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CRYSTAL ENGINEERING IN THE SOLID STATE PHOTOCHEMISTRY OF CYCLOHEXENONES

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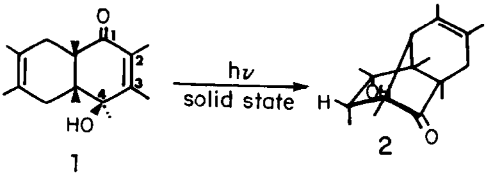
Abstract. Previous results from our laboratory plus a simple conformational analysis argument lead to the prediction that irradiation of cyclohexenone 1 in the solid state will give ketol 2. An independent synthesis of 2 plus a determination of the solid state conformation of 1 by X-ray crystallography show this prediction to be correct.

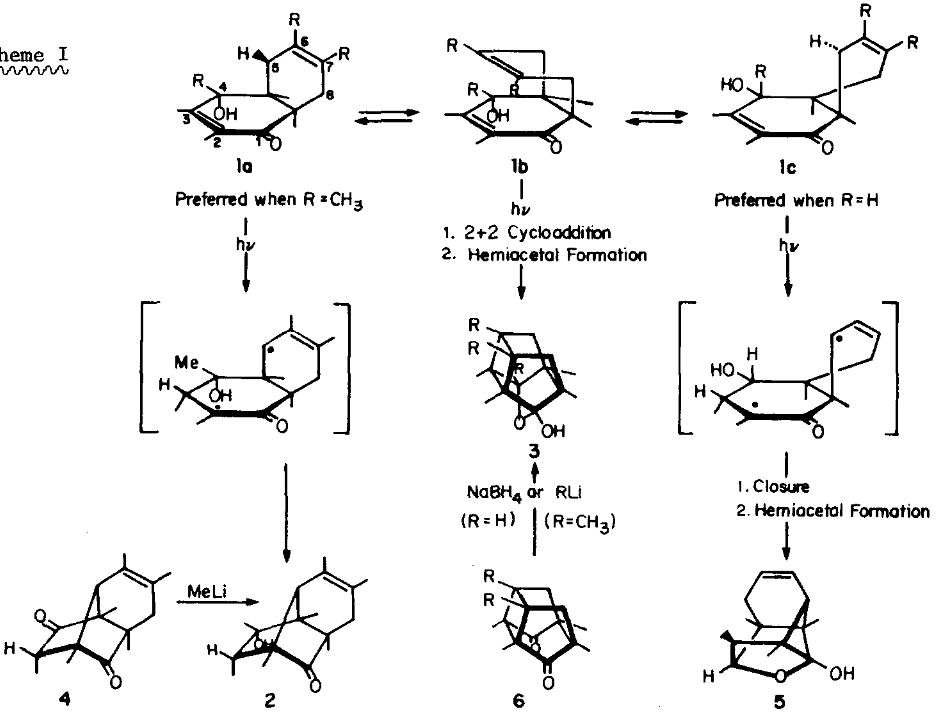
Crystal engineering refers to the design and synthesis of molecules for which there is some *a priori* reason to expect the adoption of a given crystal lattice arrangement which will in turn predispose the system toward a specific solid state reaction.[1] This has met with relatively limited success in the case of bimolecular reactions because of the difficulty involved in predicting nearest neighbor orientations in molecular crystals.[2] In principle, reactivity predictions should be easier to make for unimolecular processes because (1) *conformation* rather than intermolecular orientation is often the controlling factor, and (2) with very few exceptions, organic molecules crystallize in their lowest energy conformations which are predictable using the principles of conformational analysis. In this communication we show how we have used previous results from our laboratory plus a very simple conformational argument to correctly predict for the first time the course of a unimolecular solid state photorearrangement, namely the stereospecific formation of tricyclic keto-alcohol 2 from cyclohexenone 1.



