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Epimerization of Diastereomeric α-Amino Nitriles to Single Stereoisomers in the Solid State

Rumiko Sakurai,[†] Shuji Suzuki,[‡] Junichi Hashimoto,[‡] Manabu Baba,[‡] Osamu Itoh,[§] Akira Uchida,[§] Tetsutaro Hattori,*,[†] Sotaro Miyano,[†] and Masanori Yamaura*,[‡]

Department of Environmental Studies, Graduate School of Environmental Studies,
Tohoku University, Aramaki-Aoba 07, Aoba-ku, Sendai 980-8579, Japan,
Department of Environmental Science, Faculty of Science and Engineering,
Iwaki Meisei University, Iwaki 970-8551, Japan, and Department of Biomolecular
Science, Faculty of Science, Toho University, Funabashi 274-8510, Japan

hattori@orgsynth.che.tohoku.ac.jp; yamaura@iwakimu.ac.jp

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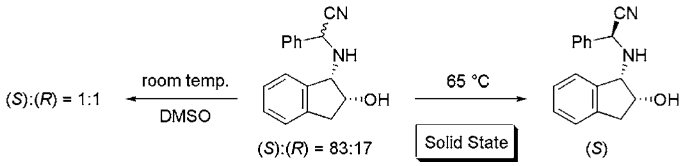
ABSTRACT



A diastereomeric mixture of the α-amino nitrile prepared by the Strecker reaction of benzaldehyde, (1*S*,2*R*)-1-aminoindan-2-ol, and cyanotrimethylsilane thermally epimerizes in the solid state to give a single diastereomer with an (*S*)-configuration at the α position to the nitrile moiety. This shows a sharp contrast to the reaction conducted in DMSO at room temperature, which gives a 1:1 mixture of (*S*)- and (*R*)-isomers. Several other α-amino nitriles also epimerize in the solid-state toward single diastereomers.

Synthesis of optical isomers in crystals, taking advantage of the well-ordered arrangement of organic molecules as well as their defined conformation, has recently been the subject of much interest. Studies on the asymmetric synthesis in inclusion crystals by using chiral hosts,[1] as well as the absolute asymmetric synthesis in crystals of achiral molecules that adopt chiral conformation or arrangement,[2] have been burgeoning. However, most of them are limited to intramolecular or intraspecific photochemical reactions, which is presumably due to the difficulty of reagent molecules to react in the substrate crystals without decomposition of the crystal lattice.[3] Another type of reaction, which is feasible in a crystal lattice but has had only limited success to date, is enantiomeric or diastereomeric enrichment, that is, deracemization or epimerization to a single isomer. Wilson and Pincock reported that metastable racemic-compound crystals of 1,1′-binaphthalene were transformed into a nonracemic mixture of stable enantiomeric crystals in an appropriate temperature range.[4] Solid-state epimerization of atropodiastereomeric teraryls has also been reported.[5] A single crystal of a racemic or diastereomeric (1-cyanoethyl)cobaloxime complex, where a racemic or diastereomeric pair of complexes are in a unit cell but occupy crystallographically distinct positions from each other, has been reported to show enantiomeric or diastereomeric enrichment on exposure to

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[†] Tohoku University.
[‡] Iwaki Meisei University.
[§] Toho University.

[1] Reviews: (a) Toda, F. *Synlett* **1993**, 303. (b) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. (c) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203. (d) Toda, F. *Aust. J. Chem.* **2001**, *54*, 573.

[2] Reviews: (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191. (b) Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 684.

[3] Sakamoto, M.; Iwamoto, T.; Nono, N.; Ando, M.; Arai, W.; Mino, T.; Fujita, T. *J. Org. Chem.* **2003**, *68*, 942.

[4] Wilson, K. R.; Pincock, R. E. *J. Am. Chem. Soc.* **1975**, *97*, 1474.

[5] Einhorn, C.; Durif, A.; Averbuch, M.-T.; Einhorn, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1926.

