Pergamon

Tetrahedron 55 (1999) 11237–11246

TETRAHEDRON

A Chiral *N*-Methylbenzamide: Spontaneous Generation of Optical Activity

Isao Azumaya,[†] Iwao Okamoto,[†] Shingo Nakayama,[†] Aya Tanatani,[†]
Kentaro Yamaguchi,[‡] Koichi Shudo[†] and Hiroyuki Kagechika*[,†]

[†]Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan and [‡]Chemical Analysis Center, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received 28 June 1999; accepted 26 July 1999

Abstract: 1,2-Bis(*N*-benzoyl-*N*-methylamino)benzene (**1**) was crystallized from distilled ethyl acetate as chiral crystals belonging to space group $P2_12_12_1$. The optically active crystals of the two enantiomers were distinguishable morphologically, and their CD spectra in KBr were mirror images. In solution, several conformational isomers due to rotations of the Ar–N bonds and the amide bonds were observed. The major conformer corresponds to the crystal structure in which the two *N*-benzoyl groups exist on opposite sides of the central benzene ring (anti conformation) and the amide bonds are both *cis*. The enantiomers in solution could be distinguished from each other by ^{1}H-NMR measurements in the presence of chiral 1,1'-bi-2-naphthol. Mixed crystals of **1** and (*R*)-1,1'-bi-2-naphthol were obtained from their 1:1 mixed solution in MeOH. An X-ray crystallographical analysis showed that the configuration of **1** in the mixed crystals was (*R,R*). ^{1}H-NMR measurements of the mixed crystals at 178 K in CD_2Cl_2 showed the absolute configuration of **1** in the CD_{260}-(+)-crystal to be (*R,R*).

Keywords: Amides; Conformation; Crystallization; Optical properties

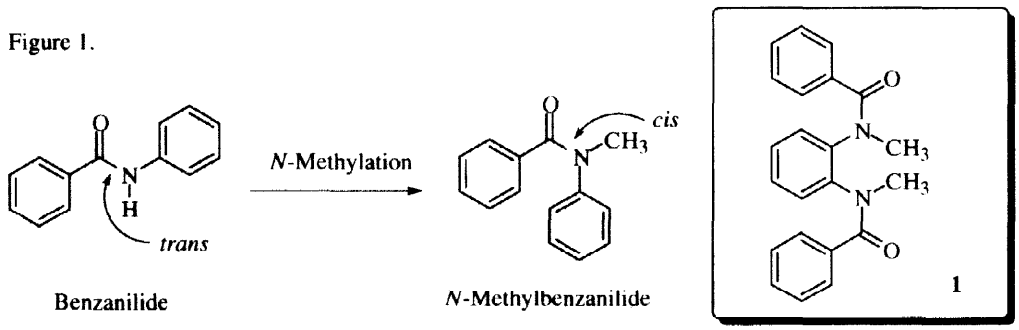
Chirality or handedness in chemistry is a common but fascinating attribute of a molecule.[1,2] Usually it is simply defined in terms of optical activity in the stationary state in the crystal and in solution. However, all so-called achiral compounds which can change their conformation have chiral conformations. For examples, in the three-dimensionally defined chiral binding sites of receptors or enzymes, achiral molecules exist in chiral conformation in most cases. Such molecules have "molecular chirality". Whether the chiral properties are stable depends on the energy barrier of racemization. In many cases of molecular chirality, the energy barrier is rather large, and the chirality is retained at ambient temperature, as observed in atropisomers, such as 1,1'-bi-2-naphthol[3] and substituted biphenyls,[4] helical compounds such as helicenes,[5] and propeller-type structures.[6]

Compounds with molecular chirality show interesting crystallization properties. Achiral molecules which can exist in stable chiral conformations usually afford racemic crystals which contain both enantiomeric conformations in a ratio of 1:1. Recently, a number of apparantly achiral organic compounds have been obtained as chiral crystals, in which each molecule is chiral or the achiral molecules are arranged in a chiral manner.[7,8] Even in the former case, most of them did not exhibit optical activity in solution due to rapid racemerization, and the two enantiomers could not be distingished by usual measurement techniques, although the chirality in the crystal can be utilized in reactions in the solid state.[9-11]

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00647-X

We have previously reported the unique stereochemical properties of *N*-methylated aromatic anilides.[12] Thus, *N*-methylation of a secondary anilide, which generally has *trans*-amide structure, results in the stabilization of the *cis* conformation (Figure 1). For example, *N*-methylbenzanilide exists in the *cis*-amide conformation in the crystal and predominantly in the *cis* structure (98.3 % in CD_2Cl_2 at 193 K) in various solvents. This *cis* conformational preference is intrinsic to *N*-methylated anilides, and allowed us to construct aromatic molecules with unique three-dimensional structures,[13] including aromatic helical layers, or with interesting functions.[14] During our investigations, we noticed that aromatic amides and guanidines afforded chiral crystals with high frequency. Among them, 1,2-bis(*N,N'*-benzoyl-*N,N'*-methylamino)benzene (**1**) exhibited chiral properties both in the crystal and in solution.[15] In this paper, we present detailed analyses of the chirality and the conformational behavior of **1**.

Figure 1.



