J. Am. Chem. Soc. **1989**, *111*, 697–699

X-ray Structural Studies of Chiral β-Lactam Formation from an Achiral Oxo Amide Using the Chiral-Crystal Environment

Akiko Sekine,[1a] Kayako Hori,[1a] Yuji Ohashi,*[,1a] Minoru Yagi,[1b] and Fumio Toda*[,1b]

Contribution from the Department of Chemistry, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112, Japan, and the Department of Industrial Chemistry, Ehime University, Matsuyama 790, Japan. *Received June 20, 1988*

Abstract: Chiral crystals of the achiral oxo amide **1**, prepared in large quantities, were irradiated in the solid state to give the optically active β-lactam **2** in high optical and chemical yields. The asymmetric induction mechanism has been elucidated by X-ray structure analyses of the crystals of **1** and **2**. Crystal **1**: *N,N*-diisopropylphenylglyoxylamide, $C_{14}H_{19}NO_2$, MW = 233.31, orthorhombic, $P2_12_12_1$, $T = 298$ K, $a = 12.794$ (1) Å, $b = 13.902$ (4) Å, $c = 7.506$ (1) Å, $V = 1335.0$ (5) Å^3, $Z = 4$, $F(000) = 504$, $D_{calcd} = 1.165$ g cm^{-3}, λ(Mo Kα) = 0.71069 Å, $\mu = 0.44$ cm^{-1}, $R = 0.057$ for 1650 observed reflections. Crystal **2**: 3-hydroxy-1-isopropyl-4,4-dimethyl-3-phenylazetidin-2-one, $C_{14}H_{19}NO_2$, MW = 233.31, orthorhombic, $P2_12_12_1$, $T = 298$ K, $a = 13.458$ (3) Å, $b = 14.159$ (5) Å, $c = 7.188$ (1) Å, $V = 1369.7$ (6) Å^3, $Z = 4$, $F(000) = 504$, $D_{calcd} = 1.132$ g cm^{-3}, λ(Mo Kα) = 0.71069 Å, $\mu = 0.43$ cm^{-1}, $R = 0.072$ for 972 observed reflections. Owing to the bulky substituents of **1**, the carbonyl group approaches the isopropyl group in the crystal and a bond is formed between the carbon atoms of the two groups upon irradiation with light, resulting in a four-membered ring of the β-lactam. The chirality of the β-lactam is brought about by the twist of the carbonyl group of **1** from the amide plane, the sense of which depends on the chirality of the crystal **1**.

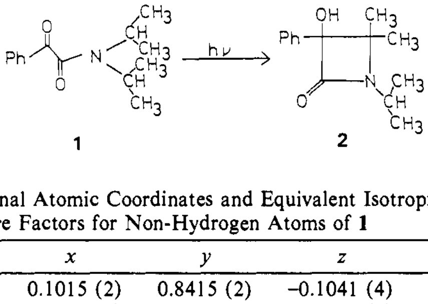
Generation of optical activity in the absence of any chiral source is interesting in relation to the origin of optically active compounds on the earth.[2] When an optically active compound is obtained in bulk, this might be an excellent preparation method of chiral compound. Although some such examples have been found in photochemistry in the solid state,[3] these are all phenomena for a fragment of the chiral crystal and are not useful for a production in bulk.

We have found that either enantiomer of the chiral crystals of *N,N*-diisopropylbenzoylformamide (**1**) is obtainable in bulk and that photocyclization using the powdered sample of one enantiomer gave optically active β-lactam derivative **2** of a high optical purity in good chemical yield[4] (Scheme I). In order to know why **1** forms chiral crystals easily and why the enantioselective photocyclization of the chiral crystals proceeds so efficiently, the crystal structures of **1** and **2** have been determined.

Experimental Section

Preparation and Photoconversion. The oxo amide **1** was prepared according to the reported method.[5] Recrystallization of the crude **1** gave pure crystals as colorless prisms, mp 124–126 °C. One single crystal (ca. 10 mg) was selected and was cut into two pieces. One piece was ground to powder and was irradiated with a high-pressure Hg lamp.[6] The spectral data of the photoproduct were consistent with those reported for the racemic **2**,[7] and the optical rotation was positive. The initial single crystal is termed (+)-**1** when it gives (+)-**2** after the irradiation. By seeding with finely powdered crystals of another piece of crystal during recrystallization of **1** from benzene, the (+)-**1** crystals can be easily prepared in large quantities. To obtain the quantitative values of the chemical and optical yields, the powdered crystals of (+)-**1** (1 g) were irradiated with the Hg lamp. The photoproduct (+)-**2**, after purification by column chromatography, revealed 93% enantiomeric excess (ee),[8] 74% chemical yield (0.74 g), $[\alpha]_D$ +123° (*c* 0.5 in $CHCl_3$), and mp 149–150 °C. It is also easy to find a single crystal of (−)-**1** from crude crystals of **1** and to obtain the (−)-**1** crystals in large quantities in the same way as that for (+)-**1**. Irradiation of powdered crystals of (−)-**1** (1 g) under the same conditions as above gave (−)-**2** of 93% ee, 0.75 g (75% chemical yield), $[\alpha]_D$ −123° (*c* 0.5 in $CHCl_3$), mp 140–150 °C.

