

Enhanced Regioselectivity of Yang
Photocyclization in the Crystalline State

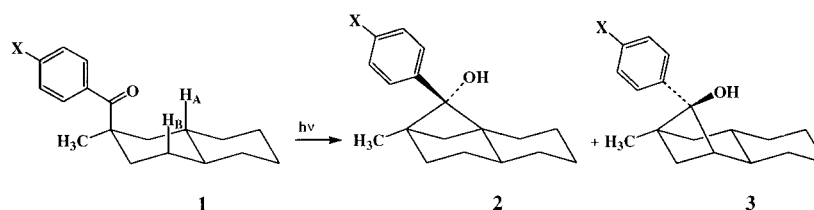
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Received November 27, 2001 (Revised Manuscript Received February 13, 2002)

ABSTRACT

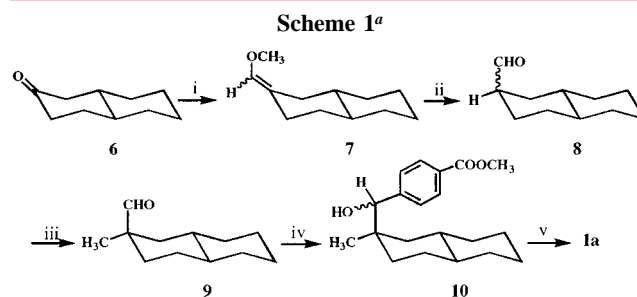


In contrast to the solution state, where Yang photocyclization of ketones of general structure **1** leads to equal amounts of cyclobutanols **2** and **3** (by abstraction of H_A and H_B , respectively), irradiation in the crystalline state is much more regioselective, favoring either **2** or **3** depending on the nature of the substituent X . X-ray crystallography and molecular mechanics calculations reveal the source of this remarkable solid-state regioselectivity.

Owing to the reversibility of initial hydrogen atom transfer in the Norrish type II reaction,¹ the structures of the final photoproducts formed in solution do not necessarily reflect abstraction of the stereoelectronically favored hydrogen. A well-known case in point is cyclodecanone, which yields photoproducts derived from ϵ -hydrogen abstraction in benzene² and affords typical γ -hydrogen abstraction products upon photolysis in *tert*-butyl alcohol.³ For reactions conducted in the crystalline state, however, recent work from our laboratory,⁴ as well as some results of Wagner et al.,⁵ strongly suggest a direct correlation between hydrogen abstractability and product structure. In the present Letter, we describe experiments designed to test this correlation further.

The compounds chosen for study were *trans*-2-decalyl aryl ketones of general structure **1**, whose synthesis is outlined in Scheme 1. This choice was based on the availability in 1

of two nonequivalent, potentially abstractable γ -hydrogen atoms—the more reactive (by a factor of 3–4)⁶ tertiary hydrogen atom H_A and the secondary axial hydrogen atom H_B . The goal of the present investigation was to determine the regioselectivity of Yang photocyclization⁷ of such ketones in solution and in the solid state and to correlate this with their structure as determined by X-ray crystallography and molecular mechanics calculations.