Results and Discussion

Chiral and Racemic Crystals of 1,2-Bis(*N,N'*-benzoyl-*N,N'*-methylamino)benzene (1)

1,2-Bis(*N,N'*-benzoyl-*N,N'*-methylamino)benzene (**1**) was prepared from *ortho*-phenylenediamine and benzoyl chloride, followed by *N*-methylation. Recrystallization of **1** from distilled ethyl acetate yielded colorless prisms, each of which is chiral, with space group $P2_12_12_1$ (orthorhombic) in X-ray crystallographical analysis (Figure 2a). The enantiomeric crystals could be distinguished by taking the CD spectra in KBr as described below. Typical examples of the recrystallization of **1** are given in Table I. The ratio of enantiomeric crystals was close to 1 when a saturated solution was cooled quickly to generate many crystals (entry 1). Slow crystallization, resulting in fewer crystals, produced a large preference for one or other of the enantiomeric crystals. In some cases, all the crystals exhibited the same chirality. We could also obtain single large crystal in good yield (entry 2), i. e., complete generation of a single chirality . Seeding of a chiral crystal afforded crystals possesing the same chirality as the seed crystal (entries 3 and 4). The racemization of **1** under the recrystallization conditions should be fast, because the both enantiomeric crystals were generally obtained from a solution prepared by dissolving crystals of one chirality.

Table I. Results of crystallization of **1** under various conditions at 293 K

			number of crystals[a]		
entry	solvent	seed	(+)-crystal	(–)-crystal	racemic
1[b]	AcOEt	none	21	29	0
2[c]	AcOEt	none	1	0	0
3[d]	AcOEt	(+)-**1**	5	0	0
4[d]	AcOEt	(–)-**1**	0	5	0
5[b]	wet AcOEt	none	0	0	20
6[b]	aqueous EtOH	none	0	0	20

[a] Chiral crystals were identified from the CD spectra, and designated as (+)- and (–)-crystals according to the sign of the ellipticity at 260 nm (see Figure 3). [b] Totals from several runs (10 – 20 crystals per run). [c] Only one crystal was generated. [d] All crystals were collected in a single run.

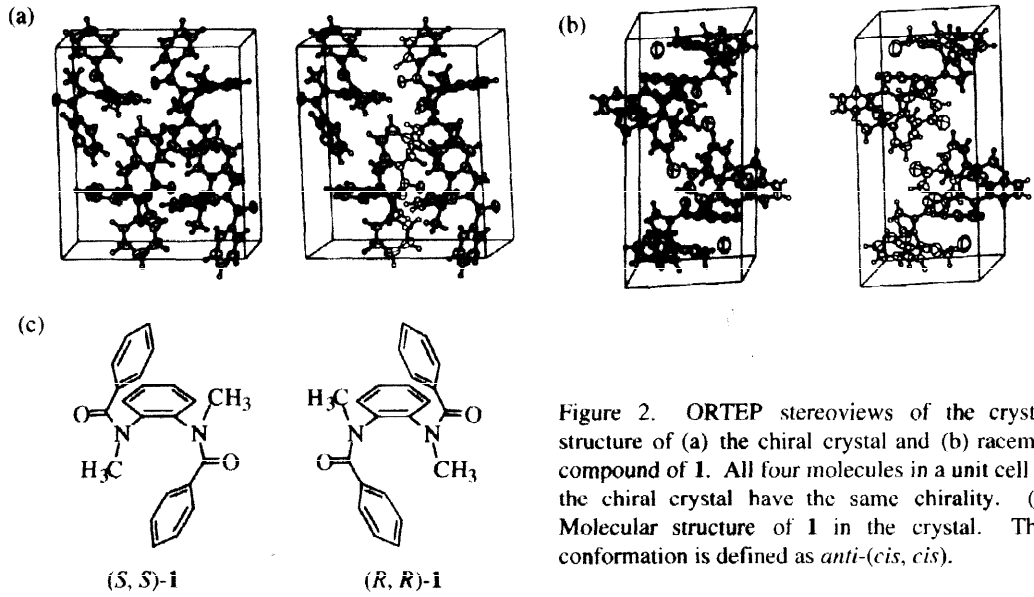


Figure 2. ORTEP stereoviews of the crystal structure of (a) the chiral crystal and (b) racemic compound of **1**. All four molecules in a unit cell of the chiral crystal have the same chirality. (c) Molecular structure of **1** in the crystal. This conformation is defined as *anti*-(*cis*, *cis*).

Chiral crystals were also obtained from chloroform, carbon tetrachloride, benzene and absolute ethanol. Interestingly, recrystallization of **1** from water-saturated ethyl acetate or aqueous ethanol always afforded achiral crystals (Table 1, entries 5 and 6) belonging to the space group $P2_1/n$ (monoclinic). The X-ray crystallographical or elemental analysis of the achiral crystals of **1** showed that they contain one molecule of water per molecule of **1** (Figure 2b). The differences in the physicochemical properties of chiral and achiral crystals of **1** are summarizaed in Table II. The achiral crystals have a slightly larger specific gravity than the chiral crystals, and exhibit two peaks in DSC measurement. The lower temperature peak (145.5 °C) is due to the dissociation of the water from the crystal, and the other, at 160.5 °C, was similar to that of the chiral crystals.

