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Control of polymorphism by crystallization of *N*,*N*-diisopropylcarbamoylisatin

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Abstract—*N*,*N*-Diisopropylcarbamoylisatin showed polymorphism and was crystallized into two different space groups, chiral $P2_12_12_1$ and racemic $P2_1/c$ from the solvent; the polymorphism could be controlled by crystallization from the melt using the difference of melting points.

Spontaneous chiral crystallization is one of the most attractive phenomena because achiral molecules are doped in molecular chirality or chiral arrangement in the crystals without any outside chiral source.[1] Optically active molecules must crystallize into chiral space groups, but nonchiral molecules may crystallize into either a nonchiral or a chiral space group.[2] However, the crystallization of achiral molecules in the chiral space groups is rare and unpredictable. If the molecular arrangement can be controlled by crystallization, chiral crystallization will be extended to a variety of new systems such that it can now be regarded as an important branch of organic chemistry.[3] Now we have found that

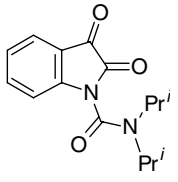

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Figure 1.

N,*N*-diisopropylcarbamoylisatin **1** showed polymorphism and it could be controlled by temperature-controlled crystallization (Fig. 1).

N,*N*-Diisopropylcarbamoylisatin **1** was conveniently prepared by condensation reaction of commercially available isatin with diisopropylcarbamoyl chloride in the presence of triethylamine. When the yellowish solid was recrystallized from a mixed solvent of $CHCl_3$ and hexane, two types of crystals, one orange cubes and the other yellow needles, were obtained. Each crystal was subjected to X-ray single crystal structural analysis, and it was revealed that they aggregated in two different fashions. The space group of the cubic crystal was a $P2_12_12_1$ system and was composed of one enantiomer (Fig. 2),[4] and that of the needle crystal was racemic $P2_1/c$ which included both enantiomers in the crystal lattice (Fig. 3).[5] Furthermore, Figure 3 also shows that the racemic crystal was composed of two rotamers.

The X-ray structural analysis also indicated that the cubic and needle types tend to have almost the same molecular structure except the torsion angles between the isatin and amide groups. Comparing the torsion angles of the carbamoyl moiety of these conformations, remarkably, the cubic chiral crystal (torsion angle ω for C1–N1–C2–O1: 81.2°) was considerably bigger than that of the needle crystal (ω_1 for C1–N1–C2–O1: 57.2° and ω_2 for C1′–N1′–C2′–O1′: 62.9°).

Keywords: Polymorphism; Chiral crystal; Racemic crystal; Isatin; Amide; X-ray.
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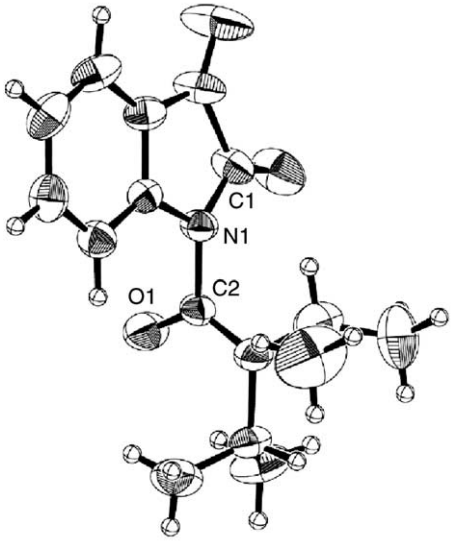


Figure 2. Ortep view of orange cubic crystal. The space group is $P2_12_12_1$ (torsion angle ω for C1–N1–C2–O1: 81.2°).

