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Photochemistry of 1-Isopropylcycloalkyl Aryl Ketones: Ring Size Effects, Medium Effects, and Asymmetric Induction

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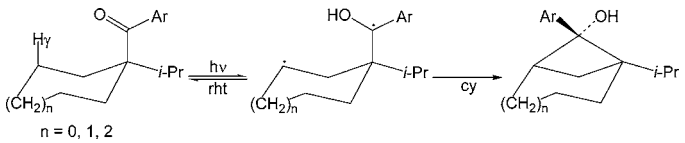
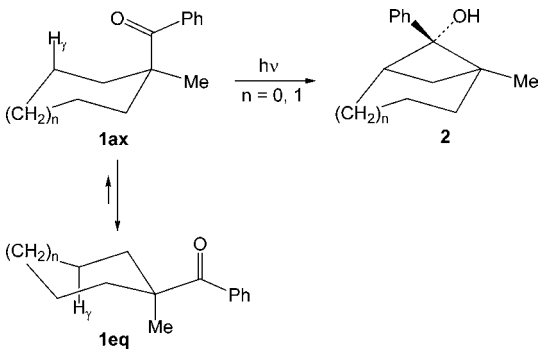
ABSTRACT



The *n* = 0, 1, and 2 ketones shown above undergo Yang photocyclization in solution, but only the *n* = 1 analogues react this way in the solid state. Based on X-ray crystallography, these differences in reactivity are attributed to an unusually large distance for 1,4-hydroxybiradical cyclization in the solid state for the *n* = 0 and 2 ring systems, which leads to predominant reverse hydrogen transfer (rht). Enantiomeric excesses of up to 99% can be achieved in the case of the *n* = 1 system through the use of the solid-state ionic chiral auxiliary method of asymmetric synthesis.

In an important 1974 publication, Lewis, Johnson, and Johnson reported the solution-phase photochemistry of 1-methylcyclopentyl phenyl ketone (**1**, *n* = 0) and 1-methylcyclohexyl phenyl ketone (**1**, *n* = 1).[1] In solution, both compounds were shown to undergo Yang photocyclization[2] via their axial and pseudoaxial conformers (**1ax**) to afford the corresponding cyclobutanols (**2**, *n* = 0, 1) (Scheme 1). These reactions, which convert achiral reactants into chiral products, appeared to be ideal for studying asymmetric induction in organic photochemistry, and motivated by the paucity of general methods of asymmetric photochemical synthesis,[3] we embarked on a program designed to achieve this goal.

Scheme 1



The plan was to use the solid-state ionic chiral auxiliary method of asymmetric synthesis developed in our laboratory over the past several years.[4] In this procedure, the reactant is equipped with a carboxylic acid substituent to which an optically pure ammonium ion (the ionic chiral auxiliary) is attached by means of a salt bridge. Such salts are required

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(1) Lewis, F. D.; Johnson, R. W.; Johnson, D. E. *J. Am. Chem. Soc.* **1974**, *96*, 6090.

(2) Yang cyclization refers to cyclobutanol formation in the Norrish type II reaction and was first reported by: Yang, N. C.; Yang, D. H. *J. Am. Chem. Soc.* **1958**, *80*, 1958. For a recent review, see: Wagner, P. J. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, 2004; Chapter 58-1.

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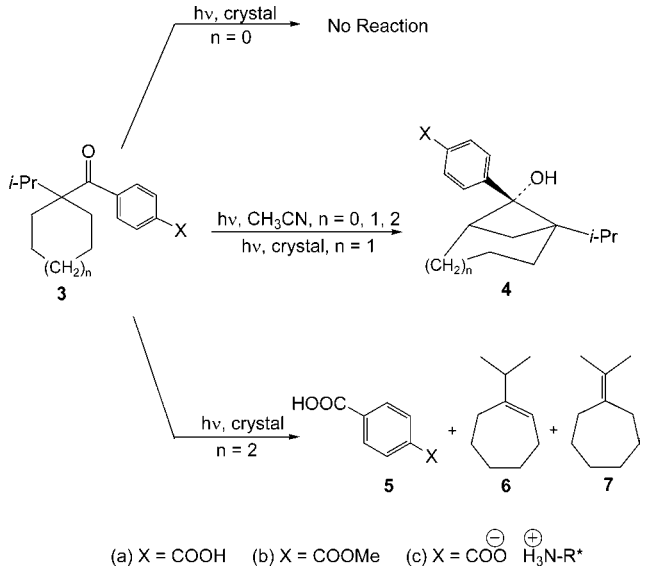
to crystallize in chiral space groups, which provide the asymmetric environment responsible for chiral induction when the compounds are photolyzed in the solid state.

