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<td>Author(s)</td>
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Formation of racemic compound crystals by mixing of two enantiomeric crystals in the solid state. Liquid transport of molecules from crystal to crystal

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Introduction

Because of the strong influence of the famous Aristotelian philosophy "no coopora nisi fluida" which means "no reaction occurs in the absence of solvent", most organic reactions have been studied in solution. We have found, however, that many organic reactions can be carried out in the absence of solvent and that indeed many solid state reactions proceed more selectively and efficiently than do solution reactions. Such solid state reactions show that molecules move easily from reagent crystal to reactant crystal. After this molecular movement, reaction occurs on the surface of the reactant crystal. This process has been studied by AFM (atomic force microscopy) experiments. The molecular movement in the solid state has also been observed spectroscopically. For example, host–guest inclusion complexation in the solid state can be followed by IR or UV spectroscopy. Host–guest inclusion complexation in the solid state proceeds stereo- and enantio-selectively. When powdered optically active crystals are mixed with powdered racemite guest crystals, enantioselective molecular movement occurs and optical resolution of the racemic guest compound can be achieved in the solid state. By a combination of the enantioselective molecular movement in the solid state and fractional distillation, optical resolution can be achieved by distillation in the presence of an optically active host. By mixing an optically active host and racemic guest in the solid state, one enantiomer of the guest forms an inclusion complex with the host by molecular movement and then the uncomplexed enantiomer distils at a relatively low temperature without degradation of the inclusion complex. By further heating at a relatively high temperature, the inclusion complex decomposes and the complexed enantiomer distils out. By this method, very efficient resolution of various kinds of guest compounds has been accomplished. By a similar procedure, stereoisomers with the same or very similar boiling points can be separated by distillation in the presence of a host compound. Much more interesting molecular movement in the solid state occurs between a chiral host and prochiral guest. Mixing of powdered optically active host and prochiral guest gives the host–guest inclusion complex in which the latter molecules are arranged in a chiral form and which upon photoirradiation in the solid state gives an optically active photoresist material. Formation of charge-transfer (CT) complex crystals by mixing powdered acceptor and donor crystals in the solid state has also been known for a long time. Quinhydrone is easily formed without degradation of the inclusion complex. By further heating, the complex decomposes and the complexed enantiomer distils at a relatively low temperature. Formation of various CT complex crystals by the mixing method has been reported, and the CT complex crystals produced by the mixing method showed comparable electrical conductivity to that of the complex prepared by crystallization of the components from a solvent. Formation of co-crystals of nitrile derivatives with anthracene by mixing both components in the solid state has also been reported. Formation of co-crystals of nitrile derivatives with anthracene by mixing both components in the solid state has also been reported.
In order to understand the molecular movement from crystal to crystal more precisely, we studied the formation of racemic host compound crystals by mixing two enantiomer crystals in the solid state using IR spectroscopic and X-ray crystal structural studies. We mostly studied the formation of racemic host crystals from (−)- and (+)-host crystals. During these studies on molecular movement, we found that the formation of racemic crystals is accelerated by liquids such as liquid paraffin, seed oil, silicone oil, and water, although the same phenomenon also occurs slowly in the absence of the liquid.

**Materials**

Optically active 2,2′-dihydroxy-1,1′-binaphthyl (1a, 1b) and its 6,6′-dibromo derivative (2a, 2b) were prepared by optical resolution of their racemates 1c and 2c, respectively, through inclusion complexation with N-benzylcinchoninium chloride. The monomethyl ether of 2a (3a) was prepared according to the reported method. Optically active 10,10′-dihydroxy-9,9′-biphenanthryl (4a, 4b) were prepared by resolution of its racemate (4c) through complexation with N-butylcinchoninium bromide.

Optically active 2,2′-dihydroxy-4,4′,6,6′-tetramethylbiphenyl (5a, 5b) and 4,4′-dihydroxy-2,2′,3,3′,6,6′-hexamethylbiphenyl (8a, 8b) were prepared by optical resolution of their racemates by complexation with N-benzylcinchoninium chloride and (−)-trans-2,3-bis[hydroxy(diphenyl)methyl]-1,4-dioxaspiro[4.4]nonane (18a), respectively, according to the reported method. However, these methods were not applicable to the resolution of 6c and 7c. Optically active 3,3′,4,4′,6,6′-hexamethyl-6a, 6b and 5,5′-dichloro-4,4′,6,6′-tetramethyl-2,2′-dihydroxybiphenyl (7a, 7b) were obtained by complexation of their racemates with (−)-trans-1,2-diaminocyclohexane (9a).

