of solid state hydrogen abstraction in **1a** could be related to differences in the abstraction geometries as determined by X-ray crystallography. Such, indeed, turned out to be the case.



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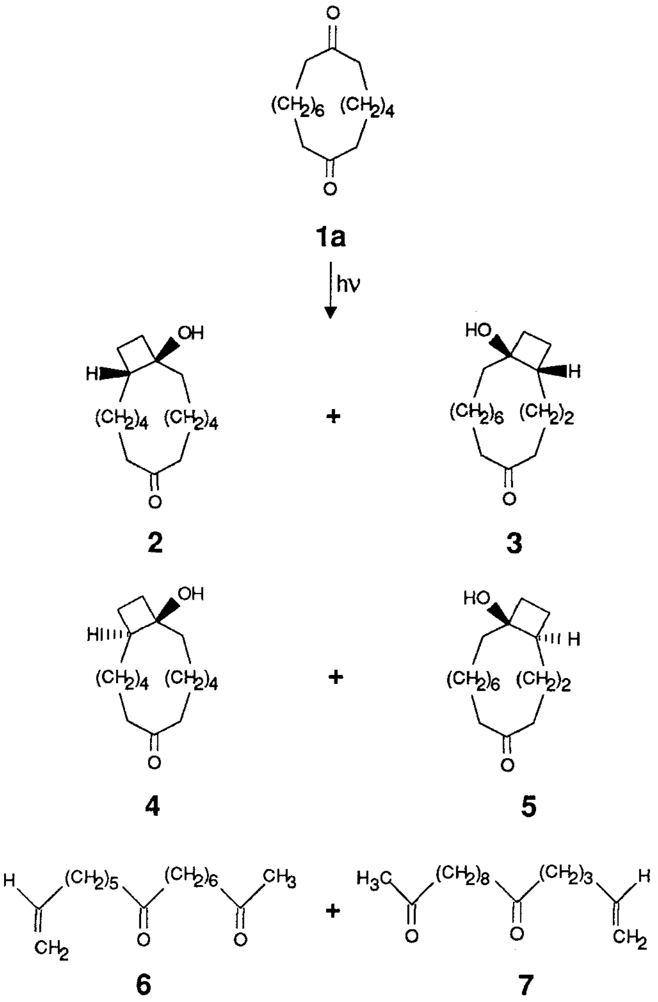
SCHEME I Compounds Studied.

RESULTS AND DISCUSSION

Macrocyclic diametric diketones were first synthesized by Ruzicka and co-workers in the 1920s;[10] a more recent synthesis is that due to Blomquist, Prager and Wolinsky,[11] in which an α,ω-diacid chloride is reacted with triethylamine followed by hydrolysis and decarboxylation of the resulting bis-ketene dimer. This is the method we used, and by starting with a mixture of two *different* diacid chlorides (suberyl chloride and sebacoyl chloride), a low yield (ca. 11%) of the desired diketone **1a** was obtained along with the 14- and 18-membered ring diametric analogues. Diketone **1a** proved to be a crystalline solid with a melting point of 73-74°. Its photochemistry was studied in the solid state, and for comparison purposes, in hexane solutions as well.

Like all the other macrocyclic diketones whose photochemistry we have investigated,[8,9] diketone **1a** underwent smooth type II photochemistry, both in the solid state and in solution. In order to avoid double photoreactions involving both carbonyl groups, conversions were kept low, generally below ca. 15%. Gas chromatographic analysis of the reaction mixture obtained by photolysis in the solid state at 30° showed the formation of essentially a single photoproduct. This substance could be isolated by column chromatography on silica gel and proved to be a crystalline solid with a melting point of 122-123°. Based on its spectroscopic properties and, ultimately, on an X-ray crystal structure determination,[12] this material was shown to have the cis-fused cyclobutanol structure **2** (Scheme II), the result of γ-hydrogen atom abstraction from the longer methylene chain of diketone **1a**.[13]

Like the 16-membered diametric diketone **1b**,[8] diketone **1a** exhibits interesting solid-solid phase transition behavior. In the case of diketone **1a**, there are *two* phase transitions below the melting point, one at 37° and the other at 55°. It therefore became of interest to investigate the photochemistry in these other solid phases. Accordingly, crystals of diketone **1a** were irradiated at 40° and at 60°; as expected,[8] photobehavior very different from that seen at 30° was observed. At 40°, a mixture of six photoproducts could be detected. One of these, formed in a relative yield of approximately 20%, proved to be identical to photoproduct **2** described above. A second (ca. 9% relative yield) could also be isolated by column chromatography (melting point 82-83°) and was shown by X-ray crystallography[12] to have structure **3**, the cis-cyclobutanol resulting from γ-hydrogen atom abstraction on the *shorter* methylene chain of diketone **1a**. The corresponding trans-fused cyclobutanols **4** and **5** could not be separated from one another and were therefore characterized as a mixture by ^{13}C



