Asymmetric Induction in Photochemical Reactions Conducted in Zeolites and in the Crystalline State

Mordechai Leibovitch,[‡] Gunnar Olovsson,[‡]
Gajendran Sundarababu,[†] V. Ramamurthy,*[,†]
John R. Scheffer,*[,‡] and James Trotter[‡]

Departments of Chemistry
Tulane University
New Orleans, Louisiana 70118
University of British Columbia
Vancouver, BC, Canada V6T 1Z1

Received September 22, 1995

In comparison to the enormous effort expended in developing general methods of asymmetric synthesis for ground state reactions, relatively little attention has been paid to the subject of *photochemical* asymmetric synthesis; a review article summarizes the field to 1992.[1] In the present communication, we report two complementary approaches to photochemical asymmetric synthesis: (1) the use of modified zeolites as "microreactors" [2] in which a certain proportion of the cages have been rendered chiral by preadsorption of an optically active inductor molecule and (2) the use of optically active ammonium ions as ionic chiral auxiliaries for photochemistry in the crystalline state. The first approach is completely new, and the second represents an extension of previous work on the solid state photochemistry of organic salts.[3] In general, we find that the zeolite method, while potentially more versatile, at the moment affords lower optical yields than the ionic crystal method.

For the present work, we chose to investigate the ubiquitous and well-understood Norrish/Yang type II reaction[4] —specifically, the conversion of *cis*-4-*tert*-butylcyclohexyl ketones of general structure **1** into the corresponding cyclobutanols of structure **2** (Scheme 1). This reaction was first reported in 1974 for ketone **1a** by Lewis *et al.*[5] and appeared to be ideal for our purposes, since it converts an achiral starting material into a chiral photoproduct in high chemical and quantum yield; virtually no type II cleavage was observed. As we hoped, ketones **1b**−**e** behaved similarly, and a major bonus was the discovery that the enantiomers of photoproducts **2b**,**d** could be separated with baseline resolution on Chiralcel OD and OJ HPLC columns.[6]

Scheme 1

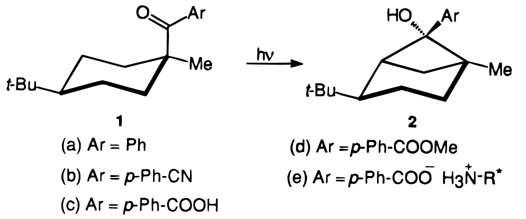

Table 1. Asymmetric Induction in the Photochemistry of Zeolite/Chiral Inductor/Ketone Complexes[a,b]

ketone	chiral inductor	quantity[c] (mg)	occupancy number ⟨*S*⟩[d]	*T* (°C)	ee (%)[e]
1b	(−)-ephedrine	5	0.3	20	10*
		15	0.8	20	22*
		25	1.3	20	25*
1d	(−)-ephedrine	10	0.5	20	<5*
		20	1.0	20	19*
		25	1.3	20	30*
		25	1.3	0	28*
		25	1.3	-40	27*
		35	1.8	20	10*
		50	2.6	20	<5*
1d	(−)-menthol	30	1.6	20	8
1d	(−)-borneol	30	1.7	20	9
1d	(+)-bornylamine	30	1.7	20	6
1d	L-proline *tert*-butyl ester	30	1.5	20	<5*

[a] Photolyzed to ∼20% conversion in hexane slurries by using the Pyrex-filtered output of a 450 W Hanovia medium-pressure mercury lamp. Chemical yields estimated to be 90−95% by GC analysis using an internal standard. Recovery of the chiral inductor could not be quantitated owing to poor GC and HPLC characteristics. [b] In each case, 5 mg of ketone was complexed with 200 mg of Na−Y (⟨*S*⟩ ≅ 0.14). [c] Amount of chiral inductor per 200 mg of zeolite Na−Y. [d] The occupancy number, represented by ⟨*S*⟩, is defined as the average number of guest molecules per supercage. [e] An asterisk indicates that the second enantiomer of the photoproduct eluted from HPLC was in excess. In the case of **2d**, this is the dextrorotatory enantiomer; the absolute configuration has not been determined.