Scheme I



1 **2**

Table I. Final Atomic Coordinates and Equivalent Isotropic Temperature Factors for Non-Hydrogen Atoms of **1**

atom	x	y	z	B_{eq}/Å^2
C(1)	0.1015 (2)	0.8415 (2)	−0.1041 (4)	2.7
C(2)	0.2099 (2)	0.8261 (2)	−0.0935 (4)	2.9
C(3)	0.2772 (2)	0.8959 (2)	−0.1555 (5)	3.5
C(4)	0.2393 (3)	0.9796 (2)	−0.2298 (5)	3.9
C(5)	0.1328 (3)	0.9956 (2)	−0.2376 (5)	4.0
C(6)	0.0637 (2)	0.9274 (2)	−0.1770 (4)	3.3
C(7)	0.0274 (2)	0.7684 (2)	−0.0365 (4)	2.8
O(1)	−0.0663 (2)	0.7790 (2)	−0.0394 (4)	4.5
C(8)	0.0726 (2)	0.6718 (2)	0.0232 (4)	2.7
O(2)	0.0833 (2)	0.6117 (2)	−0.0963 (3)	4.0
N(1)	0.0940 (2)	0.6575 (2)	0.1952 (3)	2.9
C(9)	0.0832 (3)	0.7362 (2)	0.3292 (4)	3.6
C(10)	−0.0008 (4)	0.7151 (4)	0.4647 (6)	5.6
C(11)	0.1878 (4)	0.7600 (3)	0.4135 (7)	5.7
C(12)	0.1357 (2)	0.5636 (2)	0.2579 (4)	3.3
C(13)	0.0585 (4)	0.4821 (3)	0.2254 (8)	5.4
C(14)	0.2437 (3)	0.5455 (3)	0.1793 (7)	5.2

Crystal-Structure Analysis of 1. Preliminary unit-cell dimensions and the space group were determined from photographs; systematic absences were $h = 2n + 1$ for $h00$, $k = 2n + 1$ for $0k0$, and $l = 2n + 1$ for $00l$. A crystal of approximate size 0.3 × 0.3 × 0.5 mm was mounted on a Rigaku AFC-4 four-circle diffractometer. Mo Kα radiation monochromated by graphite was used. Unit-cell dimensions were obtained from 2θ values of 15 reflections in the range of $19 < 2\theta < 30°$. Intensities were measured up to $2\theta = 50°$; ranges of h,k,l were 0–16, 0–18, and 0–9, respectively. The $\omega/2\theta$ scan technique was applied, the scan rate and

---

[1] (a) Ochanomizu University. (b) Ehime University.

[2] Addadi, L.; Lahav, M. *Origin of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: New York, 1979; Chapter 14.

[3] Evans, S. V.; Marcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Rireko, F. *J. Am. Chem. Soc.* **1986**, *108*, 5648 and references cited therein.

[4] Toda, F.; Yagi, M.; Soda, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1413.

[5] Campainge, E.; Skowronski, G.; Rogers, R. B. *Synth. Commun.* **1973**, *3*, 325.

[6] When a single crystal was irradiated with the Hg lamp, only the surface of the crystal became opaque and the photoreaction scarcely occurred inside the crystal.

[7] Aoyama, H.; Hasegawa, T.; Omote, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5343.

[8] The optical purity of **2** was determined by HPLC on an optically active solid phase, Chiralcel OC of Daicel Chemical Industries, Ltd., Himeji, Japan.