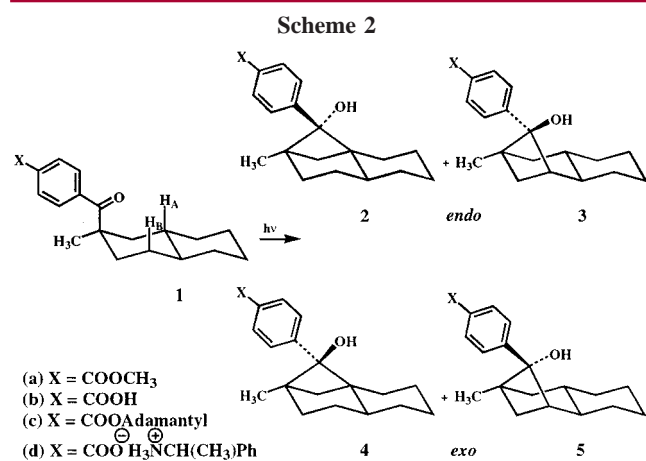


- (1) Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898.
 (2) Bernard, M.; Yang, N. C. *Proc. Chem. Soc.* **1958**, 302.
 (3) Sauer, R. R.; Huang, S.-Y. *Tetrahedron Lett.* **1990**, *31*, 5709.
 (4) (a) Gudmundsdottir, A. D.; Lewis, T. J.; Randall, L. H.; Scheffer, J. R.; Rettig, S. J.; Trotter, J.; Wu, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 6167.
 (b) Leibovitch, M.; Olovsson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755. (c) Cheung, E.; Kang, T.; Raymond, J. R.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1999**, *40*, 8729.
 (5) Wagner, P. J.; Pabon, R.; Park, B.-S.; Zand, A. R.; Ward, D. L. *J. Am. Chem. Soc.* **1994**, *116*, 589.

- ^a (i) $\text{CH}_3\text{OCH}_2\text{PPh}_3\text{Cl}$, diethyl ether, *n*-BuLi, 10–12 °C, 82%; (ii) 70% HClO_4 , H_2O , diethyl ether, reflux 1h, 88%; (iii) $(\text{CH}_3)_3\text{COK}$, DME, excess CH_3I , rt, 3 h, 84%; (iv) $\text{IC}_6\text{H}_4\text{COOCH}_3$, *i*-PrMgCl, THF, –40 °C, 1 h, 78%; (v) PCC, CH_2Cl_2 , rt, 4 h, 80%.

Recrystallization of ketone **1a** by slow evaporation of its ethyl acetate solution at room temperature afforded two types of crystals: long needles, mp 123–125 °C, and small prisms, mp 104–106 °C. The two types of crystals were separated manually under a microscope and subjected to analysis on a Chiralcel AS chiral HPLC column. The HPLC results indicated that the lower melting prisms were racemic and that the higher melting needles were a conglomerate consisting of >98% of a single enantiomer of ketone **1a**. In other words, ketone **1a** had undergone a partial spontaneous resolution.⁸ Optically pure ketone **1a** could also be prepared by hydrolysis to the corresponding carboxylic acid **1b** followed by resolution using optically pure 1-phenylethylamine and reesterification with diazomethane.

In addition to the photochemistry of ketone **1a**, we investigated the photochemical reactivity of compounds **1b–d** (Scheme 2). All four compounds underwent smooth



Yang photocyclization in the crystalline state as well as in solution. In the case of racemic ketone **1a**, irradiation in acetonitrile afforded cyclobutanols **2a**, **3a**, **4a**, and **5a** in isolated yields of 42%, 42%, 3%, and 3%, respectively. Cyclobutanols **2a** and **3a** were produced in a 1:1 ratio in *tert*-butyl alcohol as well, but in this solvent, photoproducts **4a** and **5a** were absent. Identical product distributions were obtained in the photolysis of optically pure **1a**. Table 1 summarizes the results for all four starting ketones. In every case except that of keto-acid **1b**, the **2:3** ratio in solution was 1:1; for **1b** it was 1:2.

The photochemical reactions of ketones **1a–d** in the solid state proved to be much more regioselective than their

Table 1. Results of Photolysis of Aryl Ketones **1a–d** in the Crystalline State and Solution Phase

ketone	medium	2:3 ^a
rac. 1a	acetonitrile	1:1
	crystal	2:1
opt. 1a	acetonitrile	1:1
	crystal	4.6:1
1b ^{b,c}	acetonitrile	1:2
	crystal	1:5.5
1c ^c	acetonitrile	1:1
	crystal	2.4:1
1d ^{b,d}	acetonitrile	1:1
	crystal	2:1

^a The product ratios were constant below approximately 50% conversion. At higher conversions, crystal breakdown and melting led to reduced regioselectivity. Photoproducts of type **4** or **5** were not observed in the photolysis of compounds **1b–d**, either in solution or the solid state. ^b Photolysis mixture worked up with diazomethane to form corresponding methyl esters **2a** and **3a**. ^c Racemic. ^d Single diastereomer.

solution phase counterparts. Irradiation of crystals of racemic ketone **1a** led to a **2a:3a** ratio of 2:1, which increased to 4.6:1 in the case of optically pure **1a**; no trace of photoproducts **4a** or **5a** could be detected in either photolysis. Interestingly, the **2:3** ratio was reversed to 1:5.5 in the case of crystalline keto-acid **1b**. As a result, either cyclobutanol can be obtained as the major product simply by changing the functional group on the aromatic ring.