When a solution of 9a (0.63 g, 5.52 mmol) and 6c (2 g, 7.4 mmol) in toluene (0.3 ml) was kept at room temperature for 2 h, a 1:1 inclusion complex of 9a and 6b was obtained (1.18 g). Recrystallization of the crude crystal (1.18 g) from toluene gave pure crystals (0.8 g, mp 117–125°C). These were dissolved in AcOEt (20 ml)-dil. HCl (20 ml), and the AcOEt layer was washed with water and dried over Na2SO4. Evaporation of the solvent from the dried AcOEt solution gave 6b of 100% enantiomeric excess (ee) as colorless needles (0.39 g, 39% yield, mp 127°C, [α]D +23.7 (c 1.0, MeOH)). The filtrate left after separation of the crude 1:1 complex of 9a and 6b was dissolved in AcOEt (20 ml)-dil. HCl (20 ml), and the AcOEt layer was washed with water and dried over Na2SO4. Evaporation of the filtrate from the dried AcOEt solution gave 6a of 90% ee (0.88 g, 88% yield) which upon recrystallization from toluene gave 6a of 100% ee (0.25 g, 25% yield). By a similar resolution, 7a and 7b of 100% ee were obtained. When a solution of 9a (1.14 g, 9.98 mmol) and 7c19 (2 g, 6.68 mmol) in toluene (0.4 ml) was kept at room temperature for 5 h, a 2:1 crude complex of 9a and 7b was obtained, which upon two recrystallizations from toluene gave the pure complex (1.52 g) (1.52 g) was dissolved in AcOEt (20 ml)-dil. HCl (20 ml), and the AcOEt layer was washed with water and dried over Na2SO4. Evaporation of the filtrate from the AcOEt solution gave 7b of 100% ee (0.94 g, 0.39 mmol, 70% yield, mp 235°C, [α]D +67.2 (c 1.0, MeOH)). From the toluene solution left after separation of the crude 2:1 complex of 9a and 7b, 7a of 100% ee (0.25 g, 25% yield) was obtained by the same procedure as that applied to the isolation of 6b. Very interestingly, however, 9a formed a 1:1 complex with racemic guests 7c, although 9a formed a 2:1 complex with optically active guest 7b as described above. For example, when a solution of 9a (0.76 g, 6.66 mmol) and 7c (2 g, 6.68 mmol) in toluene (0.3 ml) was kept at room temperature for 2 h, a 1:1 complex of 9a and 7c was formed as colorless needles (2.43 g, 88% yield), from which 7c was isolated (1.6 g, 80% yield). The optical purity of 6 and 7 was determined by HPLC on the chiral stationary phase Chiralpak A5.

A cetylenic alcohol host compounds (11, 12, 14–16) were prepared by the following method. Optically active 1,6-dial(o-chlorophenyl)-1,6-diphenyloxepha-2,4-diyne-1,6-diol (11a, 11b), its bromoanalog (12a, 12b), and 1,6-diphenyl-1,6-di(tert-butyl)- hexa-2,4-diyne-1,6-diol (16a, 16b) were prepared according to the reported method. Optically active 1,6-bis(o-toly)-1,6-diphenyloxepha-2,4-diyne-1,6-diol (14a, 14b) (mp 109–112°C, [α]D 19 (c 0.9, MeOH)) and 1,6-diphenyloxepha-2,4-diyne-1,6-diol (15a, 15b) (mp 118–120°C, [α]D 0.4 (c 0.6, MeOH)) were prepared as described above.
prepared by CuCl₂-catalyzed coupling reaction in pyridine of the optically active 1-(o-tolyl)-1-phenylprop-2-yn-1-ol (13a) and 1-phenylhepta-2,4-diyne-1,6-diol (13b), respectively. Optically active trans-4,5-bis(hydroxy(diphenyl)methyl)-2,2-dimethyl-1,3-dioxacyclopentane (17a, 17b)²¹ and trans-2,3-

bis[hydroxy(diphenyl)methyl]-1,4-dioxaspiro[5.4]decane (19a, 19b)²¹ were prepared according to the reported methods. Commercially available samples of optically active tartaric acid (20), dimethyl tartrate (21), malic acid (22), mandelic acid (22), and norephedrine (24) were used for the experiments.

Cocrystallizations

Powdered (−)- and (+)-crystals (5 mg each) were mixed with liquid paraffin (20 mg) to give the Nujol mull as a paste, the IR spectrum of which was recorded. Racemic crystals for X-ray analysis were prepared by crystallization of the same amount of (−)- and (+)-enantiomeric crystals from the appropriate solvent, toluene or diethyl ether. For example, recrystallization of 16a (100 mg) and 16b (100 mg) from toluene (5 ml) gave 16c as colorless prisms (140 mg, 70% yield, mp 141 °C).