A second requirement for the success of the solid-state ionic chiral auxiliary method of asymmetric synthesis is that the reactant must crystallize in a conformation favorable for reaction. For photochemical reactions involving intramolecular hydrogen atom abstraction, this requires a conformation in which the carbonyl oxygen is within approximately 2.7 ± 0.2 Å of a γ-hydrogen atom.[5,6] This presented a problem in the case of ketones **1** (n = 0, 1) because the photochemically reactive conformers **1ax** are not the minimum energy conformers[1] and are therefore not likely to be present in the crystalline state.[7] Molecular mechanics calculations, however, indicated that a simple change of the α-methyl group in ketones **1** (n = 0, 1) for the bulkier isopropyl group would favor conformers having axial or pseudoaxial ketone substituents, and for this reason, the compounds chosen for study were the α-isopropyl-containing ketones **3** (n = 0, 1) as well as the corresponding seven-membered ring homologue (n = 2) (Scheme 2).[8] In this

Scheme 2



paper, we report the contrasting solution-phase and solid-state photochemical behavior of these compounds as well as highly successful asymmetric induction in the solid-state photochemistry of salts of ketone **3a** (n = 1).

The required starting materials were synthesized by LDA-induced alkylation of methyl cyclopentane-, cyclohexane-, and cycloheptanecarboxylate with 2-bromopropane followed by appropriate functional group modification of the ester substituent. Prior to the solid-state studies, the photochemistry of keto esters **3b** (n = 0, 1, 2) was investigated in solution. In each case, irradiation through Pyrex in acetonitrile produced the corresponding cyclobutanol (**4b**, n = 0, 1, 2) in excellent chemical yield (>95% by GC). These photoproducts were isolated by column chromatography and fully characterized by 1D ^{1}H, 1D NOE and ^{13}C (BB and APT) NMR, 2D ^{1}H-^{1}H COSY, ^{1}H−^{13}C HMQC and HMBC NMR, FT-IR, HRMS, as well as by elemental analysis. The cyclobutanols were found to have the same general structure and stereochemistry as those reported by Lewis et al. for cyclobutanols **2** (n = 0, 1).[1]

Turning now to the solid-state studies, irradiation of crystals of keto ester **3b** (n = 1) led exclusively to cyclobutanol **4b** (n = 1), the same product formed in acetonitrile. In the case of the n = 0 and 2 keto esters, however, there was a striking difference between the results obtained in solution and those observed in the crystalline state. No products were detectable by GC following photolysis of crystals of keto ester **3b** (n = 0), and solid-state photolysis of keto ester **3b** (n = 2) led to the formation of Norrish type I products **5b**, **6**, and **7** (Scheme 2).[9] In neither case were any cyclobutanol-type photoproducts formed.

Additional solid-state photochemical studies were carried out on salts prepared from keto acids **3a** (n = 0, 1, 2) and a variety of optically pure primary and secondary amines. The procedure consisted of crushing ca. 5 mg of each salt between two Pyrex microscope slides, taping the plates together, sealing the resulting sandwiches under nitrogen in polyethylene bags, and irradiating the ensembles on both sides for varying lengths of time by using a 450 W medium-pressure mercury lamp. Following photolysis, the samples were treated with ethereal diazomethane to form the corresponding methyl esters and subjected to GC and chiral HPLC analysis. The results were identical with those obtained when keto esters **3b** (n = 0, 1, 2) were photolyzed in the crystalline state, namely, no observable reaction for the 5-ring salts, formation of cyclobutanol **4b** in the case of the 6-ring salts, and Norrish type I cleavage for the 7-ring salts.

Table 1 shows the enantiomeric excess (ee) in which cyclobutanol **4b** (n = 1) was formed in the solid-state photolysis of salts of keto acid **3a** (n = 1). A total of 10 salts was investigated, of which four gave ee values greater than 90%. Strikingly, two of these (the (*R*)-(−)-1-aminoindan and the (*S*)-(−)-1-*p*-tolylethylamine salts), led to essentially

(3) For recent reviews dealing with asymmetric induction in organic photochemistry, see: (a) Griesbeck, A. G.; Meierhenrich, U. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3147. (b) Toda, F.; Tanaka, K.; Miyamoto, H. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 2001; Volume 8; Chapter 6. (c) Everitt, S. R. L.; Inoue, Y. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1999; Vol. 3, Chapter 2. (d) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3419.