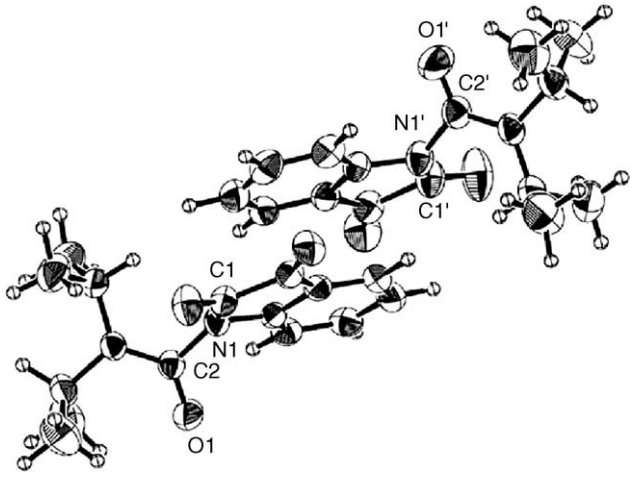
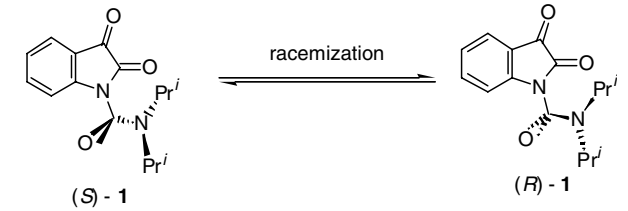


Figure 3. Ortep view of yellow needle crystal. The space group is racemic $P2_1/c$. This crystal was composed of two rotamers, the torsion angle (ω_1 for C1–N1–C2–O1: 57.2° and ω_2 for C1′–N1′–C2′–O1′: 62.9°).

The bond rotation between the isatin ring and the amide carbonyl group corresponds to racemization of **1**, and the rate is considerably affected by the substituent of the amide group (Scheme 1). For example, naphthamides with a bulky group such as *N*,*N*-diisopropyl amide group have stable axial chirality,[6] which is utilized in many asymmetric synthetic methods.[7]

Activation-free energies for racemization of **1** were studied by the use of VT NMR spectroscopy[8] (Fig. 4). Figure 4e shows the NMR spectrum at −20 °C where we can estimate the difference in the chemical shift between two diastereotopic CH_3 groups of the isopropyl moiety at the slow-exchange limit. According to a rise in temperature, the coalescence temperature T_c of the signals was determined to be 5 °C (Fig. 4a). From these facts, the barrier to interconversion of the enantiomers



Scheme 1.

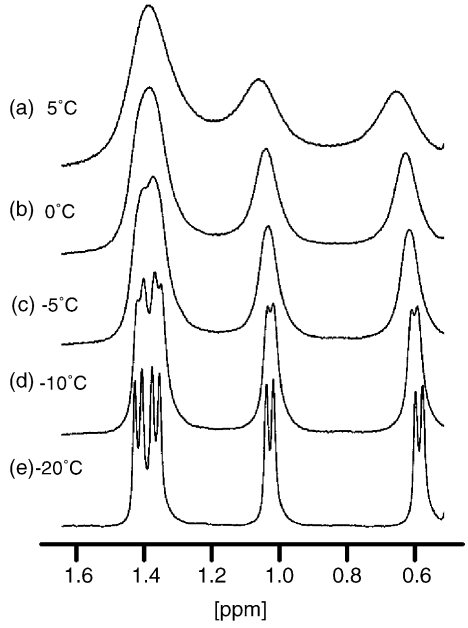


Figure 4. VT NMR spectroscopy of **1**.

in toluene-d_6 was 60.1 kJ mol^{-1}, corresponding to a half-life for racemization of 0.01 s at 5 °C. These facts indicate that the enantiomerization occurs too fast so that the resolution of the enantiomers is not possible.