IR spectra

All IR spectra were recorded on a Jasco FT-IR Spectrophotometer FT-IR 300 for Nujol mulls using NaCl windows unless otherwise stated. FT-IR spectra were recorded on a Shimazu FT-IR Spectrophotometer FT-IR 4200 in the absence of liquid paraffin.

X-ray analyses

The single crystals suitable for X-ray analysis were obtained by recrystallization from EtOH for 1a, from MeCN for 1c, from toluene for 5b, 7c, 7c, 1:1 complex of 8b with 10b, 11c, 1:1 cocrystal of 11b and 12a, 16b, 16c, 17a, 19a, and 19c, from either for 18a and 18c, and from EtCN for 17c. All the data were collected on a Rigaku AFC7R four circle diffractometer with graphically monochromated CuKα or MoKα radiation and a rotating anode generator (50 K V, 200 mA). All these data are summarized in Table 1. The structures were solved using direct methods.²⁸ The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were included in the structure factor calculations, except for 11b. No absorption correction was applied except that mentioned in the crystal data. All calculations were performed using the teXsan crystallographic software package.²⁷ Although X-ray data for 1a,²⁸ and 17a and 17c²⁹ have been reported, we used our own data, because of their improved quality.

Results and discussion

Formulation of 1c, 2c and 4c in the solid state

When IR spectra of a 1:1 mixture of 1a and 1b were measured as a Nujol mull every 5 min for 1 h, the O-H absorptions of 1a and 1b at 3510 and 3435 cm⁻¹ decreased gradually and finally disappeared after 1 h, and new O-H absorptions of 1c appeared at 3485 and 3405 cm⁻¹ [Fig. 1(a)]. The latter two O-H absorptions are identical to those of 1c prepared by crystallization of 1a and 1b from a solvent. This result shows that optically active molecules of 1a and 1b move between their crystals and form

Table 1  Summary of crystal data

<table>
<thead>
<tr>
<th>Compound</th>
<th>Space group</th>
<th>a/Å</th>
<th>b/Å</th>
<th>c/Å</th>
<th>β° (α, β, γ)</th>
<th>Z</th>
<th>D, g cm⁻³</th>
<th>R</th>
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<tr>
<td>1a</td>
<td>P₃₉</td>
<td>10.795(9)</td>
<td>—</td>
<td>10.865(2)</td>
<td>—</td>
<td>3</td>
<td>1.301</td>
<td>0.038</td>
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<tr>
<td>1c</td>
<td>P3₁</td>
<td>10.795(9)</td>
<td>15.687(2)</td>
<td>8.617(1)</td>
<td>—</td>
<td>8</td>
<td>1.303</td>
<td>0.040</td>
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<tr>
<td>5b*</td>
<td>P2₁2₁2₁</td>
<td>8.905(1)</td>
<td>20.546(2)</td>
<td>7.463(1)</td>
<td>—</td>
<td>4</td>
<td>1.179</td>
<td>0.042</td>
</tr>
<tr>
<td>5c</td>
<td>P2₁</td>
<td>11.181(3)</td>
<td>7.653(2)</td>
<td>16.590(2)</td>
<td>106.43(1)</td>
<td>4</td>
<td>1.162</td>
<td>0.047</td>
</tr>
<tr>
<td>7b</td>
<td>P2₁</td>
<td>8.381(2)</td>
<td>8.522(3)</td>
<td>41.651(3)</td>
<td>8</td>
<td>1.390</td>
<td>0.058</td>
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<tr>
<td>7c</td>
<td>P2₁</td>
<td>8.561(3)</td>
<td>8.310(3)</td>
<td>21.093(5)</td>
<td>94.662(4)</td>
<td>4</td>
<td>1.382</td>
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<td>8b-10b</td>
<td>P2₁</td>
<td>9.085(5)</td>
<td>11.050(3)</td>
<td>11.520(2)</td>
<td>97.233(2)</td>
<td>2</td>
<td>1.192</td>
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<tr>
<td>11a</td>
<td>P₂₁2₁2₁</td>
<td>16.78(4)</td>
<td>41.5(1)</td>
<td>8.030(8)</td>
<td>—</td>
<td>8</td>
<td>1.147</td>
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<tr>
<td>11c</td>
<td>C2</td>
<td>21.209(2)</td>
<td>11.5299(9)</td>
<td>9.627(1)</td>
<td>93.910(9)</td>
<td>4</td>
<td>1.367</td>
<td>0.033</td>
</tr>
<tr>
<td>11b-12a</td>
<td>C2</td>
<td>21.209(2)</td>
<td>11.5394(9)</td>
<td>9.619(2)</td>
<td>93.94(2)</td>
<td>4</td>
<td>1.481</td>
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<tr>
<td>16b</td>
<td>P2₁2₁2₁</td>
<td>14.048(3)</td>
<td>25.726(2)</td>
<td>6.069(2)</td>
<td>—</td>
<td>4</td>
<td>1.134</td>
<td>0.046</td>
</tr>
<tr>
<td>16c</td>
<td>P1</td>
<td>12.209(2)</td>
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<td>102.30(1)</td>
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<td>1.105</td>
<td>0.071</td>
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<tr>
<td>17a</td>
<td>P1</td>
<td>11.870(1)</td>
<td>12.847(1)</td>
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<td>97.361(1)</td>
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<tr>
<td>17c</td>
<td>P1</td>
<td>11.324(3)</td>
<td>12.081(3)</td>
<td>9.679(2)</td>
<td>102.051(1)</td>
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<td>0.071</td>
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<tr>
<td>18a</td>
<td>C2</td>
<td>15.700(2)</td>
<td>9.325(1)</td>
<td>18.455(1)</td>
<td>105.372(7)</td>
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<td>1.256</td>
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<tr>
<td>18c</td>
<td>P2₁m</td>
<td>14.042(2)</td>
<td>13.100(3)</td>
<td>14.400(2)</td>
<td>95.99(1)</td>
<td>4</td>
<td>1.242</td>
<td>0.058</td>
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<tr>
<td>19a</td>
<td>P2₁2₁2₁</td>
<td>10.212(4)</td>
<td>29.284(3)</td>
<td>9.314(2)</td>
<td>—</td>
<td>4</td>
<td>1.208</td>
<td>0.036</td>
</tr>
<tr>
<td>19c</td>
<td>P1</td>
<td>12.322(9)</td>
<td>13.1134(6)</td>
<td>9.140(6)</td>
<td>93.099(5)</td>
<td>2</td>
<td>1.228</td>
<td>0.059</td>
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* Absolute configuration not determined
crystals of the racemic compound 1c in the solid state. This molecular movement is surprisingly fast. This phenomenon is not special for 1 but rather common. When IR spectra of a 1 : 1 mixture of 2a and 2b were measured for 20 min, their OH absorptions at 3470 and 3430 cm\(^{-1}\) disappeared completely and new OH absorptions of 2c appeared at 3455 cm\(^{-1}\). Such molecular movement was also observed for 4. During IR measurement of a 1 : 1 mixture of 4a and 4b for 1 h, their OH absorptions at 3520, 3500 and 3480 cm\(^{-1}\) disappeared completely and new absorptions for 4c appeared at 3520, 3500 and 3485 cm\(^{-1}\). The absorptions of 4c were identical to those of the racemic compound prepared by crystallization of 4a and 4b from a solvent.