The crystal structures of **1** in both crystals are similar, as shown in Figure 2. As anticipated on the basis of our previous work,[12,13] the two amide bonds are both *cis*. The molecule has an approximate C_2 symmetry and the two phenylcarbamoyl groups are located on opposite sides of the central benzene ring (defined as *anti* conformation). In this structure, the molecule has two chiral axes (Ar–N bonds), and the two enantiomeric *anti*-(*cis*, *cis*) conformers of **1** are assigned (*S*, *S*) and (*R*, *R*) configurations as shown in Figure 2c. In the chiral crystals, four molecules exist in the unit cell, all having the same chirality, while the achiral crystals contains two of both enantiomers together with four molecules of water in the unit cell, i.e., racemic compounds.

Table II. Physical data for the chiral and the racemic crystals of **1**

crystal	chiral crystals [(+)- or (–)-crystals]	Achiral crystals [racemic compounds]
recrystn solvent	AcOEt, CCl_4, benzene, absolute EtOH	wet AcOEt, wet EtOH
formula (elemental analysis)	$C_{22}H_{20}N_2O_2$	$C_{22}H_{20}N_2O_2 \cdot H_2O$
d (20 °C *n*-hexane-CCl_4; KI-H_2O)	1.181	1.240
(25 °C X-ray anal. calc.)	1.191	1.264
mp (DSC)	162.0 °C	145.5 °C (major peak) 160.5 °C (minor peak)

The enantiomeric crystals of **1** were characterized by CD spectroscopy in KBr. The two types of chiral crystals are optically active, and afforded mirror-image CD spectra; they were designated as (+)- and (–)-crystals according to the sign of the ellipticity at 260 nm (Figure 3a). On the other hand, the racemic crystals of $\mathbf{1}\cdot H_2O$ did not exhibit any CD spectrum. Furthermore, the chiral crystals were distinguishable morphologically (Figure 3b), like the enantiomeric crystals of sodium ammonium tartarate described by Pasteur.

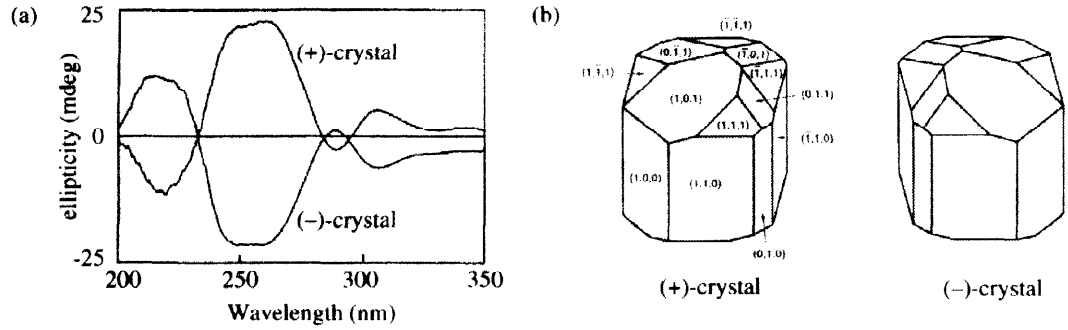


Figure 3. (a) CD spectra of the two enantiomic crystals of **1** (100 μg) in KBr (100 mg). (b) Morphology of the two enantiomeric crystals. The (0, $\bar{1}$, 0) face is divided into two small faces with similar reflection angle, and the (0, $\bar{1}$, 0) face is divided into one large and two small faces with similar reflection angle. Differentiation between the enantiomers could be done (10 out of 10 crystals) based on the positions of these small faces and the position of the top in the direction of (0, 0, 1).

Conformational Equilibrium of 1 in Solution

Dynamic ^{1}H-NMR measurements of **1** showed equilibria between various conformers (Figure 4). Only one singlet peak, corresponding to *N*-methyl groups, was observed at 408 K. The signal become broader as the temperature was lowered, and split into seven singlet peaks in the region of 2.1 – 3.5 ppm at 183 K (Figure 4h). The conformers of **1** arise from *cis*/*trans* conversion of the amide groups, and rotation around the Ar–N bonds (chiral axes). We defined *syn* and *anti* conformations in terms of the two *N*-benzoyl groups being located at the same and opposite sides of the plane of the central benzene ring, respectively. In this case, carbonyl–phenyl rotation should have a negligible effect, because it causes little conformational change and is so fast on the ^{1}H-NMR time scale that the two *ortho* protons on the phenyl group can not be distinguished. Possible conformations of **1** are shown in Figure 5. The amide configurations are denoted as " c " or " t " for *cis* and *trans*, respectively. The steric relationships of the two *N*-benzoyl moieties are denoted by adding an apostrophe (" c' " or " t' ") when the *N*-benzoyl group exists below the central benzene ring. For example, the expressions (c, c) and (c', c') indicate the same *syn*-(*cis*, *cis*) conformation. The expressions (c, c') and (c', c) indicate the two enantiomers of the *anti*-(*cis*, *cis*) conformation as observed in the crystal. Six conformations are distinguishable by ^{1}H-NMR; typical representations are (c, c), (c, c'), (c, t), (c, t'), (t, t) and (t, t'). Other conformations are their enantiomers or equivalents.