When **1** was recrystallized from a mixed solvent of $CHCl_3$–hexane, both types of crystals, orange cubes and yellow needles, were formed in the batch in the ratio of cubic/needle = 3/7 (crystals were separated with tweezers). Figure 5 shows the CD spectra of **1** in the solid-state (KBr method).[9] Figure 5a exhibits the CD spectrum of cubic (+)-crystal, and Figure 5b shows that of cubic (−)-crystal. Both enantiomorphic crystals

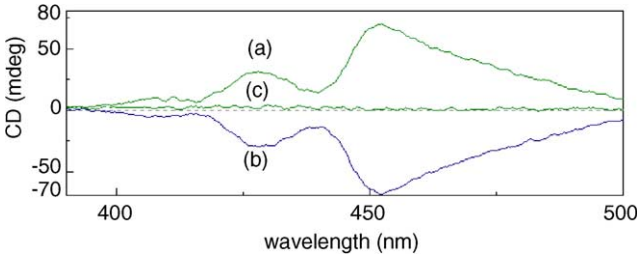


Figure 5. CD spectra of **1** in the solid-state (KBr method). (a) CD spectrum of cubic (+)-crystal. (b) CD spectrum of cubic (+)-crystal. (c) CD spectrum of needle racemic crystal.

exhibit strong Cotton effects with mirror images in the region from 400 nm to 500 nm. On the other hand, as a matter of course, needle racemic crystal did not show a Cotton effect as shown in Figure 5c.

We tried recrystallization from various kinds of solvents such as ether, THF, AcOEt, hexane, $CHCl_3$, benzene, toluene, MeCN and combination of solvents; however, racemic yellow needle crystals were mainly obtained with a minor amount of chiral crystals. We were not able to obtain chiral crystals selectively by recrystallization from the solution, even if the chiral crystals were added as seed crystals among recrystallization.

Next, we tried crystallization from the melt to obtain chiral crystals selectively by using the difference in the melting point between two types of crystals.[10] Chiral cubic crystals exhibited higher melting points of 166–168 °C than that of racemic needle crystals at 153–155 °C. The selective crystallization was achieved from the melt without any solvent. The needle crystals were melted completely at 180 °C above the melting point; decomposition of **1** was not observed under these conditions. Then, the melted isatin was gradually cooled down to the melting point of chiral crystals (166 °C) with stirring. The seed chiral crystal, which was obtained by usual recrystallization from chloroform–hexane, was added and chiral crystals were multiplicated at 163 °C. The seed crystal makes all the crystals in the batch turn out to have the same optical rotation. We were able to selectively obtain a large amount of the desired enantiomorphic crystals by seeding the desired crystals through crystallization.

Figure 6 shows the CD spectra of (a) racemic crystals and (b) the solid crystallized from the melt at 166–163 °C. It was shown that racemic crystals were selectively converted to optically active crystals only by crystallization; the same Cotton effect of (−)-crystal was observed at 400–500 nm as the single cubic crystal (Fig. 6b and Fig. 5b). When (+)-crystal was used as a seed, we could obtain a bulk of enantiomorphic crystals. Polymorphism could be controlled by crystallization using the difference in melting points.

In conclusion, we have found that *N*,*N*-diisopropylcarbamoylisatin **1** showed polymorphism and was crystallized into two different space groups, chiral $P2_12_12_1$ and racemic $P2_1/c$, from the solvent. Furthermore, polymorphism could be controlled by crystallization from the melt, and the chiral crystals could be selectively obtained as bulk by the seeding method. These results provided not only new insight into spontaneous chiral crystallization but also the possibility of asymmetric synthesis of nitrogen-containing heterocycles because it is well known that isatin derivatives show various biological activities and are also an important synthetic precursor of many naturally occurring alkaloids.[11]

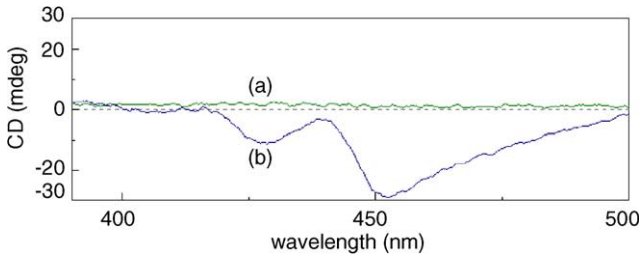


Figure 6. CD spectra of **1** in the solid-state (KBr method). (a) CD spectrum of needle racemic crystal. (b) CD spectrum of recrystallized solid at 166–163 °C.

