

## Determination of the Absolute Steric Course of an Enantioselective Single Crystal-to-Single Crystal Photorearrangement

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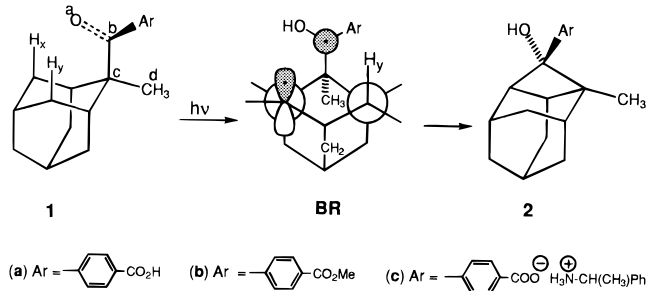
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Because they proceed with high selectivity, can be driven to completion without crystal melting or disintegration, and can be followed by X-ray diffraction methods, single crystal-to-single crystal (topotactic) transformations occupy a preeminent position in the field of solid state chemistry.<sup>1</sup> In the present paper, we report the first example of a crystalline phase photorearrangement that is not only topotactic, but which also (i) occurs with a high degree of asymmetric induction (*ca.* 90% enantiomeric excess) and (ii) involves an ionic chiral auxiliary of known absolute configuration, so that X-ray diffraction studies of the same single crystal at the beginning, midpoint, and final stages of reaction allow the absolute steric course of the photochemical reaction to be mapped.<sup>2</sup>

The reaction chosen for investigation was the Yang photocyclization<sup>3</sup> of ketones of general structure **1** (Scheme 1).<sup>4</sup> On the basis of studies with closely related compounds,<sup>5</sup> we were confident that irradiation of **1** would lead to cyclobutanols of general structure **2**, and this proved to be the case. Thus, photolyses of ketone **1b** in benzene or *tert*-butyl alcohol afforded

Scheme 1



essentially quantitative chemical yields of racemic **2b** with quantum yields of 0.073 (benzene) and 0.17 (*tert*-butyl alcohol). Stern–Volmer plots (benzene, 2,5-dimethyl-2,4-hexadiene as quencher) were linear with  $k_q\tau = 2.07 \text{ M}^{-1}$ , indicating reaction through the triplet manifold. The stereochemistry of cyclobutanol **2b** follows from crystallographic measurements on the corresponding salt **2c** (*vide infra*).

Our plan was to carry out an asymmetric Yang photocyclization by preparing salts of keto acid **1a** with optically active amines and irradiating the resulting crystals—the so-called solid state ionic chiral auxiliary approach to asymmetric synthesis.<sup>6</sup> Crystals composed of optically active components are required to crystallize in chiral space groups, and these materials provide an asymmetric environment in which to carry out enantioselective chemical reactions.<sup>7</sup> For ketone **1**, the two axial  $\gamma$ -hydrogen atoms  $H_x$  and  $H_y$  are enantiotopic, and two enantiomeric forms of photoproduct **2** are therefore possible.

Keto acid **1a** was treated with a variety of optically active amines, including  $\alpha$ -methylbenzylamine, norephedrine, pseudoephedrine, ephedrine, and prolinol, and the resulting crystalline salts were irradiated through Pyrex under nitrogen to conversions with a range of <5% to >90%. Aqueous acidic workup followed by treatment with ethereal diazomethane afforded unreacted starting material and photoproduct in the form of their methyl esters **1b** and **2b**, and this mixture was analyzed for the extent of conversion by capillary gas chromatography and for enantiomeric excess by chiral HPLC (Chiralcel OD column). The results showed that the best ionic chiral auxiliaries were  $\alpha$ -methylbenzylamine and norephedrine, which led to enantiomeric excesses in photoproduct **2b** of *ca.* 90% at 5% conversion. The other ionic auxiliaries were much less effective, giving ee values of 20–30% at low conversions; these materials were not investigated further.

X-ray quality crystals of the  $\alpha$ -methylbenzylamine salt **1c** could be grown in the form of long, thin plates (mp 210–212 °C) by recrystallization from acetonitrile containing a small amount of ethanol. The appearance of these crystals did not change during photolysis, even at conversions as high as 90%. This suggested the occurrence of a single crystal-to-single crystal process, and this salt was therefore investigated in some detail. Photolysis of the (*S*)-(–)- and (*R*)-(+)- $\alpha$ -methylbenzylamine salts afforded the optical antipodes of cyclobutanol **2b**,<sup>8</sup> indicating the system is well behaved, and studies as a function of conversion showed a slight diminution in ee from 88% at 3.5%

