Total Asymmetric Transformation of an *N*-Methylbenzamide

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The amide bond of *N*-methylbenzanilides prefers the cis conformation.[1] This discovery led us to construct several structurally characteristic compounds. During the investigations, we found an interesting compound, 1,2-bis(*N*-benzoyl-*N*-methylamino)benzene (**1**), which exists in an optically active form in solution and in the crystal.

Compound **1** can be prepared by a conventional method. Crystals (mp 148 °C) obtained from wet ethyl acetate included one molecule of water per molecule of **1** and were optically inactive.[2] Recrystallization of **1** from dry ethyl acetate yielded beautiful crystals, each of which was optically active (mp 164.5 °C). Sometimes all the crystals belonged to the same chiral group, or one large crystal spontaneously formed from a solution in good yield (complete generation of single chirality: total asymmetric transformation). If we used a seed crystal, we could obtain crystals with the same chirality as the seed crystal. The optically active crystals are orthorhombic and are classified into the space group $P2_12_12_1$.[2] As shown in Figure 1, the molecule has C_2 symmetry and the amide structures are cis. Two phenylcarbamoyl groups are located on opposite sides of the central benzene ring (anti conformation[3]). In a unit cell, there exist four molecules, all having the same chiral conformations.

The circular dichroic (CD) spectra of the two chiral crystals in KBr are shown in Figure 2a: the crystals are optically active and enantiomeric, designated as (+) and (−) crystals by the sign of ellipticity at 260 nm. The solutions prepared by dissolving optically active crystals at 173 K showed CD spectra similar to those of the crystals (Figure 2b). The CD curves became flat when the solutions were warmed to room temperature. The racemization is fast in solution at room temperature.

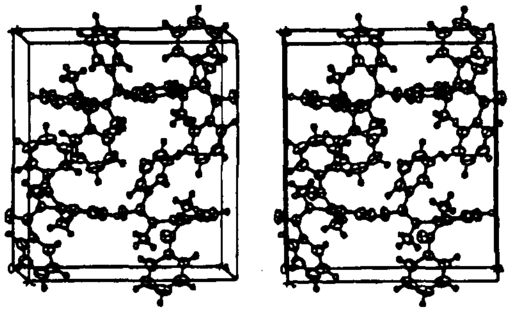


Figure 1. ORTEP stereoview of the crystal structure of **1**.

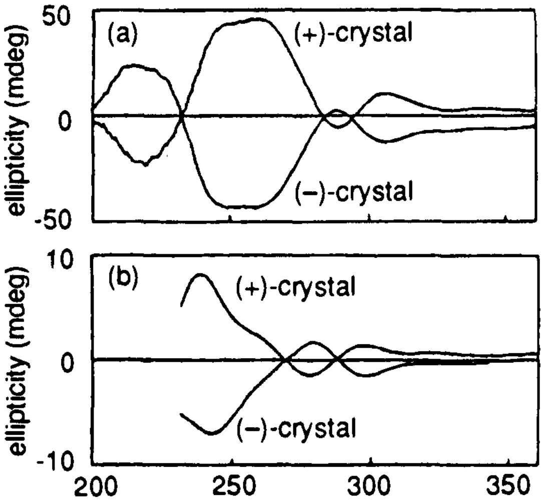
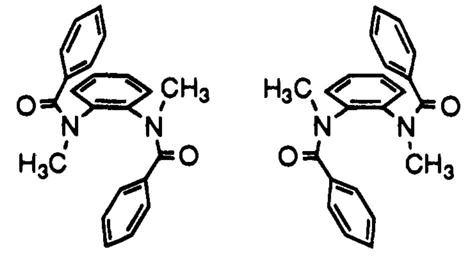


Figure 2. (a) CD spectra of two enantiomeric crystals of **1** in KBr. A mixture of 100 μg of **1** and 100 mg of KBr was well ground and formed into a disk with a radius of 5 mm. (b) CD spectra of the two enantiomers of **1** (2×10^{-3} M) in methanol/ethanol (1:3 v/v) at 173 K after dissolution at that temperature. The spectra below 250 nm are not accurate because the transmitted light is faint in that region.