From the ¹³C NMR attached proton test, it was a simple matter to distinguish between photoproducts of type **2** and **4** on one hand (one methine proton) and photoproducts **3** and **5** on the other (three methine protons). The complete structure and stereochemistry of the photoproducts were assigned on the basis of their spectroscopic data, particularly their NOE difference and 2D NMR spectra. These assignments were confirmed in the case of photoproducts **2a** and **3a** by X-ray diffraction studies. Compound **3a** was crystalline and could be analyzed directly;⁹ isomer **2a**, on the other hand, proved to be an oil, and it was therefore hydrolyzed and analyzed as the corresponding crystalline carboxylic acid **2b**.¹⁰ In addition to X-ray diffraction studies on photoproducts **3a** and **2b**, the crystal and molecular structure of optically pure ketone **1a** was determined (Figure 1).¹¹ Unfortunately, none of the other starting ketones formed crystals suitable for X-ray crystallography. From Figure 1 it is evident that optically pure ketone **1a** crystallizes in a conformation that favors abstraction of γ -hydrogen atom H_A, as is observed

(6) Wagner, P. J.; Kempainen, A. E. *J. Am. Chem. Soc.* **1972**, *94*, 7495.

(7) Yang photocyclization refers to the formation of cyclobutanols in Norrish type II photochemistry, a reaction that was first reported by Yang and Yang: Yang, N. C.; Yang, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913.

(8) According to Eliel and Wilen (Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 7, p 30), if the melting point of the enantiomerically pure compound exceeds that of the racemate by 25 °C or more, the probability of conglomerate formation is high. Generally, the difference in melting point is in the range 25–35 °C, although differences of 20 °C or even less are not uncommon.

(9) X-ray crystal structure **3a**: mp 172–174 °C. Prisms (from ethyl acetate), size 0.15 × 0.15 × 0.15 mm, triclinic, space group *P1*bar, *a* = 6.228(1) Å, *b* = 7.698(2) Å, *c* = 19.051(5) Å; α = 97.594(9)°, β = 95.863(4)°, γ = 110.716(2)°; *Z* = 2, *V* = 835.8(4) Å³, *R* = 0.055.

(10) X-ray crystal structure **2b**: mp 231–233 °C. Prisms (from ethyl acetate), size 0.45 × 0.20 × 0.15 mm, monoclinic, space group *P2*₁/*n*, *a* = 15.273(3) Å, *b* = 10.321(4) Å, *c* = 21.934(4) Å; β = 107.46(1)°; *Z* = 8, *V* = 3298(2) Å³, *R* = 0.051.

(11) X-ray crystal structure optically pure **1a**: mp 123–125 °C. Needles (from ethyl acetate), size 0.25 × 0.25 × 0.15 mm, orthorhombic, space group *P2*₁2₁2₁, *a* = 10.949(2) Å, *b* = 23.356(7) Å, *c* = 6.778(3) Å; *Z* = 4, *V* = 1733(1) Å³, *R* = 0.046.

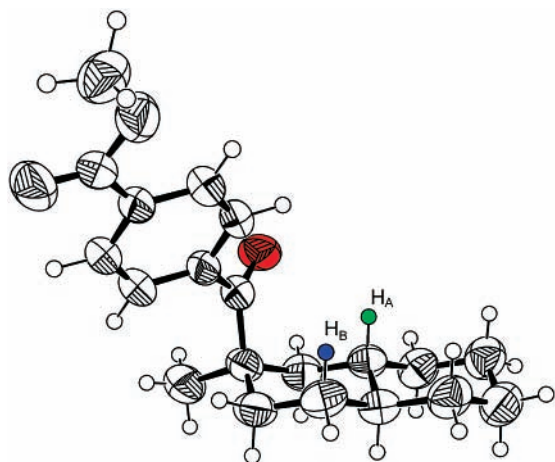


Figure 1. Solid-state conformation of optically pure ketone **1a**. Abstraction of H_A (green) by the carbonyl oxygen atom (red) is favored over abstraction of H_B (blue).

