Enantioselective Photocyclization of 2-Arylthio-3-methylcyclohexen-1-ones to Dihydrobenzothiophene Derivatives in an Inclusion Crystal with an Optically Active Host

Fumio Toda,* Hisakazu Miyamoto, and Shiro Kikuchi

Department of Applied Chemistry, Faculty of Engineering
Ehime University, Matsuyama, Ehime 790, Japan

Reiko Kuroda* and Fuji Nagami

Department of Life Sciences, Graduate School
of Arts and Sciences, The University of Tokyo,
Komaba, Meguro-ku, Tokyo 153, Japan

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High enantioselective photocyclization of 2-arylthio-3-methylcyclohexen-1-ones to dihydrobenzothiophene derivatives was achieved in an inclusion crystal with chiral host molecules. The prochiral compounds, when trapped in the inclusion crystals, exhibited strong CD peaks in the Nujol mull. Together with the X-ray structural analysis, the solid-state CD spectroscopy clearly revealed the origin of the high enantioselectivity, demonstrating the power of the spectroscopic approaches.

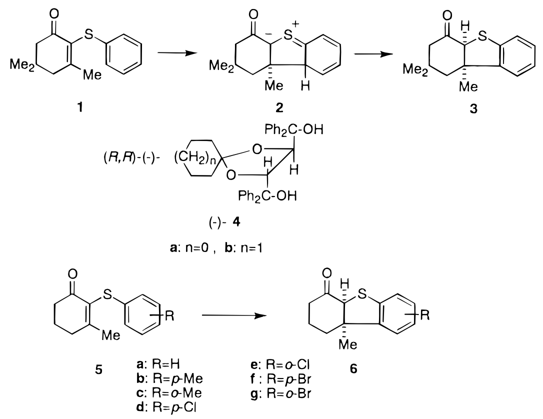
In 1974, Schultz reported the photocyclization reaction of 2-phenylthio-3,5,5-trimethylcyclohexen-1-one (**1**) to the dihydrobenzothiophene derivative **3** *via* a thiocarbonyl ylide intermediate (**2**) in benzene−MeOH solution (Scheme 1).[1] Although it is a useful procedure for the synthesis of **3**, steric control of the reaction is not trivial. For instance, irradiation of **1** in benzene gives **3** (27% yield, CH δ 3.8 ppm) and its *trans*-isomer (27% yield, CH δ 4.71 ppm) while that in benzene−MeOH (3:1) gives only **3** in 91% yield without enantioselectivity in both cases, as expected.[3]

We have been studying several enantioselective photoreactions of prochiral compounds (e.g., prochiral amide) in the solid state,[4] either in their own crystal lattices[5] or in inclusion compounds with optically active host molecules.[6] We have successfully applied the inclusion method to the phototocyclization reaction of **1** to **3** and of analogous 2-arylthio-3-methylcyclohexen-1-ones (**5**) to the corresponding dihydrobenzothiophenes (**6**).

From an ether−hexane (1:1) solution of equimolar **1** and (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane ((−)-**4a**),[7] a 1:1 inclusion compound of **1** and (−)-**4a** was obtained as colorless fine crystals in 90% yield, mp 73−75 °C. The powdered crystals (1.25 g) were suspended in water (200 mL) containing a small amount of surfactant hexadecyltrimethylammonium bromide. Irradiation of the sample for 30 h[8] with a 400 W high-pressure Hg lamp gave (−)-**3** of 37% ee (ee = enantiomeric excess) as an oil (0.3 g, 71% yield, $[\alpha]_D$ −121° (*c* 0.8, MeOH), δ 3.8 ppm).[9]