This prediction was based on our previous observation[3] that altering the configuration at C(4) in analogues of **1** changes the solid state photoproducts formed. This led to the idea that the bulkier of the two groups at C(4) adopts the pseudo-equatorial position which in turn determines the preferred conformation of the molecule in the solid state and hence governs the photochemistry. Our previous work[3] involved hydrogen versus hydroxyl at C(4). The present paper corroborates the theory with hydroxyl versus methyl, i.e., cyclohexenone **1**.

Cyclohexenone **1**, mp 156-157°, is readily available by treatment of the corresponding ene-dione[4] with methyllithium. This produces both C(4) epimers (ratio ca. 1:1) from which **1** can be separated by fractional crystallization from cyclohexane-ethyl acetate. Either direct or benzophenone-sensitized irradiation (λ > 330 nm) of **1** in benzene leads to very high yields of the cage compound **3** (Scheme I).[5] In contrast, photolysis (λ > 330 nm, 95% conversion) of crystals of **1** at -20° affords mainly **2** (75%). Some **3** (20%) is also observed in the solid state. The solid state photoproduct structure was verified by independent synthesis involving treatment of the known[6] diketone **4** with methyllithium to give **2** in 75% yield. Similarly, solution photoproduct **3** was prepared in 95% yield by treatment of diketone **6**[3] with methyllithium.

Scheme I



The photochemical results are interpreted as shown in Scheme I. The solid state conformation of cyclohexenone **1** is predicted to be **1a** in which the bulkier methyl group at C(4) is pseudo-equatorial despite an unfavorable $A^{(1,2)}$ interaction[7] with the C(3) methyl group. This prediction was verified by a single crystal X-ray diffraction study, R = 0.041 (R_w = 0.056). A computer-drawn stereodiagram of conformation **1a** (R = CH_3) is shown in Fig. 1. On the other hand, when the methyl group at C(4) is replaced by a hydrogen atom, conformation **1c** (bulkier OH pseudo-equatorial) is preferred with the result that the solid state irradiation of this material leads to hemiacetal **5**.[3]

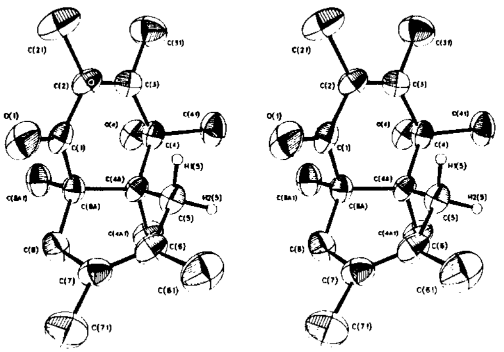


Figure 1. Stereodiagram of the conformation of cyclohexenone **1** in the solid state. The methyl hydrogen atoms have been omitted for clarity.

The photoreactions of both **1a** and **1c** are seen to involve initial allylic hydrogen abstraction by the β-carbon atom of an α,β-unsaturated enone moiety followed by coupling of the biradicals so produced. In the case of **1a**, abstraction occurs through a five-membered transition state, whereas for **1c**, a six-membered transition state is involved. In both instances however, the β-carbon to allylic hydrogen abstraction distances are nearly the same, 2.81(2) Å for **1a** (R = CH_3) and 2.84(4) Å for **1c** (R = H). Both values lie within the suggested[8] van der Waals radii sum limit of 2.90 Å for abstraction of hydrogen by carbon.

The formation of [2+2] cage compounds from the irradiation of dienones analogous to **1** in solution appears to be general.[3,9] We attribute their formation to rapid photocycloaddition from minor conformational isomers (e.g., **1b**, Scheme I) in which the reacting double bonds are favorably oriented. Photocycloaddition from **1a** or **1c** is geometrically impossible without extensive molecular motion and hence is disfavored in the solid state. The amount of internal cycloaddition which *is* observed in the solid state (ca. 20% at -20°) decreases with decreasing temperature and extent of conversion which lends support to the idea that this "topochemically disallowed" photoproduct is formed in regions of local melting within the crystal. Lowering the temperature below -20°, while increasing the abstraction:cycloaddition ratio, also necessitates the use of longer reaction times to achieve the same degree of conversion.

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