experimentally. From the crystal structure data, the precise geometric relationship between H_A and H_B and the carbonyl oxygen atom can be calculated. As summarized in Table 2,

Table 2. Crystallographically Derived $C=O\cdots H\gamma$ Geometric Parameters for Optically Active Ketone **1a**

H_A/H_B	d (Å) ^a	ω (deg) ^b	Δ (deg) ^c	θ (deg) ^d	D (Å) ^e
H_A	2.66	57	82	115	3.10
H_B	3.57	44	45	105	3.13

^a $C=O\cdots H\gamma$ distance. ^b Deviation of $H\gamma$ from the mean plane of the carbonyl group. ^c $C=O\cdots H\gamma$ angle. ^d $C-H\gamma\cdots O$ angle. ^e Carbonyl carbon-to- γ -carbon distance.

the $C=O\cdots H_A$ distance is 2.66 Å, whereas the $C=O\cdots H_B$ distance is 3.57 Å. Previous work from our laboratory¹² has shown that hydrogen atom abstraction is optimal for $C=O\cdots H$ distances close to the sum of the van der Waals radii of hydrogen and oxygen (2.72 Å), which clearly predicts preferential abstraction of H_A over H_B in the case of ketone **1a**. We note also that the value of the H_A out of plane angle ω , at 57°, is typical for successful hydrogen atom abstraction,¹² although far from the ideal value of 0°.

To gain more insight into the conformational properties of ketone **1a**, molecular mechanics calculations were carried out using the MM+ force field in Hyperchem Pro, v. 5.11. This showed that ketone **1a** has three nearly isoenergetic conformers within 0.3 kcal/mol of one another, the highest energy conformer of the three being essentially identical to that formed in the solid state (calculated $C=O\cdots H_A = 2.70$ Å; $C=O\cdots H_B = 3.70$ Å).¹³ On the other hand, the global minimum energy conformer has the structure shown in

(12) Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.

(13) Computer overlap of the X-ray structure with the calculated structure gives an average root-mean-square deviation between the two of 0.069 Å.

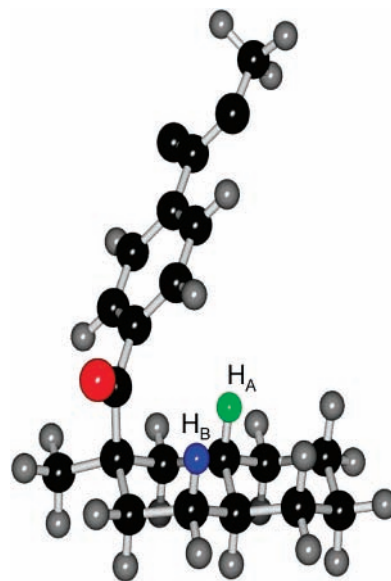


Figure 2. Calculated global minimum energy conformation of ketone **1a**. Abstraction of H_B (blue) by the carbonyl oxygen atom (red) is favored over abstraction of H_A (green).

Figure 2, which clearly predicts abstraction of H_B (calculated $C=O\cdots H_A = 3.63$ Å; $C=O\cdots H_B = 2.73$ Å). The third conformer differed only slightly from the global minimum and also favored abstraction of H_B . Similar results were obtained from MM+ calculations on ketones **1b** and **1c**.

Combining the photochemical results with the crystallographic and molecular mechanics data, the following structure–reactivity picture emerges. Like ketone **1a**, compounds **1c** and **1d** afford cyclobutanols derived from abstraction of H_A as the major solid-state photoproducts and may reasonably be assumed to crystallize in and react via nonminimum energy conformations similar to that shown in Figure 1. Although most organic compounds crystallize in minimum energy conformations, when two conformers are very close in energy, as they are in this case, crystal lattice packing effects can overcome intrinsic conformational energy as the conformation-determining factor.¹⁴

