

## Thermal and Photochemical Transformation of Conformational Chirality into Configurational Chirality in the Crystalline State

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In recent years, the chiral crystalline environment has been employed to carry out a variety of photochemical asymmetric syntheses and has given very encouraging results.<sup>1</sup> Because such reactions occur in a confining chiral crystal lattice medium, molecular motions are severely restricted, and high enantioselectivities can be achieved. In principle, this concept can be applied to ground-state as well as excited-state reactions. However, it is usually difficult to preserve crystallinity during reactions at elevated temperatures, and as a result, examples of solid-state thermal asymmetric syntheses are usually limited to ambient temperature processes.<sup>2</sup> It occurred to us that this problem could be overcome by using high-melting ionic crystals. In this communication, we report the successful utilization of ionic chiral auxiliaries<sup>3</sup> in the crystalline state to synthesize an optically active olefin via a thermal as well as a photochemical process. As far as we are aware, these results represent the first example of asymmetric induction in the Norrish type II cleavage reaction as well as the first report of an enantioselective thermal pericyclic reaction in the crystalline state.

The compounds chosen for study were ketones possessing the achiral tricyclo[4.4.1.0]undecane ring system **1** (Scheme 1).<sup>4</sup> Such compounds are photochemically as well as thermally labile. Irradiation causes efficient Norrish type II cleavage to give chiral olefins of general structure **3**,<sup>5</sup> and the same products are formed thermally via a 1,5-sigmatropic shift process known as the enolene rearrangement.<sup>6</sup> Salts **1c–h** were prepared by reacting achiral carboxylic acid **1a** with optically pure amines. The ammonium ions act as chiral auxiliaries, causing the salts to crystallize in homochiral space groups.<sup>1b</sup> When the salts are irradiated or thermolyzed in the solid state, the diastereomeric transition states leading to **3** or ent-**3** are differentiated by the chiral reaction medium, thereby leading to asymmetric induction. This study is the first to allow a direct comparison of ee in a thermal and photochemical solid-state asymmetric synthesis.

We turn first to the photochemical study. Irradiation of an acetonitrile solution of keto-ester **1b** produces **3b**, which undergoes a second Norrish type II cleavage upon prolonged photolysis to give a mixture of hexahydronaphthalenes **4** and methyl 4-acetylbenzoate (**5b**). When compound **1b** was photolyzed in the crystalline state, only traces of secondary photoproducts were formed. The fate of enol intermediate **2** in the solid state was followed by FT-IR. When a KBr pellet of compound **1b** was irradiated, the ketone stretch at 1666 cm<sup>-1</sup> disappeared, and a new peak was observed at ~3400 cm<sup>-1</sup>, which corresponds to the OH stretch of enol **2**. There was no significant change in the IR spectrum over a period of days at room temperature under nitrogen, but upon heating, the enol OH stretch diminished, and a new absorption at ~1680 cm<sup>-1</sup> corresponding to compound **3b** was observed. These experiments explain the absence of secondary photochemistry in the crystalline state.

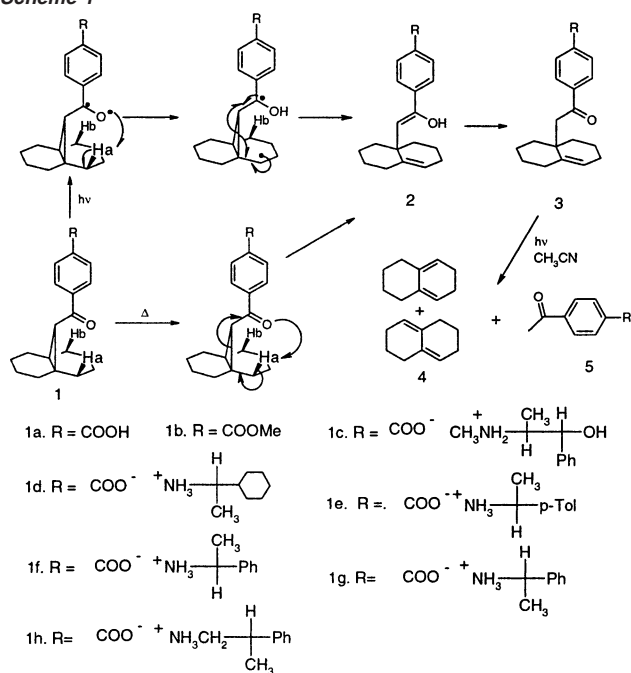
Crystals of salts **1c–h** were crushed between Pyrex microscope slides, sealed in polyethylene bags under nitrogen, and irradiated