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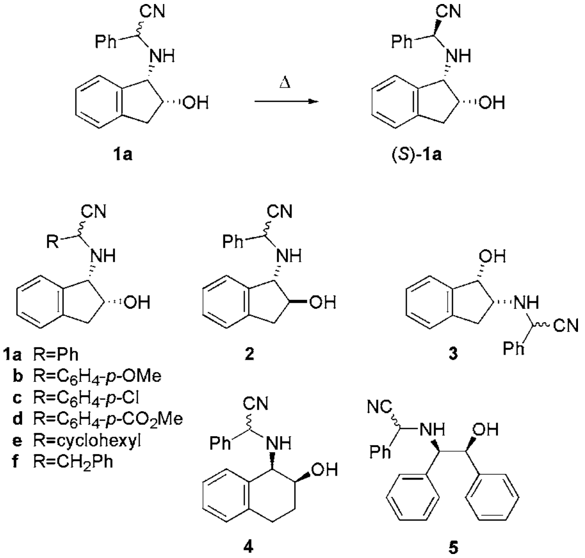
X-rays or UV light.[6] In the course of our studies on the optical resolution of *cis*-1-aminoindan-2-ol for application to asymmetric synthesis,[7,8] we have found that a diastereomeric mixture of α-amino nitriles, which was prepared by the diastereoselective Strecker reaction using the amino alcohol as a chiral auxiliary,[9,10] thermally epimerizes to a single stereoisomer in the solid state.[11] To the best of our knowledge, such a diastereomeric enrichment phenomenon of organic molecules in crystals caused by inversion of *C*-centrochirality has yet to be disclosed with the exception of the recent report by Rao and co-workers dealing with the dynamic kinetic resolution of epoxides by means of aminolysis in the inclusion complex with *β*-cyclodextrin.[12]

The diastereoselective Strecker reaction of benzaldehyde was performed by modifying the literature procedure and using cyanotrimethylsilane (TMSCN) as a cyanide source and ytterbium tris(trifluoromethanesulfonate) [$Yb(OTf)_3$] as a Lewis acid catalyst.[10b] Thus, the aldehyde was allowed to react with 1.0 mol equiv of (1*S*,2*R*)-1-aminoindan-2-ol in DMF at room temperature for 2 h with the aid of 5.0 mol % $Yb(OTf)_3$, and the resulting imine was cyanated in a one-pot manner by addition of 1.5 mol equiv of TMSCN with induction of desilylation of the *O*-silylated intermediate by simultaneous addition of 4.0 mol equiv of methanol and continuous stirring for 3 h. The reaction gave a diastereomeric mixture of α-amino nitrile **1a** in an almost quantitative yield after column chromatography on silica gel. The diastereomeric excess of the sample determined by ^{1}H NMR analysis varied from 53 to 66% de with every experiment repeated, the reason for which was suspected to be incidental epimerization. To our surprise, the de value of the crystalline sample stored at room-temperature had increased from 66 to 90% de after one month, which prompted us to examine the epimerization of **1a** in the solid state (Scheme 1). The absolute stereochemistry of the major diastereomer was determined to be 1*S*,2*R*,(*S*), which is denoted hereafter as (*S*), by X-ray crystallographic analysis (vide infra).

Scheme 1



The differential scanning calorimetric (DSC) analysis of (*S*)-**1a** of 66% de showed a broad exothermic peak between 65 and 90 °C with a maximum at 72 °C, followed by a sharp endothermic peak at 124 °C, which may be attributed to the epimerization and melting (decomposition), respectively. Therefore, the de change of the same sample was followed at 65 °C, revealing that it epimerized thermally to a single stereoisomer within 24 h. During the experiment, macroscopic change, particularly melting or even partial melting, was not observed. Interestingly, diastereomerically pure (*S*)-**1a** thus obtained, on standing at room temperature for one week as a DMSO solution, epimerized to a 1:1 mixture of (*S*)- and (*R*)-**1a**.[11] In chloroform, however, the sample of 66% de showed no change in the diastereomeric composition after one week at room temperature but decomposed on heating at reflux, giving an unidentifiable complex mixture; dissociation of the cyanide anion from the amino nitrile[9b] and subsequent reaction of the resulting iminium species, e.g., intramolecular cyclization to an oxazolidine, may be responsible.

The Strecker reaction of several other aldehydes gave the corresponding α-amino nitriles **1b**−**f** with moderate to low diastereoselectivity, except in the case of **1b**, where 100% de was achieved. Heating the crystalline solids of **1c**−**f** to below their melting temperatures also led to epimerization toward single diastereomers (Table 1, entries 2−5). It is of interest to note that complete diastereomeric enrichment could be achieved for α-amino nitriles similarly prepared

Table 1. Thermal Epimerization of Diastereomeric α-Amino Nitriles in the Solid State

entry	compound	temp (°C)	time (h)	de (%) change
1	**1a**	65	24	66→100
2	**1c**	60	48	24→100
3	**1d**	60	48	44→100
4	**1e**	40	3 weeks	8→61
5	**1f**	60	50	3→63
6	**2**[a]	65	48	29→100
7	**3**[a]	80	36	12→100
8	**4**	65	56	46→100
9	**5**	70	48	17→100

[a] Racemate.