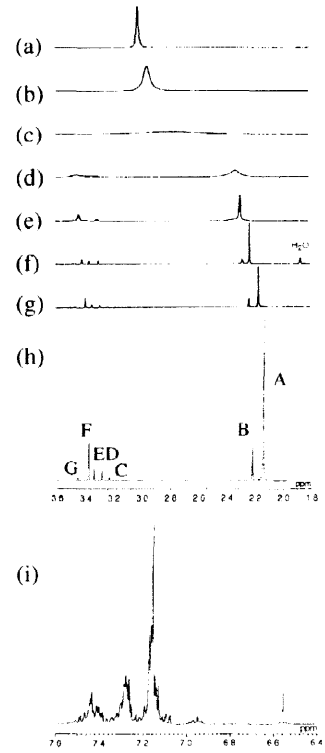


Figure 4. ^{1}H-NMR spectrum of **1** in the *N*-methyl region (a – h) and the aromatic region (i, 183 K): The temperatures of measurement were (a) 408 K, (b) 373 K, (c) 338 K, (d) 303 K, (e) 273 K, (f) 243 K, (g) 213 K, and (h) 183 K. The solvents were $CDCl_2CDCl_2$ for (a) – (d) and CD_2Cl_2 for (e) – (i).

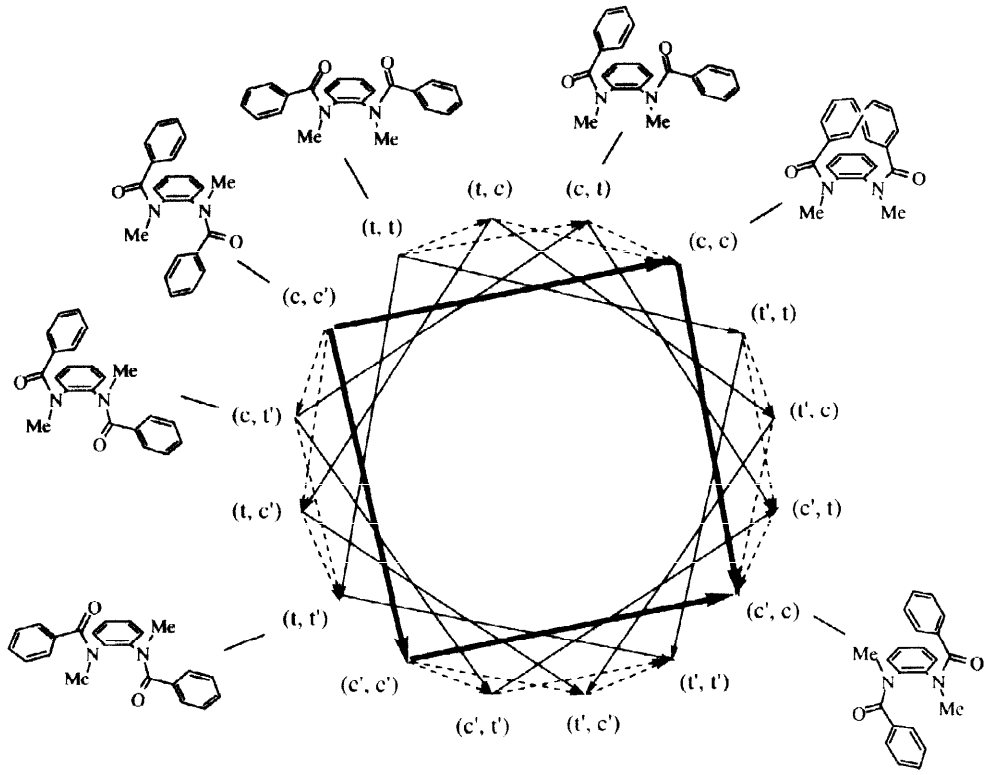


Figure 5. Schematic representation of conformational interconversion of **1**. Solid arrows and dotted arrows correspond to the rotation of Ar–N bonds and the *cis/trans* conversions of the amide bonds, respectively.

The predominant *N*-methyl peak (60 %, 2.15 ppm), named peak A in Figure 4h (or Figure 7a), was assigned to the conformer corresponding to the crystal structure [(c, c') and (c', c)], because the chemical shift is very high compared with those of typical *N*-methyl peaks of aromatic amides, due to the anisotropic effect of the phenyl ring on the other *cis*-amide group. In addition, when the crystal was dissolved in CD_2Cl_2 at 178 K and the NMR spectrum was taken immediately at the same temperature, only the signal corresponding to peak A was observed. In this experiment, the same spectrum as shown in Figure 4h was obtained upon measurement after raising the temperature or after waiting. Therefore, the major conformer in the racemic solution is conformer (c, c') / (c', c).