**Table 1.** Solid-State Photolysis and Thermolysis of Chiral Salts of Keto-acid **1a**

salt	photochemical <sup>a</sup>			thermal			α <sup>c</sup>	
	conv <sup>b</sup> (%)	ee (%)	α <sup>c</sup>	temp (°C)	time (h)	conv (%)		ee (%)
<b>1c</b>	>98	95	+	52–56	48	>98	36	+
				70–74	15	94	27	
				90–95	10	>98	20	
<b>1d</b>	>98	91	–	45–50	48	42	56	–
				90–95	0.5	52	48	
				90–95	10	>98	40	
<b>1e</b>	75	73	–	45–50	96	32	58	–
				90–95	10	>98	30	
				110–120	15	>98	10	
<b>1f</b>	>98	65	–	85–90	12	28	16	–
				110–120	15	>98	10	
<b>1g</b>	>98	63	+	110–120	15	>98	12	+
				90–95	4	>98 <sup>d</sup>	<5	–

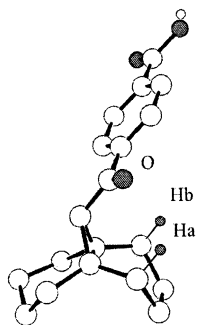
<sup>a</sup> Samples were irradiated at –25 °C through Pyrex using a 450-W Hanovia medium-pressure mercury lamp. <sup>b</sup> Conversion % based on NMR. <sup>c</sup> Sign of rotation of **3b** at the sodium D-line. <sup>d</sup> Sample melted.

**Scheme 1**



at –25 °C. The reaction mixtures were then converted to methyl ester **3b** by treatment with ethereal diazomethane and analyzed by chiral HPLC. Enantiomeric excesses obtained for photoproduct **3b** in the solid state ranged from fair (63%) to excellent (95%) (Table 1). In contrast, photolysis of the optically active salts in solution led only to racemic **3b**, a result that highlights the critical role played by the chiral crystal lattice in controlling enantioselectivity.

The high ee's observed in the solid state can be explained by a



**Figure 1.** Molecular mechanics calculation of the most stable conformation of compound **1a**. Ha and Hb are the two abstractable  $\gamma$ -hydrogen atoms; O is the oxygen atom of C=O.

conformational effect. Molecular mechanics calculations indicate that the minimum-energy conformation of ketones of general structure **1** is a chiral one in which  $\gamma$ -hydrogens Ha and Hb become diastereotopic rather than enantiotopic (Figure 1).<sup>7</sup> In this conformation the carbonyl oxygen is much closer to Ha (2.5 Å) than to Hb (3.3 Å), and if, as seems likely, salts **1c–h** adopt a similar conformation in the solid state the asymmetric induction can be explained by preferential abstraction of the more favorably located  $\gamma$ -hydrogen in the initial step of the photoreaction.<sup>8</sup> The role of the ionic chiral auxiliary in this process is thus a relatively passive one. It is not directly involved in the transition state and serves simply to preorganize the counterions in a homochiral conformation favorable for the formation of a single enantiomer of the product, thereby transforming conformational chirality into configurational chirality.