For the zeolite work, incorporation of various optically active amines and alcohols within the supercages was accomplished by stirring hexane solutions of the chiral inductors in the presence of anhydrous Na−Y zeolite,[7] followed by filtration and thorough washing with hexanes. Analysis of the hexane washings revealed no residual inductor material. The vacuum-dried (10^{-4} Torr) complexes were then transferred to a hexane solution of ketone **1b** or **1d** and again stirred, filtered, washed, and dried; as before, the washings were clean, indicating complete incorporation of the substrate within the zeolite cages. Typical loadings were 5−50 mg of chiral inductor and 5 mg of ketone in 200 mg of zeolite. This corresponds to an occupancy number ⟨*S*⟩ (defined as the average number of guest molecules per zeolite supercage) of 0.3-2.6 for the chiral inductors and ∼0.14 for the ketones. The zeolite/chiral inductor/ketone complexes were photolyzed both as dry powders and as hexane slurries. Similar enantiomeric excesses were obtained by each method, but the solid state runs were slower. Approximately 20% conversions could be realized in 10 min in the hexane slurries, but ∼1 h irradiations were required to achieve the same conversion in the solid state. Following photolysis, the organic materials were extracted from the zeolites with ether (mass balances were excellent) and analyzed by chiral HPLC. The results of the hexane slurry photolyses are compiled in Table 1.[8]

[†] Tulane University.

[‡] University of British Columbia.

(1) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741.

(2) For reviews on photochemistry in zeolites, see: (a) Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; Chapter 10. (b) Ramamurthy, V.; Eaton, D. F.; Caspar, J. V. *Acc. Chem. Res.* **1992**, *25*, 299.

(3) Gudmundsdottir, A. D.; Scheffer, J. R.; Trotter, J. *Tetrahedron Lett.* **1994**, *35*, 1397 and references therein.

(4) Reviews: Wagner, P.; Park, B.-S. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, Chapter 4. Wagner, P. J. *Acc. Chem. Res.* **1989**, *22*, 83.

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

(6) Ketones **1b**−**d** were prepared according to standard procedures and fully characterized by spectroscopic methods as well as elemental analysis; photoproducts **2b**−**d** were characterized similarly. The relative stereochemistry of these photoproducts, which is the same as that proposed for **2a** by Lewis *et al.* from a 90 MHz NMR spectrum,[5] was assigned on the basis of an X-ray crystal structure of the *p*-methoxy derivative carried out at UBC (Olovsson, G.; Trotter, J., unpublished results). The absolute configuration of the photoproducts has not been assigned. The possibility that what we took to be the minor enantiomer of photoproduct **2d** on HPLC was an unidentified impurity was ruled out by (1) showing that this peak had exactly the same retention time as in the case of the racemic mixture, (2) checking the UV absorption spectrum of each peak (diode array detector), and (3) checking the enantiomeric excesses on two different HPLC columns (Chiralcel OD and OJ). Attempted determination of the enantiomeric excesses by chiral shift reagent NMR techniques was unsuccessful.

(7) (a) Breck, D. W. *Zeolite Molecular Sieves: Structure, Chemistry, and Use*; Wiley: New York, 1974. (b) van Bekkum, H.; Flanigen, E. M.; Jansen, J. C. *Introduction to Zeolite Science and Practice*; Elsevier: Amsterdam, 1991. (c) Dyer, A. *An Introduction to Zeolite Molecular Sieves*; Wiley: Chichester, 1988.

0002-7863/96/1518-1219$12.00/0

Table 2. Asymmetric Induction in the Solid State Photochemistry of Salts of Keto Acid **1c**[a]

optically active amine	mp (°C) and morphology of salt	irradiation time (min)	conversion (%)	ee[b] (%)
(+)-prolinol	167−169 (powder)	40	31	9
(+)-pseudoephedrine	151−154 (plates)	73	40	79
(+)-α-methylbenzylamine	224−225 (needles)	5	7	97
		15	24	96
		25	66	94
		45	85	92
(−)prolinamide	147−148 (plates)	30	51	68*
(−)-norephedrine	171−174 (plates)	5	8	97*
		15	34	96*
		42	58	86*
		90	97	81*

[a] Irradiations were carried out at room temperature as described in ref 3. [b] An asterisk indicates that the second (dextrorotatory) enantiomer of keto ester **2d** eluted from HPLC was in excess (absolute configuration unknown).

Ephedrine proved to be the best of the chiral inductors tested, giving enantiomeric excesses in the range of 25−30%. The use of (+)-ephedrine afforded the optical antipode of the photoproduct produced by the use of (−)-ephedrine, indicating that the system is well behaved. Decreasing the photolysis temperature had little effect on the enantiomeric excesses, and the use of chiral inductor loadings different from $\langle S \rangle \cong 1.5$ had a deleterious effect. Control runs showed that irradiation of ketones **1b**,**d** in hexane in the presence of ephedrine, as well as photolyses in Na−Y in the absence of ephedrine, led to racemic photoproducts. Also, there was no selective inclusion of either of the photoproduct enantiomers within the modified zeolite. This was demonstrated by including a racemic mixture of cyclobutanol photoproduct in the ephedrine-containing Na−Y zeolite and showing that the cyclobutanol obtained after extraction with ether was still racemic.