The next most major signals consist of two peaks with the same integrations (28%), one of them (peak B in Figure 4h) being at higher field like peak A for the (c, c'), and the other (peak F) at rather lower field, at a chemical shift typical of *N*-methyl of an aromatic amide group. The two signals were assigned to the conformer (c, t') [and (t', c)] because one *N*-methyl group is exposed to the anisotropic effect of the phenyl ring on the *cis*-amide group and the other is free from the anisotropic effect. Peak D at 3.27 ppm (5 %) was assigned to conformer (c, c), because the conformer corresponding to peak D has aromatic proton signals at higher field (doublet at 6.5 – 6.7 ppm indicated by an arrow in Figure 4i), which can be assigned to the *ortho* protons of the benzoyl groups in this conformer. Then, peaks C and G with the same integration values should be assigned to the same conformer, i. e., (c, t). The other minor peak E at 3.45 ppm was assigned to the conformer (t, t) or/and (t, t'). It is uncertain whether the failure to observe the conformer (t, t') [or t, t)] is due to the small existence ratio or whether the peaks can not be distinguished owing to the fast equilibrium between the conformers (t, t) and (t, t').

Chirality of 1 in Solution

In solution at room temperature, **1** is in equilibrium between various conformers, and consequently is racemic. Indeed, even when crystals with one chirality were dissolved, both chiralities could be generated by recrystallization, and no CD spectrum was observed at room temperature. However, the chirality of **1** was retained in solution at low temperature. Thus, solutions prepared by dissolving optically active crystals at 173 K showed CD spectra (Figure 6), which became flat when the solutions were warmed to room temperature. The shapes of the CD spectra for the solutions of enantiomeric crystals are mirror images, and similar to those observed for the corresponding chiral crystals in KBr.

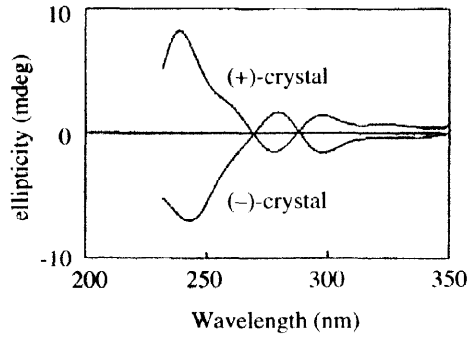


Figure 6. CD spectra of the two enantiomers of **1** (2×10^{-3} M) in methanol : ethanol (1:3 v/v) at 173 K. A chiral crystal of **1** was dissolved at 173 K, and the spectrum was immediately measured.

The enantiomers are distinguishable by ^{1}H-NMR in a solution containing a chirally interacting reagent. Chiral 1,1'-bi-2-naphthol is so stable in solution that racemization does not occur during measurements even at room temperature. When chiral 1,1'-bi-2-naphthol was added to a racemic solution of **1**, all the observed *N*-methyl peaks were split into two (Figure 7b, c). The peak separation became larger as the molar ratio of 1,1'-bi-2-naphthol to **1** was increased. When a chiral crystal of **1** was dissolved at low temperature in a solution of the chiral 1,1'-bi-2-naphthol, the enantiomers (c, c') and (c', c) could be distinguished. In the ^{1}H-NMR spectrum of **1** just after the (+)-crystal was dissolved at 178 K in CD_2Cl_2 solution containing (*S*)-1,1'-bi-2-naphthol, the observed singlet peak for *N*-methyl groups corresponds to the right peak (peak A_1 at higher field) of the divided major peaks in Figure 7c. The (−)-crystal afforded the singlet peak corresponding to the left peak (peak A_2 at lower field) in (*S*)-1,1'-bi-2-naphthol solution. Opposite spectra were obtained by dissolving (+)- or (−)-crystals in (*R*)-1,1'-bi-2-naphthol. Thus, the chirality of **1** was retained at low temperature. When the chiral solution was racemized by raising the temperature, it afforded the same spectrum as that shown in Figure 7c.

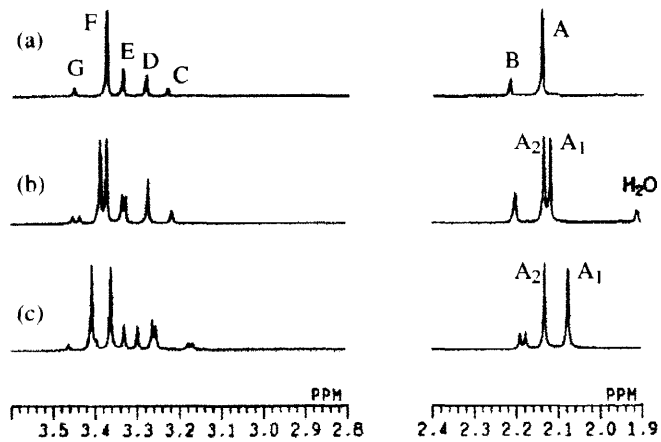


Figure 7. ^{1}H-NMR spectra of **1** in CD_2Cl_2 at 193 K in the absence (a) or presence of chiral 1,1'-bi-2-naphthol (b, 1 equiv, and c, 15 equiv). The peak heights were normalized based on the highest peak in each chart, i.e., the vertical scales are not the same.