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(7) For utilization of *cis*-1-aminoindan-2-ol in asymmetric synthesis, see: Ghosh, A. K.; Fidanze, S.; Senanayake, C. H. *Synthesis* **1998**, 937.

(8) Sakurai, R.; Sakai, K. *Tetrahedron: Asymmetry* **2003**, *14*, 411.

(9) Recent reviews on the asymmetric Strecker reactions: (a) Gröger, H. *Chem. Rev.* **2003**, *103*, 2795. (b) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(10) For utilization of amino alcohols as chiral auxiliaries for the Strecker reaction, see: (a) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115. (c) Ma, D.; Tian, H.; Zou, G. *J. Org. Chem.* **1999**, *64*, 120. (d) Dave, R. H.; Hosangadi, B. D. *Tetrahedron* **1999**, *55*, 11295.

(11) A crystallization-induced asymmetric transformation in the Strecker reaction has been reported: Boesten, W. H. J.; Seerden, J.-P. G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L. M.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 1121.

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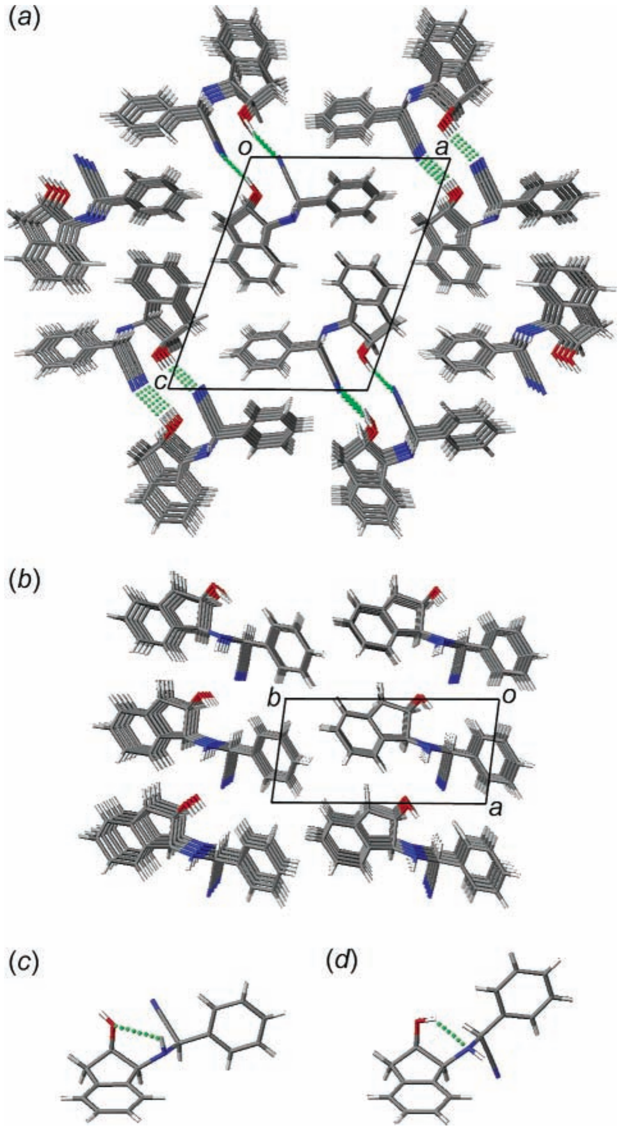

Figure 1. Crystal and molecular structures of (*R*)-**1a** (a,c) and (*S*)-**1a** (b,d). Dotted lines indicate intermolecular (a) and intramolecular hydrogen bonds (c,d).

by using racemic *trans*-1-aminoindan-2-ol (**2**), *cis*-2-aminoindan-1-ol (**3**), and even other optically pure β-amino alcohols bearing no indan skeleton (**4**, **5**[10b]) as the amine component (entries 6−9).