0002-7863/89/1511-0697$01.50/0

Table II. Final Atomic Coordinates and Equivalent Isotropic Temperature Factors for Non-Hydrogen Atoms of **2**

atom	x	y	z	$B_{eq}/Å^2$
N(1)	0.6741 (4)	0.6468 (3)	0.7886 (7)	4.9
C(8)	0.6819 (5)	0.5541 (4)	0.8185 (8)	4.4
O(2)	0.7475 (3)	0.5060 (4)	0.8860 (7)	5.7
C(7)	0.5809 (4)	0.5337 (4)	0.7348 (7)	4.1
O(1)	0.5786 (3)	0.4721 (3)	0.5818 (5)	4.8
C(9)	0.5778 (5)	0.6436 (5)	0.6897 (10)	5.2
C(11)	0.4974 (6)	0.7004 (5)	0.7842 (15)	7.2
C(10)	0.5858 (6)	0.6660 (5)	0.4843 (10)	6.5
C(12)	0.7353 (7)	0.7294 (7)	0.8302 (15)	7.8
C(13)	0.8319 (7)	0.7255 (9)	0.7369 (18)	9.9
C(14)	0.7383 (8)	0.7487 (9)	1.0320 (19)	10.3
C(1)	0.5018 (4)	0.4984 (4)	0.8697 (7)	4.0
C(6)	0.4075 (4)	0.4810 (5)	0.8019 (9)	4.7
C(5)	0.3324 (5)	0.4516 (4)	0.9231 (10)	5.2
C(4)	0.3515 (5)	0.4409 (5)	1.1078 (10)	5.5
C(3)	0.4447 (6)	0.4585 (6)	1.1764 (9)	6.1
C(2)	0.5190 (5)	0.4881 (5)	1.0558 (9)	5.3

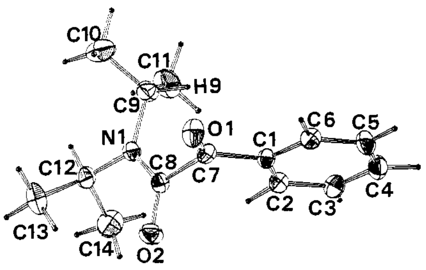


Figure 1. The ORTEP[13] drawing of the molecule **1**. The thermal ellipsoids are drawn at 50% probability. The absolute configuration is tentative.

width being 4° (θ) min^{-1} and $(1.0 + 0.35 \tan \theta)°$, respectively. Stationary background counts were accumulated for 5 s before and after each scan. Three standard reflections 044, 611, and 450, were measured every 50 reflections. No significant intensity change was observed. A total of 1779 independent reflections were measured, of which 1650 with $|F_o| > 3\sigma(|F_o|)$ were used for structure determination. Lorentz and polarization, but no absorption and extinction, corrections were applied.

The structure was solved by the direct method by using the program MULTAN 78[9] and were refined by full-matrix least-squares fit with SHELX 76.[10] Positions of all the H atoms were obtained from a difference map. Final refinement was performed with the anisotropic thermal parameters for the non-hydrogen atoms and with isotropic ones for the hydrogen atoms. The weighting scheme was $w = [\sigma(|F_o|)^2 + 0.02008(|F_o|)^2]^{-1}$. The maximum values of (Δ/σ) and $\Delta\rho$ were 0.1 and 0.2 e Å^{-3}, respectively. The final R and R_w were 0.057 and 0.075, respectively. The atomic parameters for the non-hydrogen atoms are given in Table I.

Crystal-Structure Analysis of 2. Experimental details are almost the same as those of the crystal **1**. A crystal of approximate size 0.3 × 0.3 × 0.3 mm was mounted on a rotating-anode RIGAKU off-centered four-circle diffractometer. Intensities were measured up to $2\theta = 45°$. A total of 1064 reflections were measured, of which 972 reflections with $|F_o| \geq 3\sigma(|F_o|)$ were used for structure determination.

The structure was solved by the direct method and were refined by full-matrix least-squares fit. The weighting scheme was $w = [\sigma(|F_o|)^2 + 0.03277(|F_o|^2)]^{-1}$. The maximum values of (Δ/σ) and $\Delta\rho$ were 0.1 and 0.2 e Å^{-3}, respectively. Final R and R_w values were 0.072 and 0.086 for 972 reflections, respectively. The final atomic parameters for the non-hydrogen atoms are listed in Table II.[11] Although the absolute configurations for both crystals have not been determined by using the anomalous scattering technique, the crystals of (+)-**1** and (+)-**2** were used for the structure determination. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[12] Computation was performed on the M-280H computer at the Computer Center of the University of Tokyo.

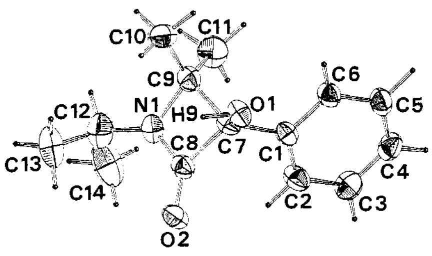


Figure 2. The ORTEP drawing of the molecule **2**. The thermal ellipsoids are drawn at 50% probability. The configuration of R is assumed.