Measurements of the time course of the ratio of the *N*-methyl proton signals at various temperatures (193 - 173 K) allowed us to examine the kinetics of the racemization. However, the kinetic process proved to be too complicated, as shown in Figure 5, to permit accurate determination of kinetic constants for interconversion between the isomers. We could estimate the rate of racemization from the *N*-methyl signals of the two major enantiomeric conformers, (c, c') and (c', c). Thus, the energy barrier ($\Delta G^{\ddagger}$) of apparent racemization was calculated from the temperature dependence of the kinetic constant (223 K: 5.50×10^{-4} s^{-1}, 213 K: 9.46×10^{-5} s^{-1}, 203 K: 1.16×10^{-5} s^{-1}) to be $17.1 - 3.3 \times 10^{-3}T$ kcal/mol. This value ($\Delta G^{\ddagger}$ = 16.4 – 16.1 kcal/mol at 200 – 300 K) is slightly smaller than that of *cis/trans* isomerization of *N*-methylbenzanilides with methyl group(s) at the *ortho* position to the amide group.[12c] In a solution of **1**, many interconversion processes occur among the six types of conformers (one of them was not observed). Figure 5 illustrates possible conversion processes

from one enantiomer (c, c') to the other (c', c), including rotation of Ar–N bonds in *cis*- or *trans*-amides, and *cis/trans* conversions. Many routes for racemization can be imagined, for example, the direct process via conformer (c, c) [or (c', c')], or an indirect process via (c, t'), (t, t'), or (t', t'). In the kinetic process examined by ^{1}H-NMR, two peaks corresponding to the conformer (c, c) / (c', c') appeared quickly with the same integration values. Therefore, the racemization occurs predominantly through conformer (c, c) / (c', c'), as indicated by bold arrows in Figure 5. This process does not include the *cis/trans* conversion of the amide groups, which is consistent with the smaller energy barrier of the racemization than that of *cis/trans* isomerization of *N*-methylbenzanilides.

Absolute Configuration of 1 in the Chiral Crystal

The absolute configuration of **1** was determined from the configuration of the molecule in the mixed crystal with chiral 1,1'-bi-2-naphthol. The cocrystallization of **1** with (*R*)-1,1'-bi-2-naphthol from the 1:1 methanol solution afforded colorless prisms, $C_{42}H_{34}N_2O_4$. In the crystal structure of the mixed crystal, an asymmetric unit contains one molecule of **1** and one molecule of 1,1'-bi-2-naphthol, which interact with each other via hydrogen bondings (Figure 8). The cocrystallization of **1** using (*S*)-1,1'-bi-2-naphthol yielded enantiomeric crystals. This should be regarded as an example of chirality induction from a racemic solution of **1**. As 1,1'-bi-2-naphthol does not racemize under the crystallization conditions, the absolute configuration of **1** in the mixed crystal using (*R*)-1,1'-bi-2-naphthol is (*R*, *R*). Consequently, the enantiomeric mixed crystals contain (*S*)-1,1'-bi-2-naphthol and (*S*, *S*)-**1**.

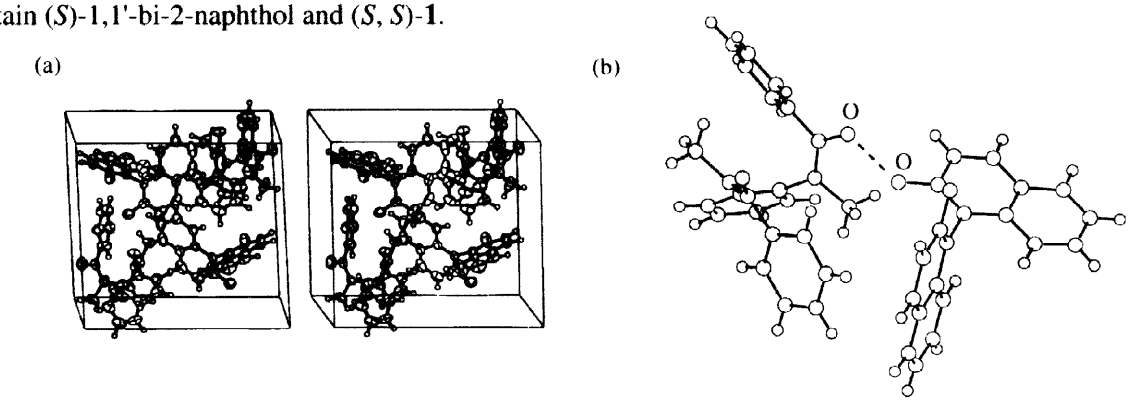


Figure 8. (a) An ORTEP stereoview of the crystal structure in the mixed crystal of **1** with (*R*)-1,1'-bi-2-naphthol. (b) Molecular structure of **1** and (*R*)-1,1'-bi-2-naphthol in the mixed crystal.

When the mixed crystals were dissolved in a solvent at low temperature, the same phenomena were observed as the case that the chiral crystals of **1** were dissolved in a solution of chiral 1,1'-bi-2-naphthol at low temperature. In the ^{1}H-NMR spectrum at 203 K just after the dissolution of the mixed crystals of (*R*, *R*)-**1** and (*R*)-1,1'-bi-2-naphthol at 203 K, only one singlet in the *N*-methyl region was observed, which corresponds to the peak A_2 in Figure 7b.[15] Enantiomeric crystals containing (*S*, *S*)-**1** and (*S*)-1,1'-bi-2-naphthol also exhibited the same signal. As time passed, another peak A_1 at higher field appeared, as well as the signals of other conformers. The signal observed first (peak A_2) corresponds to that of the (+)-crystal in the presence of (*R*)-1,1'-bi-2-naphthol, or of the (–)-crystal in the presence of (*S*)-1,1'-bi-2-naphthol. Thus, the absolute configurations in the (+)- and (–)-crystals were assigned as (*R*, *R*) and (*S*, *S*), respectively.