(1) Topotactic solid state reactions are rare. The following references plus those given in ref 2 represent the majority of known examples. (a) Enkelmann, V.; Wegner, G.; Novak, K.; Wagener, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 10390. (b) Novak, K.; Enkelmann, V.; Wegner, G.; Wagener, K. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1614. (c) Ohashi, Y. *Acc. Chem. Res.* **1988**, *21*, 268. (d) Wang, W.-N.; Jones, W. *Tetrahedron* **1987**, *43*, 1273. (e) Tieke, B. J. *Polym. Sci., Polym. Chem. Ed.* **1984**, *22*, 2895. (f) Miller, E.; Brill, T. B.; Rheingold, A. L.; Fultz, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 7580. (g) Hasegawa, M. *Chem. Rev.* **1983**, *83*, 507. (h) Thomas, J. M. *Nature* **1981**, *289*, 633. (i) Cheng, K.; Foxman, B. *J. Am. Chem. Soc.* **1977**, *99*, 8102. (j) Wegner, G. *Pure Appl. Chem.* **1977**, *49*, 443. (k) Osaki, K.; Schmidt, G. M. *J. Isr. J. Chem.* **1972**, *10*, 189.

(2) (a) The first and only other example of a topotactic, enantioselective solid state process whose absolute steric course has been elucidated by X-ray crystallography is that which occurs between deoxycholic acid and various ketones in crystalline host–guest complexes formed between the two. For a review, see: Vaida, M.; Popovitz-Biro, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 6. (b) Suzuki et al. (Suzuki, T.; Fukushima, T.; Yamashita, Y.; Miyashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 2793) have provided an example of a solid state bimolecular photoreaction that is both enantioselective and topotactic but for which absolute configuration correlations between reactant and as-prepared photoproduct were not possible owing to unresolved disorder in crystals of the latter. For enantioselective, nontopotactic reactions for which absolute configuration correlations have been carried out, see: (a) Garcia-Garibay, M.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1989**, *111*, 4985. (b) Fu, T. Y.; Liu, Z.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1993**, *115*, 12202. (c) Gudmundsdottir, A. D.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1994**, *35*, 1397. (d) Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Acta Crystallogr.* **1994**, *B50*, 601. (e) Hashizume, D.; Kogo, H.; Sekine, A.; Ohashi, Y.; Miyamoto, H.; Toda, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 61. (f) Sakamoto, M.; Takahashi, M.; Morizumi, S.; Yamaguchi, K.; Fujita, T.; Watanabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 8138.

(3) For a review, see: Wagner, P.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4.

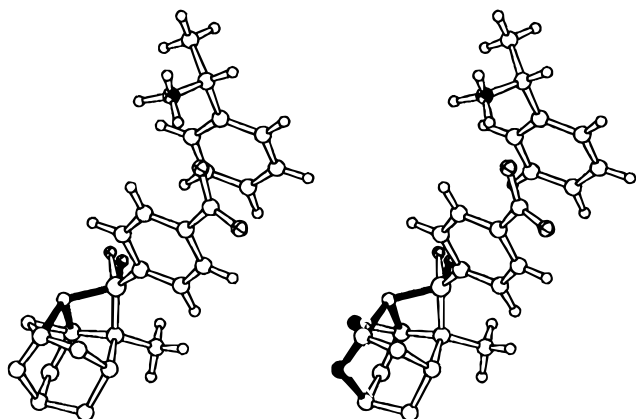
(4) Keto acid **1a** was prepared from adamantane by using standard synthetic methodology. All new compounds described in the present paper gave spectroscopic data and elemental analysis completely in accord with the assigned structures. Details will be provided in a subsequent full paper.

(5) (a) Leibovitch, M.; Olovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1996**, *118*, 1219. (b) Lewis, F. D.; Johnson, R. W.; Johnson, D. E. *J. Am. Chem. Soc.* **1974**, *96*, 6090.

(6) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203.

(7) (a) Caswell, L.; Garcia-Garibay, M. A.; Scheffer, J. R.; Trotter, J. *J. Chem. Educ.* **1993**, *70*, 785. (b) Vaida, M.; Popovitz-Biro, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991; Chapter 6.

(8) Cyclobutanol **2b** formed by photolysis of the (*R*)-(+)- $\alpha$ -methylbenzylamine salt **1c** followed by diazomethane workup [(*S*) absolute configuration at the hydroxyl-bearing carbon atom] elutes later than its enantiomer from the Chiralcel OD HPLC column and has a negative rotation at the sodium D line. Owing to the small amounts of sample used, the magnitude of the optical rotation for compound **2b** could not be determined.



**Figure 1.** Stereodiagram showing the superposition of reactant **1c** (open bonds) and photoproduct **2c** (shaded bonds) in a single crystal of the former photolyzed to 60% conversion. To improve clarity, the hydrogen atoms present in the adamantane portion of the structure have been omitted.

conversion to 82.5% at 82% conversion. Irradiation of salt **1c** in acetonitrile or methanol gave racemic **2b** after workup.