For the asymmetric induction studies in the crystalline state, keto acid **1c** was employed. This material was reacted with various optically active amines, and the resulting crystalline salts were then photolyzed in the solid state.[9] The amines were chosen so as to be optically transparent at the wavelengths employed (≥290 nm), and following irradiation, the photolysis mixtures were dissolved in a mixture of ethyl acetate and water and treated with excess ethereal diazomethane to form keto ester **2d**. This material was freed of the chiral auxiliary by short path silica gel column chromatography and then analyzed as before by chiral HPLC. The results are summarized in Table 2.

Not all of the optically active amines tested gave good results (e.g., prolinol), but most were respectable (pseudoephedrine and prolinamide), and some were outstanding (α-methylbenzylamine and norephedrine). As in the zeolite work, either enantiomer of photoproduct **2d** could be prepared as desired by using the optical antipodes of α-methylbenzylamine. Because the salts react to give products that presumably do not "fit" into the original crystal lattice, defect sites are generated, and the extent of asymmetric induction was found to decrease with increasing conversion. Table 2 includes data illustrating this point for the α-methylbenzylamine and norephedrine salts (the other salts behaved similarly). We note that in both cases, near-quantitative enantiomeric excesses can be achieved at conversions below 10%. Each of the salts was also photolyzed in benzene as well as methanol and found to give racemic **2d**. Thus, it is the rigid and highly confining environment of the chiral crystal lattice that is responsible for the asymmetric induction. It is likely that, in the crystalline state, one of the two enantiotopic γ-hydrogen atoms is closer to the oxygen atom of the carbonyl group than the other, thus leading to preferential formation of one of two possible enantiomeric 1,4-hydroxybiradicals. Absolute configuration correlation studies on this point are planned.

In summary, we have documented two approaches to asymmetric induction in organic photochemistry that derive their success from the ordered environment of an optically active supramolecular assemby. In the first, more general approach, the achiral supercages of a zeolite are loaded with an optically active and non-light absorbing guest molecule, so that when a second, photochemically reactive molecule is introduced into the same (or nearby) cage, it senses the asymmetric field due to the first and reacts enantioselectively. In principle, this approach can accommodate a wide variety of chiral inductors, photoreactants, and zeolites. At the moment, the optical yields resulting from this approach are relatively low, and we are actively seeking to improve them. The second approach, in which salts formed between prochiral, photochemically reactive carboxylic acids and optically active amines are photolyzed in the crystalline state, leads to much higher optical yields but is less general, since the photoreactants are required to be acidic (or basic, in which case one would use an optically active acid as the chiral auxiliary). On the positive side, the acidic or basic substituents do provide functionality for further synthetic elaboration of the optically active photoproducts. Both techniques complement the elegant work of Toda and others on the use of optically active host compounds for photochemical asymmetric synthesis,[10] as well as the work of the Weizmann Institute group and others on absolute asymmetric photoreactions conducted in pure molecular crystals.[11]

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Financial support by the Natural Sciences and Engineering Research Council of Canada is also gratefully acknowledged by J.R.S. V.R. thanks Tulane University for financial support of this program.

JA953238+

---

(8) Photolyses were also carried out on samples in which the order of inclusion was reversed, i.e., inclusion of ketone followed by inclusion of chiral inductor, as well as on samples prepared by simultaneous adsorption of ketone and chiral inductor from hexane solution. In both instances, the enantiomeric excesses obtained were considerably lower than those reported in Table 1.

(9) For a description of the solid state photolysis procedure, see ref 3.

(10) (a) Toda, F. *Topics Curr. Chem.* **1988**, *149*, 211. (b) Toda, F. *Mol. Cryst. Liq. Cryst.* **1990**, *41*, 187. (c) Ramamurthy, V. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; Chapter 7.

(11) (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191. (b) Vaida, M.; Popovitz-Biro, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991; Chapter 6. (c) Scheffer, J. R.; Garcia-Garibay, M. In *Photochemistry on Solid Surfaces*; Anpo, M., Matsuura, T., Eds.; Elsevier: New York, 1989; Chapter 9.3. (d) Caswell, L.; Garcia-Garibay, M. A.; Scheffer, J. R.; Trotter, J. *J. Chem. Educ.* **1993**, *70*, 785.