SCHEME II Products Formed in Photolysis of Diketone **1a**

NMR spectroscopy. For this purpose, use was made of the characteristic upfield shift of their ring junction C-H carbon atoms,[9] which could easily be identified by the attached proton test.[14] Photoproducts **4** and **5** gave rise to a single peak on gas chromatography, and their relative proportions could therefore not be determined; in total, however, they comprised approximately 33% of the product mixture at 40°. The final two products that were isolated in this photolysis proved to be the ene-diones **6** and **7** (Scheme II), the result of Norrish type II cleavage on the longer (**6**) and shorter(**7**) side of diketone **1a**. Again, owing to their very similar chromatographic behavior, compounds **6** and **7** could not be separated from one another and were characterized as a mixture; in total, they accounted for approximately 38% of the 40° solid state photolysis mixture.

The same six photoproducts were formed when crystals of diketone **1a** were photolyzed at 60° or when hexane solutions of **1a** were irradiated. The product ratios in these cases differed slightly from those observed in the solid state at 40°, and for comparison purposes, all the data are summarized in Table I.

TABLE I Photoproduct ratios as a function of temperature and medium.

Medium	Temperature (°C)	%**2**	%**3**	%**4**+**5**	%**6**+**7**
Hexane	30°	13	13	35	39
Crystal	30°	98	2	-	-
Crystal	40°	20	9	33	38
Crystal	60°	14	13	26	47

Concomitant with the photochemical studies, a single crystal X-ray diffraction investigation of diketone **1a** was undertaken.[12] This was carried out at room temperature (*ca.* 20°), well below the temperature of the first solid-solid phase transition at 37°. The results of the crystal structure determination show that diketone **1a** adopts a conformation having C_2 symmetry. A stereo drawing of this conformation is given in Figure 1.

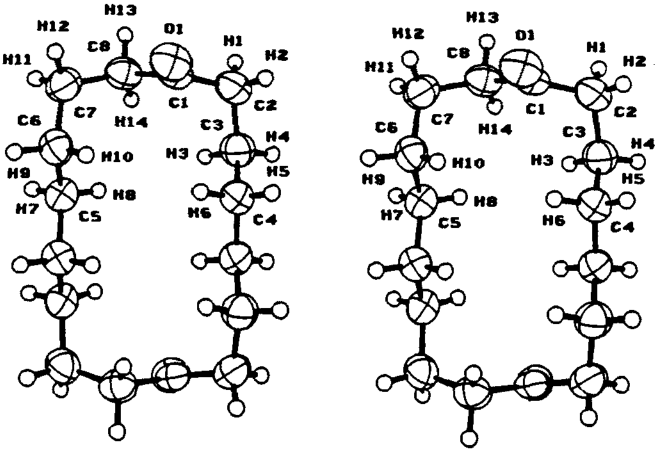


FIGURE 1 Stereodiagram of the conformation of diketone **1a** in the solid state.

Owing to its C_2 molecular symmetry, there are only two abstractable γ-hydrogen atoms to consider in analyzing the solid state photochemistry of compound **1a**. The first of these, H10, lies 2.72 Å from O1, and the other, H6, is situated at a distance of 2.99 Å from O1. On the basis of distance alone, one would expect H10 to be abstracted preferentially in the crystalline phase below 37°, and this is precisely the experimentally observed result; H10 is located on the longer methylene chain of **1a**, and abstraction of this hydrogen atom leads to the observed solid state photoproduct **2**. It is interesting to note that the C=O···H distance of 2.72 Å is exactly the sum of the van der Waals radii of hydrogen and oxygen (1.20 Å + 1.52 Å).[15]

As has been emphasized by Wagner, however, distance is not the only factor to be considered in analyzing hydrogen atom abstractability - the angular relationship between the abstracted and abstracting atoms is also important.[16] There are three angles that may be defined: ω, the degree to which the hydrogen atom lies outside the mean plane of the carbonyl group; Δ, the C=O···H angle and θ, the C-H···O angle.[17] Values of these three angles for hydrogen atoms H6 and H10 are given in Table 2 along with the hypothetical "ideal" values predicted on the basis of abstraction by the in-plane n-orbital of the carbonyl oxygen atom. As can be seen from the data, H10 wins out on angular grounds as well as distance considerations, and it is thus perfectly reasonable that this is the abstracted hydrogen atom.

Compound **1a** represents the *second* example in which the regioselectivity of solid state hydrogen atom abstraction has been correlated with crystal structure-derived geometric parameters. The first, also reported from our laboratory,[9] concerns the diametric macrocyclic diketone 1,14-cyclohexacosanedione. In this molecule we were able to show that abstraction involving a distance, *d*, of 2.74 Å with ω = 49°, Δ = 85° and θ = 115° was preferred over that in which *d* = 3.26 Å, ω = 57°, Δ = 58° and θ = 100°. Here, all four parameters favor abstraction of the same hydrogen atom.

