Deuterium Migration Mechanism in Chiral Thiolactam Formation by Neutron Diffraction Analysis

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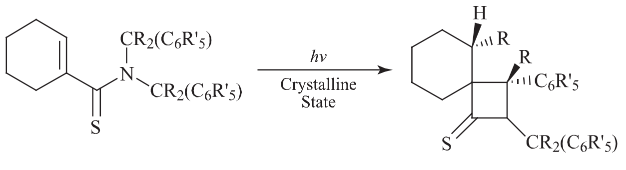
(Received April 15, 2003; CL-030321)

The single-crystal neutron diffraction revealed that in the process of photo-induced β-thiolactam formation from *N*,*N*-dibenzyl-1-cyclohexenecarbothioamide a deuterium atom bonded to the benzyl carbon atom is transferred to the intramolecular cyclohexene carbon to occupy the equatorial position of the produced cyclohexyl ring.

It has been found that α,β-unsaturated thioamides are photoisomerized to optically active β-thiolactams in the solid state.[1–4] Among them, *N*,*N*-dibenzyl-1-cyclohexenecarbothioamide, **1a**, was transformed to 1-benzyl-4-phenyl-2-thioxoazetidine-3-spirocyclohexane, **2a**, in high optical yield.[1] From the crystal structure analyses of the reactant and product crystals by X-rays, the mechanism of the asymmetric induction was proposed.[4]



1a: R=R'=H
1b: R=D, R'=H
1c: R=R'=D

2a: R=R'=H
2b: R=D, R'=H
2c: R=R'=D

Recently we succeeded in isomerizing **1a** to **2a** with retention of the single crystal form after many trials.[5] The crystal was irradiated with a xenon lamp for 330 h and then the structure was analyzed. The disordered structure composed of **1a** and **2a** appeared on the difference electron density map, which indicated that 65.7% of **1a** was converted to **2a** within the crystal. Although most of the atoms of the produced **2a** take nearly the same positions, only the atomic positions of one of the benzyl group moved to a considerable extent and the four-membered lactam ring was produced.[5] The disordered structure made clear how the benzyl carbon of **1a** makes a bond with the α carbon of the cyclohexene ring and why only one enantiomer of **2a** is produced from the chiral crystal. However, the question whether the β carbon of the cyclohexene ring abstracts the hydrogen atom within the molecule or from the neighboring molecule has not been made clear.

In the previous papers we proposed that the target hydrogen atoms should be replaced with the deuterium atoms and the structure after the reaction should be analyzed by neutron diffraction, in order to analyze the hydrogen migration mechanism in a crystal.[6–9] For the compound **1a**, four hydrogen atoms of the two benzyl groups were replaced with the deuterium atoms, **1b**.[10] If the crystal was irradiated with a xenon lamp, the photoisomerization occurred with retention of the single crystal form to produce **2b**. This work reports the deuterium-migration mechanism in the photoisomerization by neutron diffraction technique.

A large crystal of **1b**, 4.5 × 1.5 × 1.0 mm, before irradiation, was mounted on the FONDER offset 4-circle diffractometer set up at the JRR-3M reactor of the Japan Atomic Energy Research Institute (JAERI),[11] and the neutron diffraction data were collected.[12] The molecular structure is shown in Figure 1. The structure is in good agreement with that obtained by X-ray analysis except the deuterium atoms (shadowed) of the two benzyl groups. The C2···C8 distance is 2.87(9) Å and C3···D8A is 2.5(1) Å.

The reflection peak intensities of **1b** were too weak because the neutron absorption by hydrogen atoms is considerably large. Therefore all the hydrogen atoms of the two benzyl groups were replaced with the deuterium atoms, **1c**.[10] A large crystal of **1c**, 10.0 × 2.2 × 0.8 mm, was divided into two, and both of them were irradiated for 20 days at 263 K with a xenon lamp through a filter, Y-44 filter (HOYA Y-44 sharp-cut). Two small crystals were quarried out from the surface and the center of one of the crystals. The sizes of them were 0.3 × 0.3 × 0.1 and 0.3 × 0.3 × 0.15 mm, respectively. From their crystal structure analyses by X-rays, approximately 20 and 15% of **1c** were photoisomerized to **2c**, respectively. Another large crystal was irradiated with the xenon lamp in the same conditions as those for the first one, assuming that about 20% would be isomerised to **2c**.

The neutron data of the second crystal of **1c** after irradiation, 4.0 × 2.2 × 0.8 mm were also collected using FONDER in the same conditions as before.[12] The difference Fourier map around C3 is shown in Figure 2. The positive peak at H3

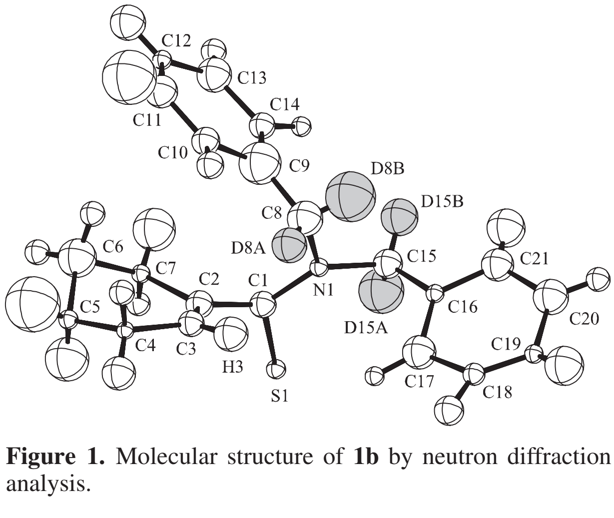


Figure 1. Molecular structure of **1b** by neutron diffraction analysis.