To gain insight into the origin of the thermal epimerization, X-ray crystallographic analysis was carried out. The requisite diastereomerically pure (*S*)- and (*R*)-**1a** could be isolated from the mixture by flash chromatography on silica gel after conversion into *O*-*tert*-butyldimethylsilyl ethers. Deprotection of the hydroxy group, followed by crystallization from toluene or 2-propanol, gave single crystals of each diastereomer, which were subjected to single-crystal X-ray analysis (Figure 1).[13] The X-ray data nicely simulated the experimental X-ray powder diffraction pattern of a diastereomeric mixture of **1a**, as well as that of (*S*)-**1a** obtained by the epimerization (Figure 2), indicating that the diastereomeric mixture consisted of the (*S*)- and (*R*)-crystals having the same structures as those of the single crystals and that the (*R*)-crystal was converted into the (*S*)-counterpart by heating. A drastic rearrangement of molecules during the epimerization is perceived from the large difference in the crystal structures between the two (Figure 1a,b).[13] Although the precise mechanism is not clear at present, hydrogen bonds seem to play an important role. Thus, the thermally unstable (*R*)-isomer had an intramolecular N−H···O bond (2.353 Å) (c), whereas an O−H···N bond (2.121 Å) existed in the (*S*)-isomer (d). In addition, a 2_1 helical structure is created along the *b*-axis by intermolecular CN···HO bonds (2.136 Å) in the (*R*)-crystals, while no intermolecular hydrogen bond could be found in the (*S*)-crystals (a as compared with b). The intramolecular hydrogen bond in the (*R*)-isomer should increase the electron density on the amino nitrogen, which will mediate dissociation of the cyanide anion with the assistance of the intermolecular hydrogen bond. On the other hand, the intra-

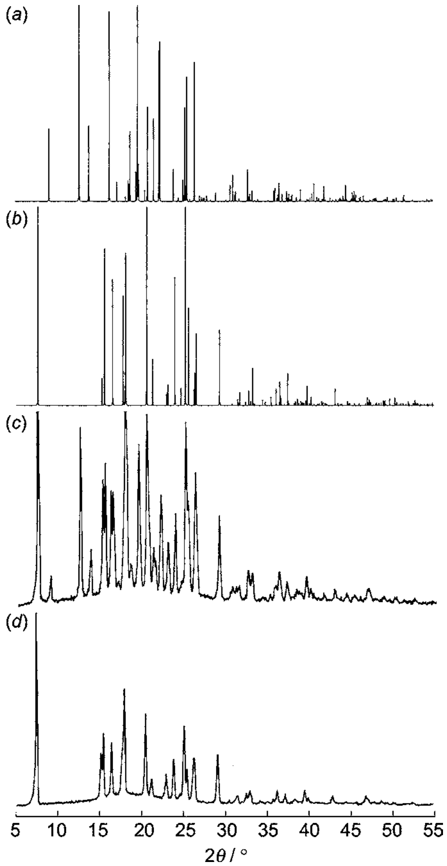

Figure 2. X-ray powder diffraction patterns of (*R*)-**1a** (a) and (*S*)-**1a** (b) simulated from each single-crystal X-ray data by using PLATON.[14] Experimental X-ray powder diffraction pattern of a diastereomeric mixture of **1a** (c) and that of the same sample measured after heating (d).

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(13) (*R*)-**1a**: monoclinic, space group $P2_1$, $a = 10.9347(14)$, $b = 5.099(3)$, $c = 13.547(2)$ Å, $\beta = 109.070(12)°$, $V = 713.8(4)$ Å^3, $Z = 2$. (*S*)-**1a**: triclinic, space group $P1$, $a = 5.7296(12)$, $b = 11.8879(19)$, $c = 5.0674(8)$ Å, $\alpha = 100.472(13)$, $\beta = 92.263(16)$, $\gamma = 83.228(15)°$, $V = 336.98(10)$ Å^3, $Z = 1$.

(14) Spek, A. L. *J. Appl. Crystallogr.* **2003**, *36*, 7.

molecular hydrogen bond in the (*S*)-isomer forms a quaternary ammonium salt, the positive charge of which retards the dissociation of the cyanide anion. As a result, the (*R*)-isomer selectively epimerizes to the (*S*)-counterpart via an iminium or imine intermediate. Therefore, it may be concluded that the relative stability between the two diastereomers in crystals is strongly affected by the hydrogen bonds, leading to the enrichment of the more stable diastereomer.

Supporting Information Available: DSC thermogram of **1a**, figure showing de % change of **1a** in the solid state, experimental details and results of the Strecker reaction, spectral and physical data of compounds **1**−**5**, and CIF data for (*R*)- and (*S*)-**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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