The analogous series of compounds, 2-arylthio-3-methylcyclohexen-1-ones (**5a**−**g**), was prepared by reaction of 3-methylcyclohexen-1-one with thiophenol derivatives, according to the method reported for compound **1**.[2] In this series, another host molecule, (−)-**4b**, with a hexane instead of the pentane ring[6] was additionally employed. In a typical experiment, when a benzene (5 mL)−hexane (5 mL) solution of (−)-**4b** (1.09 g, 2.15 mmol) and **5c** (0.5 g, 2.15 mmol) was left at room temperature for 24 h, a 1:1 inclusion compound of (−)-**4b** and **5c** was obtained as colorless crystals (1.51 g, 95% yield, mp 140−142 °C; IR 3325 (OH) and 1665 cm^{-1} (C=O)). Irradiation of the inclusion compound (1.22 g) with stirring for 30 h in water (200 mL) containing hexadecyltrimethylammonium bromide (0.1 g) gave a crude reaction product. This was filtered, air dried, and distilled at 250 °C (2 mmHg) to give (+)-**6c** of 72% ee (0.33 g, 86% yield, mp 99−100 °C, $[\alpha]_D$ +217° (*c* 0.4, MeOH); IR 1705 cm^{-1} (C=O)).

Scheme 1



A similar procedure was applied to the other members of the series **5** compounds. They all formed 1:1 inclusion compounds with either (−)-**4a** or (−)-**4b** in high yields, which exhibited sharp melting points (Table 1). Irradiation of these inclusion compounds in a water suspension gave the corresponding photocyclization products (+)-**6** with the *cis*-configuration. Chemical and optical yields of the reactions are summarized in Table 1. In all cases, optical yields were higher with (−)-**4b** than with (−)-**4a**.

The products which have a substituent at the *ortho*-position of the benzene ring (i.e., **6c**, **e**, and **g**) were obtained as crystalline materials. Although optical purities of **6a**−**g** obtained by the photocyclization reaction were not very high (32−83%), the crystalline compounds can be easily purified by recrystallization from solvent to give optically pure samples. For example, recrystallization of (+)-**6c** of 72% ee (0.33 g) from *n*-hexane (5 mL) gave *rac*-**6c** (0.1 g, mp 100 °C), and from the filtrate (+)-**6c** of 98% ee was obtained (0.23 g, 70% yield, mp 93 °C, $[\alpha]_D$ +332° (*c* 0.2, MeOH)). Recrystallization of (+)-**6e** of 81% ee (0.355 g) or (+)-**6g** of 83% ee (0.094 g) from *n*-hexane gave 100% ee of (+)-**6e** (0.19 g, 54% yield, mp 93 °C, $[\alpha]_D$ +330° (*c* 0.3, MeOH)) or (+)-**6g** (0.082 g, 87% yield, mp 102 °C, $[\alpha]_D$ +283° (*c* 0.3, MeOH), respectively. For **6c**, the melting point of the racemic compound is higher (mp 99−100 °C)[10] than its (+)-isomer (mp 93 °C), while (+)-**6e** (mp 93 °C) and (+)-**6g** (mp 102 °C) exhibit higher melting points than the corresponding racemic crystals (63−64 °C for *rac*-**6e** and 78−80 °C for *rac*-**6g**).

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[8] Irradiation was continued until no starting material was detected in IR.

[9] The reaction product was separated by silica gel chromatography (ethyl acetate/*n*-hexane = 1:9). Enantiomeric excess of the sample was determined by HPLC on the chiral solid stationary phase Chiralpak AS, which is available from Daicel Chemical Industries, Ltd., Himeji, Japan.

[10] Compounds *rac*-**6a** (yield = 80%, oil), **6b** (81%, mp = 56−57 °C), **6c** (85%, 99−100 °C), **6d** (83%, 75−76 °C), **6e** (87%, 63−64 °C), **6f** (86%, 73−75 °C), and **6g** (79%, 78−80 °C) were prepared by irradiation, with a 400 W high-pressure Hg lamp, of **5a**−**g** in benzene−MeOH (3:1) solution with stirring for 3 h at room temperature. Since all the *rac*-products showed a CH proton signal at δ 3.8 ppm in ^1H NMR spectra, they were assigned to be *cis*.