Chart 1



(S, S)-**1** *(R, R)*-**1**

The ^{1}H-NMR spectrum of **1** at room temperature showed only broadened peaks, but there are seven singlet peaks for *N*-methyl groups at 183 K (Figure 3a). Therefore, **1** exists in equilibrium among several conformers, which arise from *cis*/*trans*-amide configurations and syn/anti conformations.[3] When chiral crystals of **1** were dissolved in CD_2Cl_2 at 178 K and the ^{1}H-NMR spectrum was taken immediately at 183 K, only one peak for *N*-methyls was observed (Figure 3b), corresponding to the most major peak (60%) in the spectrum of an equilibrium solution of **1**, and was converted slowly at 183 K to the seven peaks. From this result and the chemical shifts of *N*-methyl groups shielded to high field due to the anisotropy of the terminal benzene ring, this major species in solution is the anti-cis/cis conformer (Chart 1).

The enantiomers could be distinguished by NMR in a solution containing chiral 1,1′-bi-2-naphthol (**2**). When **2** was added to a racemic solution of **1**, the observed peaks for the *N*-methyls were split into two sets of peaks (Figure 3c). The spectrum of **1** just after dissolving of the (+) crystal at 178 K in a CD_2Cl_2 solution of (*S*)-**2** afforded one singlet for *N*-methyls (Figure 3d) that corresponds to the right peak (higher field) of the divided

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(2) Crystal data for $C_{22}H_{20}N_2O_2{\cdot}H_2O$ (**1**·H_2O): monoclinic, space group $P2_1/n$, $a = 10.048(1)$ Å, $b = 21.441(2)$ Å, $c = 9.385(1)$ Å, $\beta = 109.67(1)°$, $V = 1903.7(4)$ Å^3, $Z = 4$, $D_{calcd} = 1.263$ g cm^{-3}, λ(Cu Kα_1) = 1.540 50 Å, $T = 293$ K, $R = 0.058$ for 1693 reflections. Crystal data for $C_{22}H_{20}N_2O_2$ (**1**): orthorhombic, $P2_12_12_1$, $a = 14.198(1)$ Å, $b = 16.374(1)$ Å, $c = 8.261(1)$ Å, $V = 1920.5(2)$ Å^3, $Z = 4$, $D_{calcd} = 1.191$ g cm^{-3}, λ(Cu $K\alpha_1$) = 1.540 50 Å, $T = 293$ K, $R = 0.046$ for 1438 reflections. Crystal data for mixed crystal of **1** and (*R*)-**2** $C_{42}H_{34}N_2O_4$: monoclinic, space group $P2_1$, $a = 14.4556(6)$ Å, $b = 13.270(4)$ Å, $c = 9.0788(4)$ Å, $\beta = 104.355(3)°$, $V = 1687.2(6)$ Å^3, $Z = 2$, $D_{calcd} = 1.241$ g cm^{-3}, λ(Cu $K\alpha_1$) = 1.540 50 Å, $T = 293$ K, $R = 0.056$ for 2441 reflections. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Center.

(3) Syn and anti are defined as conformations having *N*-benzoyl groups on the same side or opposite sides of the central benzene ring, respectively.

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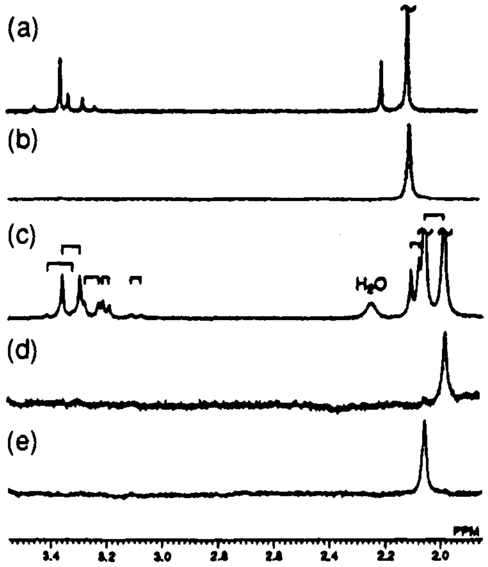