Table 2 Values of ω, Δ and θ for H6 and H10 with respect to O1.

Angle	Ideal Value	H6 Value	H10 Value
ω	0°	59°	53°
Δ	90-120°	66°	81°
θ	180°	117°	116°

It should not be concluded from these results that hydrogen abstraction is limited to hydrogen atoms that lie at or near the sum of the van der Waals radii from their abstracting partners. We have shown that values of *d* as unfavorable as 3.1 Å (albeit with relatively favorable τ and Δ values) can be tolerated in the solid state,[7] and this remains our best current estimate of the approximate upper limit to intramolecular hydrogen atom abstraction by ketonic oxygen.

Having satisfactorily explained the solid state regioselectivity, we close with a brief discussion of the solid state chemoselectivity (cyclization preferred over cleavage) and stereoselectivity (cis-cyclobutanol preferred over trans). In these cases, too, the conformation of compound **1a** in the solid state is of paramount importance.

The preference for cyclobutanol formation in the solid state photochemistry of diketone **1a** can be related to the geometry of the biradical that would be formed assuming that hydrogen abstraction occurs in the crystalline phase with minimal conformational changes (topochemical postulate). On this basis, abstraction of H10 would produce a 1,4-biradical whose p-orbitals at C1 and C6 are out of alignment with the C7-C8 bond by 66° and 26°, respectively.[18] Since there seems to be more or less general agreement that cleavage of 1,4-biradicals requires a parallel alignment of the central carbon-carbon bond with the participating p-orbitals,[19] it is not surprising that the biradical leading to photoproduct **2** prefers to cyclize rather than cleave, particularly in view of the close proximity of the two p-orbitals to one another in this arrangement. In solution and in the higher temperature solid phases, on the other hand, reaction from alternative diketone conformers as well as possible conformational isomerization of the intermediate 1,4-biradicals allows for better pi-sigma overlap and leads to a greater degree of type II elimination (cleavage). A similar analysis correctly accounts for the preference for type II photocyclization in the solid state photochemistry of the diametric macrocyclic diketones.[8,9]

Regarding the stereoselectivity of the solid state photoreaction of diketone **1a** (cis-cyclobutanol favored over trans), inspection of the stereodiagram in Figure 1 reveals that the abstracting oxygen atom O1 and the nonabstracted γ-hydrogen atom H9 bear a syn relationship to each other, and assuming a least motion (topochemical) process involving retention of configuration at C1 and C6, the hydroxyl group and H9 will end up cis to one another in the photoproduct as is observed experimentally (photoproduct **2**). Here, too, a similar analysis correctly accounts for the stereoselectivity of the solid state photocyclization reactions in the diametric diketone series.[8,9] In less restrictive media, the starting material and the biradical intermediates (both diametric and non-diametric) have time to explore other conformations which can lead to a preference for the presumably less strained trans-cyclobutanols (e.g., **4** and **5**) over their cis-fused counterparts.

SUMMARY

The similarities between our results with the macrocyclic diketones and the classic studies of Schmidt and co-workers on the solid state [2+2] photocycloaddition reactions of the cinnamic acids[20] is striking. In both cases, distance and angular requirements for photoreaction have been established, and the structure and stereochemistry of the products are directly and simply related to the molecular and crystal structures of the reactants as determined by X-ray diffraction methods. The values of d, ω, Δ and θ reported in the present study are, of course, *ground state* values and probably differ somewhat from the corresponding excited state parameters owing to changes in equilibrium geometry that accompany absorption of a photon. Nevertheless, they will doubtless serve as useful guidelines for predicting success in type II photochemistry - predictions that can be made quickly and simply using readily available and inexpensive MM2 type calculations.

ACKNOWLEDGMENTS

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12. Crystal structure data for diketone **1a**: monoclinic, C2/c, a = 19.539(1) Å, b = 8.0133(8) Å, c = 9.9005(6) Å, β = 98.628(6)°, Z = 4, R = 0.030. Crystal structure data for photoproduct **2**: triclinic, $P\bar{1}$, a = 9.1859(6) Å, b = 11.4458(9) Å, c= 8.2045(9) Å, α = 98.384°, β = 116.028(6)°, γ = 89.640(7)°, Z = 2, R = 0.039. Crystal structure data for photoproduct **3**: monoclinic, $P2_1/n$, a = 9.3267(8) Å, b = 9.801(1) Å, c = 16.7840(9) Å, β = 101.351(6)°, Z = 4, R = 0.036. Full details will be published separately.

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