Tablle III. Bond Distances (Å) and Angles (deg) for **1** and **2**

distance	**1**	**2**
C(1)–C(2)	1.406 (4)	1.366 (9)
C(1)–C(6)	1.400 (4)	1.382 (9)
C(1)–C(7)	1.480 (4)	1.524 (8)
C(2)–C(3)	1.378 (5)	1.389 (11)
C(3)–C(4)	1.378 (5)	1.370 (11)
C(4)–C(5)	1.381 (6)	1.361 (10)
C(5)–C(6)	1.373 (5)	1.398 (10)
C(7)–O(1)	1.208 (4)	1.405 (7)
C(7)–C(8)	1.530 (4)	1.513 (9)
C(8)–O(2)	1.233 (4)	1.217 (8)
C(8)–N(1)	1.335 (4)	1.334 (8)
N(1)–C(9)	1.493 (4)	1.478 (9)
N(1)–C(12)	1.486 (4)	1.461 (12)
C(9)–C(10)	1.508 (6)	1.514 (11)
C(9)–C(11)	1.517 (6)	1.510 (13)
C(12)–C(13)	1.523 (7)	1.464 (17)
C(12)–C(14)	1.524 (6)	1.477 (17)
C(7)–C(9)		1.590 (9)
angle	**1**	**2**
C(2)–C(1)–C(6)	119.5 (3)	118.8 (6)
C(2)–C(1)–C(7)	120.6 (2)	122.7 (5)
C(6)–C(1)–C(7)	119.9 (3)	118.5 (5)
C(1)–C(2)–C(3)	119.3 (3)	121.5 (7)
C(2)–C(3)–C(4)	120.8 (3)	119.3 (7)
C(3)–C(4)–C(5)	120.0 (4)	120.3 (7)
C(4)–C(5)–C(6)	120.6 (4)	120.3 (7)
C(1)–C(6)–C(5)	119.8 (3)	119.9 (6)
C(1)–C(7)–O(1)	123.1 (3)	106.2 (5)
C(1)–C(7)–C(8)	117.5 (2)	115.9 (5)
O(1)–C(7)–C(8)	119.1 (3)	116.7 (5)
C(7)–C(8)–O(2)	115.0 (2)	134.7 (6)
C(7)–C(8)–N(1)	119.5 (2)	93.0 (5)
O(2)–C(8)–N(1)	125.4 (3)	132.3 (6)
C(8)–N(1)–C(9)	121.5 (2)	96.7 (5)
C(8)–N(1)–C(12)	120.7 (2)	135.2 (6)
C(9)–N(1)–C(12)	117.7 (2)	128.1 (6)
N(1)–C(9)–C(10)	112.2 (3)	113.6 (6)
N(1)–C(9)–C(11)	111.0 (3)	113.3 (6)
C(10)–C(9)–C(11)	112.9 (4)	112.2 (7)
N(1)–C(12)–C(13)	111.7 (3)	112.1 (9)
N(1)–C(12)–C(14)	110.3 (3)	111.4 (9)
C(13)–C(12)–C(14)	113.8 (4)	115.6 (10)
C(9)–C(7)–C(1)		115.6 (5)
C(8)–C(7)–C(9)		85.3 (5)
O(1)–C(7)–C(9)		116.6 (5)
N(1)–C(9)–C(7)		84.8 (5)
C(7)–C(9)–C(11)		116.7 (6)
C(7)–C(9)–C(10)		113.7 (6)

Results and Discussion

The molecular structures of **1** and **2** with the numbering of the atoms are shown in Figures 1 and 2, respectively. Bond distances and angles of the two molecules are listed in Table III. The benzoyl moiety [C(1) to C(7) and O(1)] and the amide moiety [C(8),O(2),N(1),C(9) and C(12)] of **1** are planar within ±0.02

---

[9] Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structure from X-Ray Diffraction Data: University of York, York, England and University of Louvain, Louvain, Belgium, 1978.

[10] Scheldrick, G. M. SHELX 76, a program for crystal structure determination. University of Cambridge, Cambridge, England, 1976.

[11] See the paragraph at the end of the paper regarding supplementary material.

[12] *International Tables for X-Ray Crystallography*: Kynoch: Birmingham, 1974; Vol. 4.

[13] Johnson, C. K. ORTEP, Report ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN 1965.