Conclusion

We have described an example of spontaneous generation of optical activity in a simple organic compound, 1,2-bis(*N*-benzoyl-*N*-methylamino)benzene (**1**), in which conformational interchange between the enantiomers is easy. In this compound, the chirality generated by crystallization is retained in solution at low temperature, and could be observed by NMR spectroscopy, even though the conformational conversion is rather fast. Further, the absolute configurations of **1** in the chiral crystal and in solution in the presence of a chiral reagent were determined. This is an interesting example of molecular chirality.

Experimental Section

General. All compounds subjected to measurement were purified by means of several recrystallizations. Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo and were within ±0.3% of the theoretical values.

***o*-Bis(*N*-benzoyl-*N*-methylamino)benzene (1)** Benzoyl chloride (130.4 g, 0.928 mol) was added to a solution of *o*-phenylenediamine (51.10 g, 0.464 mol) in 600 mL of pyridine. The mixture was stirred at room temperature overnight, then poured into 1 L of 2 N HCl. The precipitates were collected, washed successively with 4 N HCl (twice), H_2O, and ether, and dried under vacuum to give crude *o*-bis(*N*-phenylcarbamoyl)benzene (186.9 g). NaH (60 %, 27.0 g) was washed twice with 10 mL of *n*-hexane, and suspended in dry DMF. A solution of *o*-bis(*N*-phenylcarbamoyl)benzene in 500 mL of dry DMF was added to the suspension, and the mixture was stirred for 30 min. To this solution, 32.5 mL of MeI was added. After 1 h, NaH (27.0 g) and MeI (32.5 mL) was added to the reaction mixture. After 1 h, the solvent and excess MeI were removed under vacuum. The residue was diluted with CH_2Cl_2, and washed with 2 N HCl, brine and water. The organic layer was dried over $MgSO_4$ and evaporated. The crude product was recrystallized from CH_2Cl_2-AcOEt to give **1**. **1**: mp 164.5-165.5°C. Anal. calcd for $C_{22}H_{22}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.46; H, 5.80; N, 8.18. Physicochemical properties of **1** are given in Table II.

X-ray Crystallography[16] Intensity data were collected with a Rigaku AFC5 diffractometer using graphite-monochromated Cu $K\alpha_1$ radiation (λ = 1.54050 Å) by the ω-2θ scan method. The typical ω scan width was $(1.3 + 0.41 \tan\theta)°$. Intensities were corrected for Lorentz and polarization factors, but no correction was made for absorption. Structures were solved by using the SAPI85 version of the program package MULTAN.[17] The refinement was carried out by the full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms. The function minimized was $\Sigma w(|(|Fo|)^2-(|Fc|)^2|)^2$ with $w = 1/[\sigma^2(Fo) + 0.02(Fo)^2]$, while $\sigma(Fo)$ was determined from counting statistics. All H atoms located from the difference map and from theoretical calculations were refined. All calculations were performed by using a Panafacom computer with the RCRYSTAN (Rigaku Corp., 1985) X-ray analysis program system. Crystal data are listed in Table III.

Table III. Crystal data for **1** and the **1**·(*R*)-1,1'-bi-2-naphthol complex

Compound	chiral crystals	achiral crystals	**1**·(*R*)-1,1'-bi-2-naphthol
Formula	$C_{22}H_{20}N_2O_2$	$C_{22}H_{20}N_2O_2 \cdot H_2O$	$C_{42}H_{34}N_2O_4$
M_r	344.41	362.43	602.73
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$	$P2_1$
a / Å	14.198(1)	10.048(1)	14.4556(6)
b / Å	16.374(1)	21.441(2)	13.270(4)
c / Å	8.261(1)	9.385(1)	9.0788(4)
β / °	–	109.67(1)	104.355(3)
V / Å^3	1920.5(2)	1903.7(4)	1687.2(6)
D_x / Mgm^{-3}	1.191	1.264	1.241
Z	4	4	2
No. of unique reflections	1504	2058	2441
R	0.047	0.067	0.056

CD Spectra CD spectra were taken with a JASCO J-600 equipped with a handmade cooling system for low-temperature measurements. A specimen for measurement of the solid state spectrum was prepared as follows: 100 μg of **1** was added to 100 mg of KBr (dried by heating before use), and the mixture was well ground, and tableted.

^{1}H-NMR Analysis ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX400 (400 MHz) spectrometer. The temperature of the measurements was taken to be the indicated temperature on the spectrometer and was checked by measuring the difference of chemical shifts between the methyl protons and the hydroxyl proton of methanol.[18] Solvents used for the measurements (range of temperature, internal standard) were dichloromethane-d_2 (183 - 293 K, $CD\underline{H}Cl_2$ as 5.30 ppm) and chloroform-d (213 - 323 K, $C\underline{H}Cl_3$ as 7.26 ppm). Measurements were started at room temperature (293 K) and the temperature was increased or reduced in steps of 10 K. The concentration of the solution was 10 mg/ml; no change of the spectra was observed at a more dilute concentration (1 mg/ml).

References

1 Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**.