Figure 3. ^{1}H-NMR spectra (*N*-methyl region) of **1** in CD_2Cl_2 at 183 K. (a) **1** was dissolved at room temperature and then cooled. (b) A chiral crystal ((+) or (−)) was dissolved at 178 K in CD_2Cl_2, and immediately measured. (c) A (+) or (−) crystal was dissolved in a CD_2Cl_2 solution of (*S*)-**2** (15 equiv) at room temperature. (d) A (+) crystal was dissolved in a CD_2Cl_2 solution of (*S*)-**2** (15 equiv) at 178 K and immediately measured. (e) A (−) crystal was dissolved in a CD_2Cl_2 solution of (*S*)-**2** (15 equiv) at 178 K and immediately measured.

major peaks in Figure 3c. As for the (−) crystal, the observed singlet peak corresponds to the left peak (Figure 3e). In each case, once the temperature was raised to room temperature and then recooled, the spectrum became the same as that shown in Figure 3c. On the contrary, using (*R*)-**2** and the (+) or (−) crystal afforded spectra like Figure 3, parts e and d, respectively.

Cocrystallization of **1** with (*R*)-**2** from a 1:1 methanolic solution afforded colorless prisms (mp 163.5−164.5 °C). The structure of the mixed crystal contains one molecule of (*R*)-**2** and one molecule of **1** in an asymmetric unit (Figure 4).[2] Since (*R*)-**2** does not racemize during the crystallization process, the absolute configuration of **1** in the mixed crystal was determined as (*R*,*R*). When this mixed crystal containing (*R*,*R*)-**1** and (*R*)-**2** was dissolved in CD_2Cl_2 at 183 K, there was one signal for the major peak of *N*-methyls just after the dissolution (Figure 5a). This peak corresponds to that in Figure 3e, the peak at the lower field among the major *N*-methyl signals divided by the chiral 1,1′-bi-2-naphthol. As time passed, another peak at higher field appeared. The (+) crystal in the presence of (*R*)-**2** afforded the peak at lower field as shown in Figure 3e. Therefore, the absolute configuration of the molecule in the (+) crystal is assigned to (*R*,*R*). In the case of another mixed crystal prepared from (*S*)-**2** and **1** [(*S*,*S*)], the same phenomenon was observed (Figure 5b), because the configurations of the molecules of **1** and **2** are both inverted: the (−) crystal is assigned to (*S*,*S*).

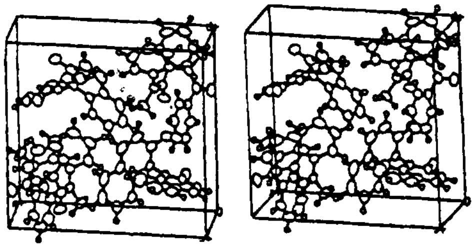

Figure 4. ORTEP stereoview of the structure of the mixed crystal of **1** with (*R*)-**2**.

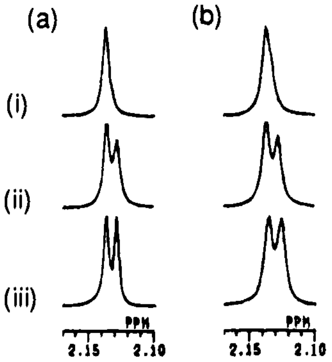

Figure 5. (a) ^{1}H-NMR (the major *N*-methyl signal) of the mixed crystal of (*R*,*R*)-**1** and (*R*)-**2** at 203 K. (i) Sample was prepared at 203 K and immediately measured. Then, the sample was kept (ii) at 213 K for 60 min and (iii) at 243 K for 10 min before measurement. (b) The same experiments for the mixed crystal of (*S*,*S*)-**1** and (*S*)-**2**.

The present observations show a simple example of molecular chirality.[4,5] This work illustrates that a differential interaction with an optically active compound, such as that of the conformationally racemic mixture, should be observed, in principle, in all compounds with restricted conformational interconversion, depending on the conversion barrier.

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