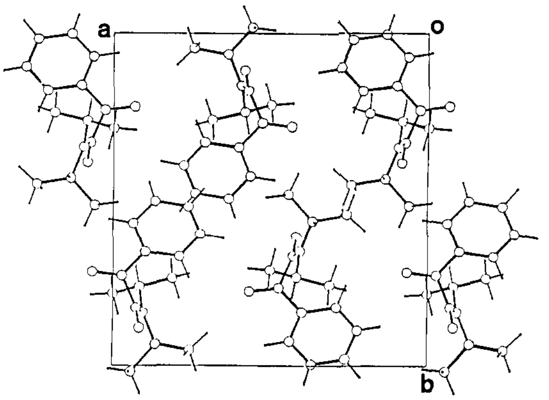


Figure 3. Crystal structure of **1** viewed along the *c* axis.

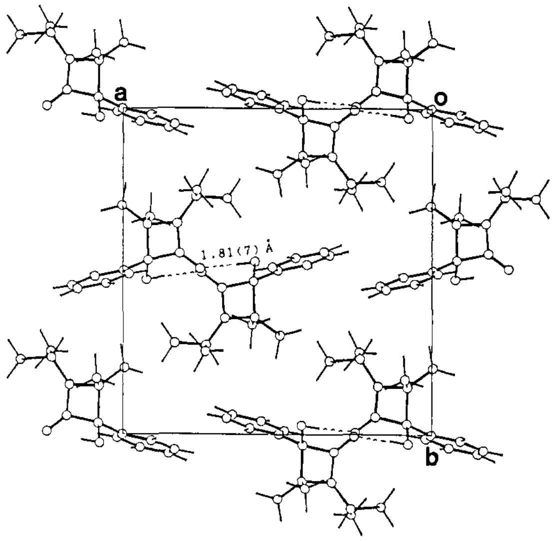


Figure 4. Crystal structure of **2** viewed along the *c* axis. The hydrogen bonds are marked with broken lines.

Å. The dihedral angle between the two mean planes is 89.9° and the torsional angle of O(1)–C(7)–C(8)–O(2) is 88.1°. Such a large torsional angle would be brought about in order to avoid the short contacts between O(1) and O(2) and between O(1) and C(9). The nonbonded distances of O(1)···O(2) and O(1)···C(9) are 3.042 (4) and 3.415 (5) Å, respectively. Owing to the torsion, the molecule **1** becomes chiral in the crystal.

The planarity of the amide moiety and the approximately right angle conformation around the C(7)–C(8) bond cause the short contacts between C(7) and C(9) and between O(1) and H(9). The nonbonded distances of C(7)···C(9) and O(1)···H(9) are 2.871 (5) and 2.78 (5) Å, respectively. Such short contacts are favorable to bond formation between the atoms upon irradiation with light. Since the absolute configuration of both crystals have not been determined yet, it remains unknown whether the crystal (+)-**1** has the structure shown in Figure 1 or its mirror image and whether the configuration of (+)-**2** is *R*, shown in Figure 2, or *S*. However, it is quite plausible to consider that the photoproduct with the *R* configuration is made from the reactant with the configuration shown in Figure 1, because it seems impossible for the molecule **1** to take the opposite configuration in the crystal even at the transition state. This is the reason why such a high optical yield was obtained in this photoreaction.

The bond distances and angles of **2** are normal except for the C(7)–C(9) (1.590 (9) Å), which is lengthened by the steric repulsion between the bulky substituents attached to the C(7) and C(9) atoms. The four-membered ring is slightly bent at the C(7)···N(1) axis; the dihedral angle between the plane of C(7), C(8), and N(1) and that of C(7), C(9), and N(1) is 5.0°.

The crystal structures of **1** and **2** are shown in Figures 3 and 4, respectively. Although the arrangements of the molecules in the two crystals are different from each other, the space groups are the same and the unit-cell dimensions are very similar to each other. This is probably a reason why the considerably high chemical yield (74 or 75%) was obtained in this solid-state photoreaction.

In the crystal of **2**, the hydroxyl group is hydrogen bonded to the oxygen atom of the carbonyl group of the neighboring molecule along the 2_1 axis. The hydrogen bond connects the molecules along the *c* axis. There are no unusually short contacts between the molecules in the crystals of **1** and **2** except for the hydrogen bond.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan (No. 63628003).

Supplementary Material Available: Anisotropic thermal parameters for non-hydrogen atoms and positional and thermal parameters for H atoms, for both of the crystals (2 pages); tables of the observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.