Concomitant with the chemical studies, a single crystal of the (*R*)-(+)- $\alpha$ -methylbenzylamine salt **1c** was subjected to X-ray diffraction analysis and then photolyzed for a time sufficient to insure complete conversion to photoproduct **2c**, whereupon a second crystallographic data set was collected.<sup>9a,b</sup> Both data sets refined successfully in space group  $P2_12_12_1$  to final *R* values of 4.6 and 4.9%, thus indicating that the solid state photorearrangement is indeed a single crystal-to-single crystal process. Remarkably, it proved possible to resolve the structures of **1c** and **2c** in the same crystal by X-ray diffraction analysis of a crystal of **1c** that had been photolyzed to approximately 60% conversion (from GC analysis and refinement of atom occupancy factors in the X-ray study).<sup>9c</sup>

Figure 1 shows a stereodiagram of the superposition of the **1c/2c** pair present in this crystal. As can be seen, there is a nearly perfect atom-for-atom correspondence between reactant and photoproduct. The major difference between the two structures is a movement of the adamantane ring and a slight shift in orientation of the carbon–oxygen bond—changes that are represented for photoproduct **2c** by the shaded bonds of Figure 1. Slightly larger values of the anisotropic displacement parameters, especially for the atoms of the adamantane group, indicate an inexact match in location of reactant and product molecules; separate atom sites could not be resolved in this (room temperature) study, except for the atoms which have moved significantly (shaded bonds in Figure 1).

Because the absolute configuration of the amine is known, the crystallographic results establish the absolute configuration of the **1c/2c** pair and allow a direct correlation between the two

to be made. The ketone component of salt **1c** adopts a chiral conformation in which the ketonic oxygen atom is much closer to one enantiotopic  $\gamma$ -hydrogen atom than the other, owing to twisting about the carbonyl carbon-to- $\alpha$ -carbon (*b*–*c*) bond. In the salt with (*R*)-(+)- $\alpha$ -methylbenzylamine (Figure 1), the absolute value of the dihedral angle *a*–*b*–*c*–*d* is +85.7°, and this situates the carbonyl oxygen a only 2.60 Å from  $H_x$  but 3.59 Å from  $H_y$ .<sup>10</sup> This predicts that  $H_x$  should be abstracted preferentially,<sup>11</sup> and in agreement with this, the crystal structure shows that the carbon atom to which  $H_x$  was attached is in fact part of the newly formed four-membered ring of photo-product **2c**.

The crystallographic results also reveal why the sterically more hindered endo arylcyclobutanol **2** is formed in preference to its exo isomer. Because of the large *a*–*b*–*c*–*d* torsion angle (85.7°), the aryl group is anti to the abstracted  $\gamma$ -hydrogen, so that the initially formed 1,4-hydroxybiradical has the conformation represented by the Newman projection in Scheme 1. This species is poorly aligned for cleavage, and its direct closure leads to the observed endo arylcyclobutanol. In contrast, exo arylcyclobutanol formation requires a 180° rotation about the *b*–*c* bond of the 1,4-hydroxybiradical, a motion that would certainly be resisted by the highly congested crystal lattice environment and one that is evidently slow relative to direct closure in liquid media as well.

We are continuing to study the photochemistry of organic salts in order to test our theory that, because of their high-melting, ionic, two-component character, salts may prove to be more topotactically inclined than purely molecular crystals.

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(9) (a) For salt **1c**:  $P2_12_12_1$ ; *a* = 11.791(2), *b* = 29.795(3), and *c* = 6.550(2) Å; *Z* = 4, *R* = 4.6%. (b) For salt **2c**:  $P2_12_12_1$ ; *a* = 12.475(2), *b* = 28.796(2), and *c* = 6.430(3) Å; *Z* = 4, *R* = 4.9%. (c) For salt **1c/2c** (60:40):  $P2_12_12_1$ ; *a* = 12.113(3), *b* = 29.419(3), and *c* = 6.507(4) Å; *Z* = 4, *R* = 6.8%.

(10) An independent crystal structure determination on the corresponding (*S*)-(–)- $\alpha$ -methylbenzylamine salt showed it to have an exact mirror image relationship to that of the (*R*)-(+)-salt, so that the dihedral angle *a*–*b*–*c*–*d* has a value of –85.7°, placing  $H_y$  much closer to the ketone oxygen than  $H_x$ .

(11) The hydrogen abstraction geometry is defined by four parameters: *d* (the C=O···H abstraction distance), which for the (*R*)-(+)- $\alpha$ -methylbenzylamine salt favors abstraction of  $H_x$  (2.60 Å) over  $H_y$  (3.59 Å);  $\omega$  (the angle by which the  $\gamma$ -hydrogen deviates from the mean plane of the carbonyl group), which slightly favors  $H_y$  (36.7°) over  $H_x$  (62.1°);  $\Delta$  (the C=O···H angle), which favors  $H_x$  (75.0°) over  $H_y$  (35.9°);  $\theta$  (the C–H···O angle), which favors  $H_x$  (114.1°) over  $H_y$  (106°). These data indicate a clear preference for abstraction of  $H_x$  over  $H_y$ . See: Scheffer, J. R. In *Organic Solid State Photochemistry*; Desiraju, G. R., Ed.; Elsevier: New York, 1987; Chapter 1.