(4) Reviews: (a) Scheffer, J. R. *Can. J. Chem.* **2001**, *79*, 349. (b) Scheffer, J. R. In *Molecular and Supramolecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 2004; Vol. 11, pp 463−483.

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

(6) A third general requirement for successful solid-state reaction is that the motions involved be compatible with the surrounding crystal lattice. For a quantitative treatment of this aspect of solid-state photochemistry, see: Zimmerman, H. E.; Nesterov, E. E. *Acc. Chem. Res.* **2002**, *35*, 77.

(7) Supporting this contention, ketone **1** (n = 1) was found to be photochemically unreactive in the solid state, presumably because it crystallizes in conformation **1eq**.

(8) Competitive abstraction of a primary γ-hydrogen atom from the isopropyl group was not expected to be a problem, and this proved to be the case.

(9) Methyl terephthalate (**5b**) is presumably formed by air oxidation of the corresponding aldehyde during workup.

Table 1. Enantiomeric Excess of Photoproduct **4b** ($n = 1$) from Solid-State Photolysis of Chiral Salts of Keto Acid **3a** ($n = 1$)

amine	T (°C)	conv (%)	ee (%)	[α][a]
(*R*)-(−)-1-aminoindan	rt	32	99	+
	rt	71	99	
	rt	100	99	
(*S*)-(−)-1-*p*-tolylethylamine	rt	43	99	+
	rt	100	99	
(1*S*,2*S*)-(+)-pseudoephedrine	rt	81	98	−
	rt	99	91	
	−20	100	98	
(1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol	rt	95	94	+
	−20	63	98	
L-prolinamide	rt	63	41	*b*
	−20	56	49	
(1*R*,2*R*)-(−)-2-amino-1-phenyl-1,3-propanediol	rt	95	13	*b*
	−20	100	53	
(*S*)-(+)-2-pyrrolidinemethanol	rt	75	11	*b*
	−20	61	28	
(*R*)-(−)-1-cyclohexylethylamine	rt	98	5	*b*
	−20	100	7	
(*S*)-(−)-*N*-methyl-1-phenylethylamine	rt	66	11	*b*
	rt	100	6	
(*S*)-(−)-1-phenylethylamine	−20	100	1	*b*

[a] Sign of rotation at the sodium D line. [b] Not measured.

quantitative ee values at 100% conversion, a result that illustrates the synthetic utility of the method.

With the photochemical results in hand, we next turned to X-ray crystallography to help elucidate the observed solid state/solution phase reactivity differences as well as to provide a rationale for the asymmetric induction results. Successful X-ray crystal structure determinations were carried out for keto ester **3b** ($n = 0$), the 1-*p*-tolylethylammonium salts of keto acids **3a** ($n = 1$) and **3a** ($n = 2$), and the 1-phenylethylammonium salt of keto acid **3a** ($n = 1$).[10] In accord with the molecular mechanics based conformational analysis of these systems discussed above, in each case there was a C═O···H_γ contact within the 2.7 ± 0.2 Å range established for successful γ-hydrogen atom abstraction.[5] A significant finding was that the carboxylate anion of the 1-phenylethylammonium salt of keto acid **3a** ($n = 1$) contained equal amounts of two independent, mirror image-related conformers in the crystal lattice, a phenomenon we have termed conformational enantiomerism.[11] For the other three compounds, the crystal contained a single conformational enantiomer of the reactant. An ORTEP drawing of each solid-state conformer is given in Figure 1.