We turn now to the thermal reactions of salts **1c–h**. Heating these compounds at various temperatures (Table 1) under an atmosphere of nitrogen followed by diazomethane workup led to clean formation of ketone **3b**; melting was observed only in the case of salt **1h**. The challenge of carrying out thermal asymmetric induction in the crystalline state is that reaction should occur prior to crystal melting. The thermal behavior of salts **1c–h** was analyzed by differential scanning calorimetry, which showed two distinct patterns of behavior. The first, characteristic of salts **1c–g**, consists of an exothermic process (enolene rearrangement plus crystallization of the products) followed by an endothermic event (melting of products). The second type, shown by salt **1h**, is one in which melting of the reactant precedes or is concomitant with rearrangement and is followed by a crystallization event and a second endotherm due to the melting of the product. As summarized in Table 1, reactions of the first type (compounds **1c–g**) gave low to moderate ee's, whereas the second type of reaction (compound **1h**) led to racemic **3b**.

Table 1 shows that, in every case, the ee for the photochemical Norrish type II cleavage reaction is greater than that observed in the thermal enolene rearrangement.<sup>9</sup> The enolene rearrangement is likely to be governed by conformational factors similar to those discussed for the photochemical reaction, since the process involves a concerted 1,5-shift of one of the two diastereotopic  $\gamma$ -hydrogen atoms.<sup>6</sup> The fact that the enantiomerically enriched products obtained thermally and photochemically have the same sign of optical rotation suggests that the two pathways are quite similar.

In line with this is the finding that enol **2** could also be detected in the thermal rearrangement.<sup>10</sup> The lower ee's obtained in the thermal reaction can be attributed to an increase in conformational flexibility accompanying softening of the crystal lattice at elevated temperatures.<sup>11</sup>

In summary, the present study demonstrates that both excited- and ground-state asymmetric induction can be achieved in the crystalline state by using the ionic chiral auxiliary approach. For the photochemical process, near quantitative ee's can be achieved at >98% conversion, a result that highlights the synthetic potential of the method for the synthesis of optically active olefins. For the thermal process, the optical yields are not outstanding. Nevertheless, this is the first example of the application of ionic chiral auxiliaries in a solid-state thermal reaction. In the future, we hope to modify the procedure and apply it to a wide variety of ground-state reactions.

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**Supporting Information Available:** Synthesis of starting materials, photochemical procedures and analytical techniques used in asymmetric induction studies, infrared and differential scanning calorimetry traces (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (4) For the synthesis of compound **1a**, see Supporting Information.
- (5) Owing to the relief of cyclopropane ring strain, Norrish type II cleavage is favored over Yang cyclization in the case of compounds of general structure **1**. For a discussion of the Norrish type II chemistry of cyclopropyl ketones, see: Dauben W. G.; Schutte, L.; Wolf, R. E. *J. Org. Chem.* **1969**, *34*, 6273; For a review of the Norrish/Yang type II reaction, see: Wagner, P. J.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4.
- (6) Roberts, R. M.; Landolt, R. G.; Greene, R. N.; Heyer, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 1404.
- (7) To date, all attempts to determine the X-ray crystal structures of salts **1c–1h** have not met with success. Because most compounds crystallize in or near their minimum-energy conformations, the analysis in this case is based on the calculated structure shown in Figure 1.
- (8) For a similar situation in which the enantioselectivity of Yang photocyclization in the crystalline state is governed by preferential abstraction of the geometrically favored  $\gamma$ -hydrogen atom, see: Leibovitch, M.; Olovson, G.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1998**, *120*, 12755. The preference for abstraction of Ha over Hb in the case of ketones of general structure **1** is in accord with previous work from our laboratory on the geometric requirements for type II hydrogen transfer. See: Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.
- (9) Because the photochemical ee's were necessarily determined under conditions where the thermal reaction was immeasurably slow, direct comparison of the thermal and photochemical ee's at the same temperature and conversion was not possible.
- (10) The enol could be detected in this case by dissolving the salt in methanol-*d*<sub>4</sub> and immediately recording the <sup>1</sup>H NMR spectrum.
- (11) In agreement with this picture, the ee obtained by heating salt **1c** to >98% conversion at 52–56 °C (36%) was nearly twice that obtained at 90–95 °C (20%). For a discussion of crystalline state thermal reactions, see: Paul, I. C.; Curtin, D. Y. *Acc. Chem. Res.* **1973**, *6*, 217.

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