Acknowledgement

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References and notes

1. (a) Addadi, L.; Lahav, M. In *Origin of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: New York and Basel, 1979; (b) Mason, S. F. *Nature (London)* **1984**, *311*, 19–23.
2. (a) Jacques, J.; Collet, A.; Wileni, S. H. *Enantiomers, Racemates, and Resolutions*; Kreiger Publishing Company: Malabar and Florida, 1991; (b) Collet, A.; Brienne, M.; Jacques, J. *Bull. Soc. Chim. Fr.* **1972**, 127–142.
3. (a) Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* **1987**, *87*, 433–481; (b) Vaida, M.; Popovitz-Bio, R.; Leiserowitz, L.; Lahav, M. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH: New York, 1991, pp 249–302; (c) Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 384–389; (d) Sakamoto, M. In *Molecular and Supramolecular Photochemistry, Chiral Photochemistry*; Inoue, Y., Ramamurthy, V., Eds.; Marcel Dekker: New York, 2004, pp 415–461.
4. X-ray crystallographic data of **1** (cubic crystal): orange prismatic crystals from chloroform–hexane, orthorhombic space group $P2_12_12_1$, $a = 13.696(5)$ Å, $b = 14.302(6)$ Å, $c = 7.672(4)$ Å, $V = 1502.7(12)$ Å^3, $Z = 4$, $\rho = 1.213$ g/cm^3, $\mu(\text{CuK}\alpha) = 0.70$ mm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final R and R_w were 0.056 and 0.315 for 1477 reflections. CCDC 268044 contains crystallographic data. These crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 (e-mail: deposit@ccdc.cam.ac.uk).
5. X-ray crystallographic data of **1** (needle crystals): yellow needle crystals from chloroform–hexane, monoclinic space group $P2_1/c$, $a = 7.455(2)$ Å, $b = 12.420(3)$ Å, $c = 31.837(8)$ Å, $\beta = 96.9(2)°$, $V = 2926.2(13)$ Å^3, $Z = 8$, $\rho = 1.245$ g/cm^3, $\mu(\text{CuK}\alpha) = 0.72$ mm^{-1}. The structure was solved by the direct method of full-matrix least-squares, where the final R and R_w were 0.044 and 0.177 for 3779 reflections. CCDC 268045 contains crystallographic data.
6. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277–13294.
7. (a) Clayden, J.; Lund, A.; Vallverdu, L.; Hellwell, M. *Nature* **2004**, *431*, 966–971; (b) Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 949–951.
8. (a) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; (b) Beak, P.; Tse, A.; Hawkins, J.; Chen, C.-W.; Milles, S. *Tetrahedron* **1983**, *39*, 1983–1989.

9. (a) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083–9084; (b) Toda, F.; Miyamoto, H.; Koshima, H.; Urbanczyk-Lipkowska, Z. *J. Org. Chem.* **1997**, *62*, 9261–9266; (c) Takahashi, M.; Sekine, N.; Fujita, T.; Watanabe, S.; Yamaguchi, K.; Sakamoto, M. *J. Am. Chem. Soc.* **1998**, *49*, 12770–12776; (d) Sakamoto, M.; Sekine, N.; Miyoshi, H.; Fujita, T. *J. Am. Chem. Soc.* **2000**, *122*, 10210–10211.
10. (a) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971**, *174*, 1018–1020; (b) Kondepudi, D. K. *J. Am. Chem. Soc.* **1999**, *121*, 1448–1449; (c) Sakamoto, M.; Utsumi, T.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360–4363.
11. (a) Kettle, A. J.; Clark, B. M.; Winterbourn, C. C. *J. Biol. Chem.* **2004**, *279*, 18521–18525; (b) Chiyanzu, I.; Clarkson, C.; Smith, P. J.; Lehman, J.; Gut, J.; Rosenthal, P. J.; Chibale, K. *Bioorg. Med. Chem.* **2005**, *13*, 3249–3261.