Conformational enantiomerism is undoubtedly the source of the low ee resulting from irradiation of the (*S*)-(−)-1-phenylethylammonium salt of keto acid **3a** ($n = 1$) in the solid state (last entry, Table 1); half the molecules in the crystal react to give one enantiomer of cyclobutanol **4b** while the other half lead to its optical antipode. The mechanism involves selective abstraction of the nearer γ-hydrogen atom,[12] leading to a 1,4-hydroxybiradical that closes to a single enantiomer of cyclobutanol **4b**.[13] A perfect racemate

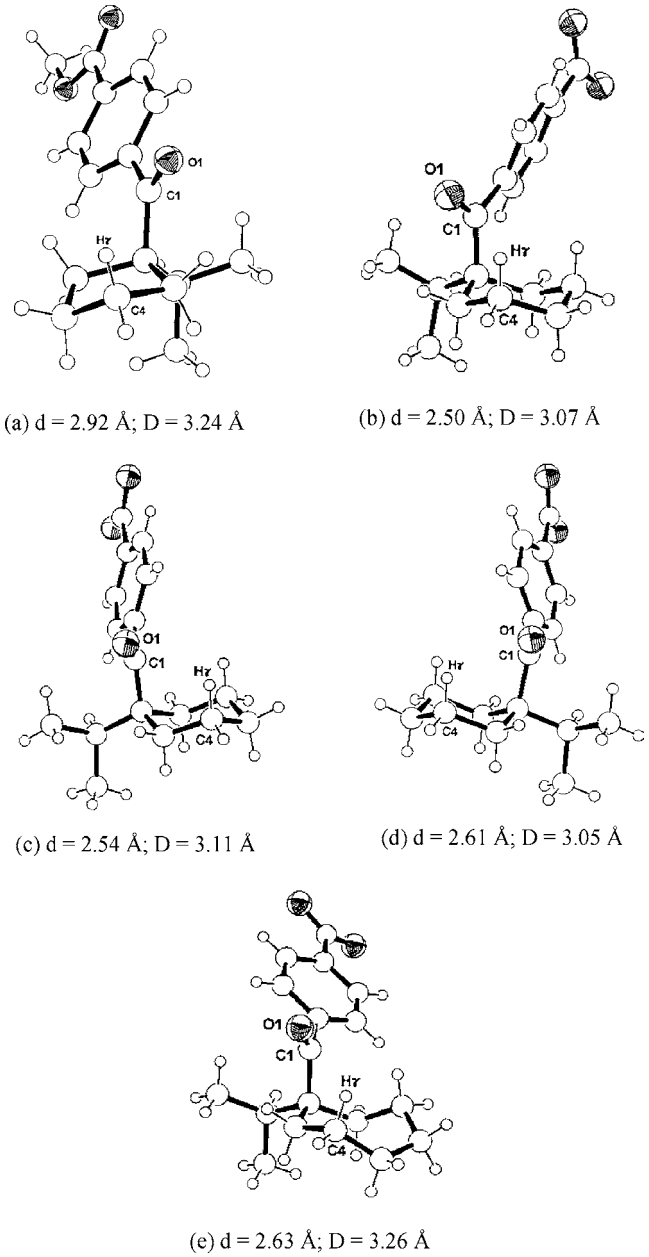


Figure 1. Solid-state conformations of (a) keto ester **3b** ($n = 0$), (b) 1-*p*-tolylethylammonium salt of keto acid **3a** ($n = 1$), (c) 1-phenylethylammonium salt of keto acid **3a** ($n = 1$), (d) conformational enantiomer of salt (c), (e) 1-*p*-tolylethylammonium salt of keto acid **3a** ($n = 2$). The letter *d* indicates the closest O1···H_γ abstraction distance, and *D* indicates the C1···C4 cyclization distance.

(10) CCDC 260763−260766 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) (a) Cheung, E.; Kang, T.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **2000**, *122*, 11753. (b) Natarajan, A.; Wang, K.; Ramamurthy, V.; Scheffer, J. R.; Patrick, B. *Org. Lett.* **2002**, *4*, 1443. We note that such conformational enantiomers can also be considered as conformational diastereomers when the presence of the optically pure ammonium ion is taken into account.

(12) See the Supporting Information for a full listing of all hydrogen abstraction distances and geometries.

is not formed because the two conformers are not exact mirror images of one another. The abstraction distances are slightly different (2.54 and 2.61 Å), and for this reason the independent, mirror image-related conformers react at slightly different rates. This interpretation is supported by the results observed in the case of the (*S*)-(−)-*p*-tolylethylamine salt of keto acid **3a** ($n = 1$) (second entry, Table 1). Here the crystal contains a single conformational enantiomer of the carboxylate anion, and all of the molecules in the crystal react to form the same enantiomer of cyclobutanol **4b**, thereby leading to a high ee. These general reactivity patterns have been found to apply to a number of other Yang photocyclization reactions studied by the solid-state ionic chiral auxiliary method.[4]