In a similar fashion, matching the observed regioselectivity of solid-state hydrogen abstraction to the regioselectivity predicted on the basis of molecular mechanics calculations leads to the reasonable conclusion that keto-acid **1b** crystallizes in and reacts from a global minimum energy conformation similar to that shown in Figure 2. We can only speculate that the reason compounds **1a**, **1c**, and **1d** on one hand and **1b** on the other crystallize in different conformations is that carboxylic acid dimer formation may be facilitated during

(14) This is necessarily the case in the phenomenon of conformational polymorphism, whereby a given substance crystallizes in two or more different conformations as well as packing arrangements. For a discussion of conformational polymorphism, see: Bernstein, J. In *Organic Solid State Chemistry*; Desiraju, G. R., Ed.; Elsevier: Amsterdam, 1987; Chapter 13, pp 471–518. For an example of conformational dimorphs that undergo different photochemical reactions in the crystalline state, see: Lewis, T. J.; Rettig, S. J.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1991**, *113*, 8180.

crystallization of keto-acid **1b** in its global minimum energy conformation.

The structure–reactivity relationships developed above also account very nicely for the *diastereoselectivity* of the photoreactions, i.e., for the prevalence of photoproducts of type **2** and **3** over photoproducts of type **4** and **5**. This can be understood by reference to Figures 1 and 2, which are representative of the conformations of ketones **1a** and **1b** in the crystalline state. In the case of ketone **1a** (Figure 1), abstraction of H_A followed by least motion closure of the resulting 1,4-hydroxybiradical *with retention of configuration at the carbonyl carbon* leads directly to the experimentally observed major photoproduct, *endo*-arylcyclobutanol **2a**. Formation of its diastereomer, **4a**, would require the 1,4-hydroxybiradical to undergo an approximate 180° rotation around the C₁–C₂ bond, a process that is topochemically forbidden in the crystalline state and is evidently slow relative to C₁–C₄ bond formation in solution as well.¹⁵ A similar analysis applies to the preference for formation of diastereomer **3b** over **5b** in the solid-state photolysis of keto-acid **1b**. Here, as can be seen by reference to Figure 2, abstraction of H_B followed by biradical closure with retention of configuration at the carbonyl carbon leads naturally and directly to the topochemically allowed *endo*-aryl isomer **3b**. As above, formation of the unobserved diastereomer, **5b**, which requires an approximately 180° rotation about C₁–C₂ at the biradical stage, is prohibited by the rigid, close-packed environment of the crystal.

Finally, we address the question of what the present results tell us about the regioselectivity of Yang photocyclization in the crystalline state relative to that in solution. The data summarized in Table 1 clearly indicate a much higher regioselectivity in the crystalline state. This is consistent with the solid-state structure–reactivity relationships developed above in which the crystal contains a single conformer whose

(15) For analogous examples in which a similar analysis applies, see ref 4b.

photolysis can give rise to abstraction of only one of the two γ -hydrogen atoms and the eventual formation of a single photoproduct. Even if reverse hydrogen transfer did occur in the crystal (and there is no reason to think that it does not), it would simply regenerate the original conformer, which has only one course of action open to it. In solution, on the other hand, equilibrium between conformers such as those shown in Figures 1 and 2 is undoubtedly established during the excited triplet state lifetime, which means that abstraction of both H_A and H_B is possible in the course of a given photolysis. In this case the final photoproduct ratio is a complex function of the partitioning of the two 1,4-hydroxybiradicals between closure and reverse hydrogen transfer.

To summarize, the present investigation has shown that Yang photocyclization reactions which show no regioselectivity whatsoever in solution can be made highly regioselective by conducting the reactions in the crystalline state. Unlike the situation in solution, where equilibration among conformers is rapid, leading to indiscriminate abstraction of nonequivalent γ -hydrogens, X-ray crystallography and molecular mechanics calculations reveal that solid-state regioselectivity stems from crystallization of the substrate in a single, fixed, and substituent-dependent conformation whose geometry permits abstraction of only one of two potentially abstractable γ -hydrogen atoms, thus leading to a single cyclobutanol.

Acknowledgment. Financial support by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

Supporting Information Available: Typical photolysis procedures, workup methods, and NMR characterization of photoproducts. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL017134H