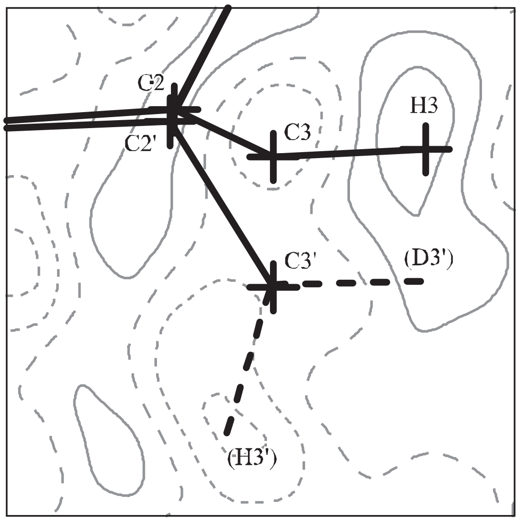


Figure 2. Difference Fourier map projected on the plane composed of H3-C3-C3′. All the atoms except H3′ and D3′ were included in the Fc calculation.[14] Solid and dotted/dashed contours indicate positive and negative ones, respectively.

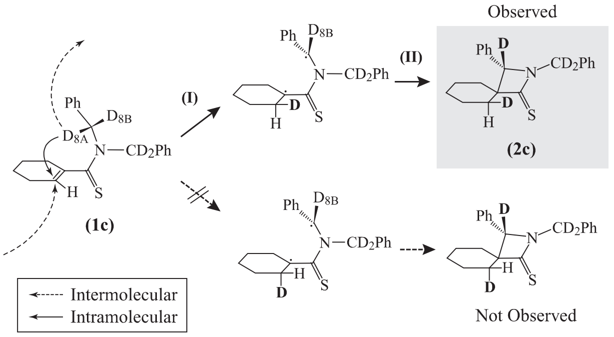


Figure 3. Reaction mechanism of **1c**: The first (I) and second (II) reaction steps indicate the intra- or intermolecular deuterium migration leaving a benzyl radical and the benzyl carbon radical makes the thiolactam ring, respectively.

indicates that a part of the H3 atom is moved to the negative peak at H3′. The positive peak at D3′ can be assigned to the position of the transfered deuterium atom. This suggests that the positions of deuterium and hydrogen atoms are equatorial and axial, respectively.

This result clearly indicates that photoreaction proceeds via the intramolecular deuterium migration as shown in Figure 3. The β carbon of the cyclohexene, C3, abstracts an intramolecular deuterium atom, D8A, involving homolytic bond cleavage. If the deuterium atom comes from the neighboring molecule, the transferred deuterium, D8AD3′, should occupy the axial position. The benzyl carbon radical would be generated after the deuterium abstraction. Then, only the produced benzyl carbon radical moves to form the β-thiolactam ring with keeping its conformation, considering from the observation by X-rays.[5]

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10 Two α,β-unsaturated thioamides **1b** and **1c** were prepared by the method reported previously.[2] The di(benzyl-α,α-d_2)amine part of **1c** was synthesized from benz(aldehyde-d) and (benzyl-α,α-d_2)amine reduced from benzamide by lithium aluminium deuteride, while di(benzyl-d_5)amine was prepared from benzaldehyde-d_6 and (benzyl-d_7)amine. Yellow prismatic crystals for neutron diffraction were obtained from diethyl ether solution.

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12 Crystallographic details: All structures were refined by *SHELXL*-97,[13] and the surface indices for absorption correction were determined using Bruker Smart CCD diffractometer, initial structure was fixed by X-ray structure.[5] (**1b**) $C_{23}H_{19}D_4NS$, *monoclinic*, $P2_1$, $a = 8.679(6)$, $b = 10.202(8)$, $c = 10.083(6)$ Å, $\beta = 99.059(5)^\circ$, $V = 881.7(11)$ Å^3, $Z = 2$, $D_{\mathrm{calc}} = 1.226$ g/cm^3, R_1 (276 with $F^2 > 2\sigma(F^2)$) $= 0.1486$, $_wR_2 = 0.2800$, R_1 (all unique 672 data) $= 0.3494$, $_wR_2 = 0.3492$, $R_{\mathrm{int}} = 0.1041$, GoF $=$ 1.657 for 180 parameters refined on F^2 (**1c**) $C_{21}H_9D_{14}NS$, *monoclinic*, $P2_1$, $a = 8.675(4)$, $b = 10.25(2)$, $c = 10.062(6)$ Å, $\beta = 99.54(5)^\circ$, $V = 883(2)$ Å^3, $Z = 2$, $D_{\mathrm{calc}} = 1.262$ g/cm^3, R_1 (953 with $F_2 > 2\sigma(F_2)$) $=$ 0.2067, $_wR_2 = 0.4611$, R_1 (all unique 1136 data) $=$ 0.2380, $_wR_2 = 0.4878$, $R_{\mathrm{int}} = 0.0847$, GoF $= 2.077$ for 35 parameters refined on F^2 (the molecule geometry was refined as a rigid body and the thermal parameters of non-hydrogen atoms and H3′ and D3′ were also refined). Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-211585, 2U586. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax:+44 1223 336033;or deposit@ccdc.cam.ac.uk).

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14 The X-ray analysis of **2a** indicates that the positions of H3′ and D3′ are almost on the plane of H3-C3-C3′.

Published on the web (Advance View) July 21, 2003; DOI 10.1246/cl.2003.742