2 Suh, I.-H.; Park, K. H.; Jensen, W. P.; Lewis, D. E. *J. Chem. Educ.* **1997**, *74*, 800-805.

3 (a) Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.*, **1973**, *95*, 2692-2693. (b) Hoyano, Y, Y.; Pincock, R. E. *Can. J. Chem.* **1980**, *58*, 134-137.

4 (a) Theilacker, W.; Hopp, R. Chem. Ber., **1959**, *92*, 2293-2301. (b) Theilacker, W.; Böhm, H. *Angew. Chem. Int. Ed. Eng.* **1967**, *6*, 251.

5 Recent selected papers on helical molecules: (a) Williams, A. *Chem. Eur. J.* **1997**, *3*, 15-19. (b) Bassani, D. M.; Lehn, J.-M.; Baum, G.; Fenske, D. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1845-1847. (c) Hamuro, Y.; Geib, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1997**, *119*, 10587-10593. (d) Grimme, S.; Harren, J.; Sobanski, A.; Vögtle, F. *Eur. J. Org. Chem.* **1998**, 1491-1509. (e) Kiupel, B.; Niederalt, C.; Nieger, M.; Grimme, S.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 3031-3034.

6 Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1997**, *30*, 307-314.

7 (a) Newman, A. C. D.; Powell, H. M. *J. Chem. Soc.* **1952**, 3747-3751. (b) Pincock, R. E.; Wilson, K. R. *J. Chem. Educ.* **1973**, *50*, 455-457. (c) Martin R. H. *Angew. Chem. Int. Ed.* **1974**, *13*, 649-660. (d)Toda, F.; Yagi, M.; Soda, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1413-1414. (e) Casarini, D.; Lunazzi, L.; Pasquali, F.; Gasparrini, F.; Villani, C. *J. Am. Chem. Soc.* **1992**, *114*, 6521-6527. (f) Maeda, K.; Okamoto, Y.; Morlender, N.; Haddad, N.; Eventova, I.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1995**, *117*, 9686-9689. (g) Gasparrini, F.; Lunazzi, L.; Misiti, D.; Villani, C. *Acc. Chem. Res.* **1995**, *28*, 163-170.

8 (a) Clarke, P. T.; Spink, J. M. *Acta Crystallogr. B* **1969**, *25*, 162. (b) Chowdhury, P. R. *Acta Crystallogr.* **1973**, *B29*, 1362.

9 Jacques, J.; Collet, A.; Wilen, S. M. *Enantiomers, Racemates, and Resolutions*, J. Wiley & Sons, NY, 1981.

10 (a) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *12*, 191-197. (b) Sakamoto, M. *Chem. Eur. J.* **1997**, *3*, 684-689.

11 Typical examples for asymmetric synthesis in solid state: (a) Penzien, K.; Schmidt, M. J. *Angew, Chem, Int. Ed. Engl.* **1969**, *8*, 608-609. (b) Sekine, A.; Hori, K.; Ohashi, Y.; Yagi, M.; Toda, F. *J. Am. Chem. Soc.* **1989**, *111*, 697-699. (c) Hasagawa, M.; Chung, C.-M.; Muro, N. Maekawa, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5676-5677. (d) Toda, F.; Miyamoto, H.; Kikuchi, S.; Kuroda, R.; Nagami, F. *J. Am. Chem. Soc.* **1996**, *118*, 11315-11316. (e) Sakamoto, M.; Takahashi, M.; Moriizumi, S.; Yamaguchi, K.; Fujita, T.; Watanabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 8138-8139. (f) Koshima, H.; Ding, K.; Chisaka, Y.; Matsuura, T. *J. Am. Chem. Soc.* **1996**, *118*, 12059-12065.

12 (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177-6180. (b) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649-10650. (c) Azumaya, I.; Yamaguchi, K.; Kagechika, H.; Saito, S.; Itai, A.; Shudo, K. *Yakugaku Zasshi* **1994**, *114*, 414-430.

13 (a) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron* **1995**, *51*, 5277-5290. (b) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1996**, *37*, 5003-5006. (c) Tanatani, A.; Kagechika, H.; Azumaya, I.; Fukutomi, R.; Ito, Y.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1997**, *38*, 4425-4428. (d) Tanatani, A.; Yamaguchi, K.; Azumaya, I.; Fukutomi, R.; Shudo, K.; Kagechika, H. *J. Am. Chem. Soc.* **1998**, *120*, 6433-6442.

14 (a) Kagechika, H.; Azumaya, I.; Yamaguchi, K.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *4*, 460-462. (b) Fukutomi, R.; Tanatani, A.; Kakuta, H.; Tomioka, N.; Itai, A.; Hashimoto, Y.; Shudo, K.; Kagechika, H. *Tetrahedron Lett.* **1998**, *39*, 6475-6478.

15 Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083-9084.

16 Yamaguchi, K. *Chem. Pharm. Bull.*, **1993**, *41*, 424-429.

17 SAPI85: Yao, J.-X.; Zheng, C.-D.; Qian, J.-Z.; Han, F.-S.; Gu, Y.-X.; Fan, H.-F. (**1985**); MULTAN78: Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. (**1978**).

18 Van Geet, A. L. *Anal. Chem.*, **1970**, *42*, 679-680.