Finally, we turn to a discussion of the possible reasons for the unusual solid-state photochemical behavior of the cyclopentyl and cycloheptyl systems. One possible explanation for the fact that these compounds do not form cyclobutanol photoproducts in the crystalline state is that hydrogen atom abstraction fails for some reason. This is unlikely, however, because the abstraction distances and geometries in these cases are as good as or better than those of dozens of compounds known to react in the solid state.[14]

We propose instead that cyclobutanol formation is not observed in these cases because the cyclization distance, *D* (the distance between the radical centers in the 1,4-hydroxybiradical), is too great. Making the reasonable assumption that hydrogen abstraction occurs with minimum movement of the associated heavy atoms,[15] the value of *D* can be approximated by the distance between the carbonyl carbon and the γ-carbon in the ground state. From X-ray crystallography, these distances are 3.24 and 3.26 Å for the cyclopentyl and cycloheptyl compounds and 3.07 Å for the cyclohexyl homologue. With hydrogen atom transfer known to be reversible, both in solution[16] and the solid state,[15] these numbers suggest that when D is greater than approximately 3.2 Å, the rate of cyclization is slowed to the point that it cannot compete with reverse hydrogen transfer. As a result, the cyclopentyl systems appear to be photochemically inert and the cycloheptyl systems undergo competitive Norrish type I photochemistry.[17]

(13) The diastereoselectivity of this reaction is the result of least motion closure with "retention" at the carbonyl carbon, a general feature of Yang photocyclization reactions in the crystalline state.[4]

(14) Scheffer, J. R. In *Molecular and Supramolecular Photochemistry: Chiral Photochemistry*; Ramamurthy, V., Inoue, Y., Eds.; Marcel Dekker: New York, 2004; Vol. 11, pp 463−483.

(15) Chen, S.; Cheung, E.; Filson, H.; Netherton, M. R.; Patrick, B. O.; Scheffer, J. R.; Scott, C.; Xia, W.; Braga, D.; Maini, L. *J. Am. Chem. Soc.* **2004**, *126*, 3511.

(16) Wagner, P. J. *J. Am. Chem. Soc.* **1967**, *89*, 5898.

Support for this interpretation comes from published and unpublished work from our group on compounds that unexpectedly failed to undergo Norrish/Yang type II photochemistry in the crystalline state despite having favorable hydrogen atom abstraction geometries. The data are presented graphically in Figure 2, and it is clear that the "unreactive"

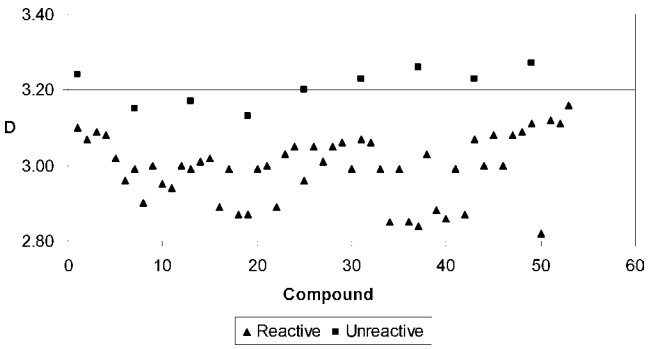


Figure 2. Values of *D* for reactive and unreactive ketones.

systems have *D* values centered around 3.2 Å (3.2 ± 0.05 Å) while the reactive compounds have *D* values in the range of 3.0 ± 0.09 Å.[18] The fact that the cyclopentyl and cycloheptyl systems undergo smooth cyclobutanol formation in solution emphasizes the point that the 3.2 Å upper limit to biradical cyclization applies only in the crystalline state. In solution, where the biradicals have sufficient lifetime to explore alternative conformations with reduced *D* values, cyclization can once again become competitive with reverse hydrogen transfer. Work is ongoing in our laboratory to provide further experimental evidence on the validity of this hypothesis.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

Supporting Information Available: Synthesis of starting ketones, photolysis procedures, characterization of photoproducts, table of hydrogen abstraction distances and geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Still unresolved is the question of why the cycloheptyl systems undergo type I photochemistry in the solid state whereas the cyclopentyl systems do not.

(18) The compounds from which the data in Figure 2 are taken are given in the Supporting Information.