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Table 1. Inclusion Compounds of (−)-**4** with **5** and Their Photoreaction Products[a]

		host−guest 1:1 complex			photoreaction product		
host	guest	yield (%)	mp (°C)	irradiation time (h)	compd	yield (%)	opti purity (% ee)
(−)-**4a**	**5a**	87	140−142	20	(+)-**6a**	90	32
(−)-**4b**	**5a**	80	171−173	30	(+)-**6a**	80	52
(−)-**4a**	**5b**	92	112−114	30	(+)-**6b**	75	60
(−)-**4b**	**5b**	90	141−143	30	(+)-**6b**	94	68
(−)-**4a**	**5c**	78	114−116	20	(+)-**6c**	92	62
(−)-**4b**	**5c**	95	140−142	30	(+)-**6c**	86	72
(−)-**4a**	**5d**	87	128−130	30	(+)-**6d**	94	65
(−)-**4b**	**5d**	95	153−154	30	(+)-**6d**	80	75
(−)-**4a**	**5e**	81	126−127	20	(+)-**6e**	85	77
(−)-**4b**	**5e**	91	154−155	20	(+)-**6e**	92	81
(−)-**4a**	**5f**	91	108−109	30	(+)-**6f**	83	59
(−)-**4b**	**5f**	90	130	30	(+)-**6f**	89	70
(−)-**4a**	**5g**	74	129−130	30	(+)-**6g**	83	82
(−)-**4b**	**5g**	92	150−151	30	(+)-**6g**	91	83

[a] Photoirradiations were carried out in a stirred water suspension of powdered inclusion compound using a 400 W high-pressure Hg lamp at room temperature. Photoreaction products were collected by filtration followed by distillation in vacuo.

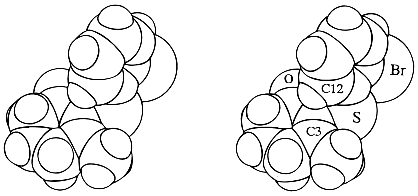

Figure 1. Molecular conformation of **5g** in the inclusion complex (−)-**4a**−**5g**.

X-ray crystal structural analysis of the inclusion complex (−)-**4a**−**5g** has been carried out.[11] Two independent host or guest molecules adopt similar molecular conformations. The crystal is made up of stacks of layers in a direction perpendicular to the crystal *b* axis (i.e., a layer of H1, a layer of G1 and G2, and a layer of H2 (H = host, G = guest)). There are strong contacts between H1 and G1 and between H2 and G2.

The two hydroxyl groups of the host seem to play a key role in the stereoselectivity of the photoreaction; the molecular conformation of the host is dictated by intramolecular hydrogen bonding between the two hydroxyl groups (O3···O4 = 2.62 Å for both H1 and H2). One of the hydroxyl groups also acts as a hydrogen donor to the carbonyl oxygen of a guest molecule (O4···O1G = 2.72 Å for H1−G1, 2.70 Å for H2−G2). The average ring plane of the guest containing the carbonyl group is almost parallel to the neighboring phenyl group of another juxtaposed host molecule. These intermolecular interactions between the host and guest molecules determine the conformation of the guest molecule (Figure 1). The dihedral angle between the two average ring planes of the guest molecule is 74.7 or 74.1°, and the photoreactive carbon C12 is either 3.71 or 3.74 Å away from the target C3 on one side of the cyclohexenone ring plane, favoring the *R*-configuration at C3. Crystal structure determination of the reaction product (+)-**6g** was carried out,[12] which unambiguously established the absolute configuration of the *cis*-isomer as 2*S*,3*R*. Thus, the conformation of the guest molecule imposed by the crystal structure explains the high enantioselectivity of the reaction.

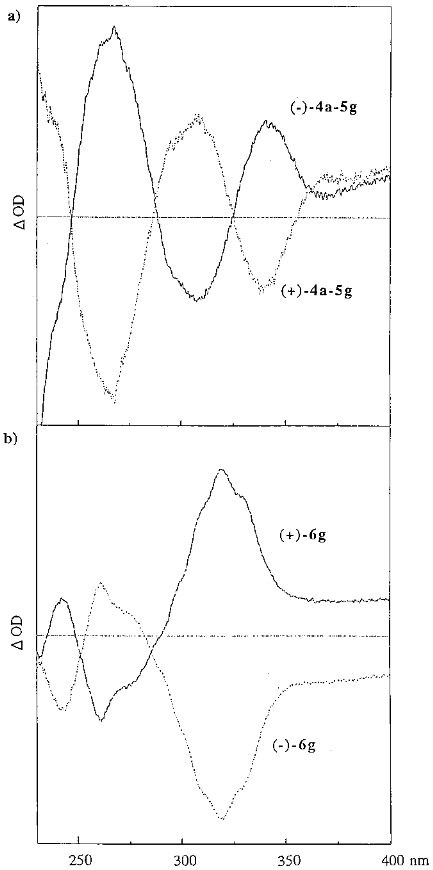

Figure 2. Solid-state CD spectra of inclusion complexes (−)-**4a**−**5g** and (+)-**4a**−**5g** (a) and their photoreaction products (+)- and (−)-**6g** (b), recorded in Nujol mull.

This hypothesis was supported by the solid state CD spectroscopy recorded in Nujol mull.[13] Chiral host molecule (−)-**4a** did not show strong absorption nor CD peaks in the 400−250 nm region. In contrast, the inclusion compound of prochiral **5g** with (−)-**4a** exhibited a rather strong CD spectrum, suggesting the spectrum mainly originates from **5g** (Figure 2). When cocrystallized with the host of opposite enantiomer, (+)-**4a**, an almost mirror image solid-state CD spectrum was obtained. Thus, prochiral compounds exhibit chirality when frozen in a chiral conformation in the solid state. This is what is expected from our X-ray crystal structural analysis. Solid-state CD spectra of the reaction product (+)-**6g** and its enantiomer also exhibited mirror image related CD spectra in the wavelength region. Further work is underway to interpret the CD spectra utilizing the crystal structures. The simple CD spectral measurement in Nujol mull is an excellent technique for the elucidation of the chiral arrangement of prochiral molecules in their own or inclusion crystals. In future, when a relationship between the CD spectral pattern and the absolute configuration of the chirally arranged prochiral molecules in crystal becomes clear through accumulation of a large body of experimental data, absolute configurations of the prochiral molecule in crystal and its photoreaction product could be easily determined by the spectral approaches.

Acknowledgment. This paper is dedicated to Professor Nelson J. Leonard on the occasion of his 80th birthday.

Supporting Information Available: Experimental details, tables of positional parameters and U valves, and ORTEP representations for (+)-**6g** and (−)-**4a**−**5g** (24 pages). See any current masthead page for ordering and Internet access instructions.

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(11) Crystal data for (−)-**4a**−**5g**: triclinic, colorless, $a = 9.812(3)$ Å, $b = 21.7121(3)$ Å, $c = 9.477(2)$ Å, $\alpha = 91.26(1)°$, $\beta = 90.24(2)°$, $\gamma = 83.68(2)°$, space group $P1$, $Z = 2$, $R = 0.069$, and GOF = 2.66.

(12) Crystal data for (+)-**6g**: orthorhombic, colorless, $a = 18.082(1)$ Å, $b = 18.793(3)$ Å, $c = 7.491(2)$ Å, space group $P2_12_12_1$, $Z = 8$, $R = 0.038$, and GOF = 1.19.

(13) CD spectra were measured on a Jasco J-720 spectropolarimeter: Kuroda, R. Ph.D. thesis, The University of Tokyo, 1975. Biscarini, R.; Franca, R.; Kuroda, R. *Inorg. Chem.* **1995**, *34*, 4618.