Since 3c was not formed by mixing 3a and 3b in the solid state, the two hydroxy groups of 1, 2 and 4 seem to be essential for the molecular movement. Furthermore, when IR spectra of a 1 : 1 mixture of 1a and 1b were measured in the absence of liquid paraffin by a diffraction method, it took 48 h to complete the formation of 1c [Fig. 1(b)], although one hour is enough to complete the molecular movement for a Nujol mull. This strongly suggests that the molecular movement in the solid state occurs even in the absence of liquid such as liquid paraffin (Nujol), but is accelerated very much by a liquid.

In order to study the mechanism of the formation of 1c crystals by molecular assembly between 1a and 1b, X-ray crystal structures of 1a and 1c were analyzed. In 1a crystals, the molecules are stacked around a 3\(_2\) screw axis to form a left-handed helical structure through a hydrogen bond O-H??O of length 2.96 Å (Fig. 2). The dihedral angles between the two naphthalene rings are 101.7\(^\circ\). In 1c crystals, 1a and 1b molecules with a dihedral angle of 90.6\(^\circ\) from a typical hydrogen bonded helical structure along the 2\(_1\) screw axis with O-H??O = 2.84 Å (Fig. 2). The crystal structure is characterized by the alternate packing of the helical structure consisting of 1a molecules and that of 1b molecules.

The inside of the 3\(_2\) and 2\(_1\) helical structures is hydrophilic and the outside is hydrophobic with van der Waals interactions only between the helical structures. Each diol molecule in the helical structure is hydrogen bonded to its neighboring molecules by one donor and one acceptor bond, resulting in one of the hydroxy hydrogen atoms being free from hydrogen bonding. From the crystal structural point of view, the formation of 1c crystals from 1a and 1b crystals looks just like a mutual penetration of 3\(_2\) and 2\(_1\) helical structures through the interface between enantiomeric crystals, followed by the conversion of
three-fold screw structures into two-fold screw structures. Since the hydrogen bond is shorter in 1c than in 1a, the dihedral angle in 1c is closer to rectangular than that in 1c and the density of 1c is slightly larger than that of 1a. Hence the molecular packing in 1c would be more favorable than that in 1a. The two OH absorptions of 1a at 3510 and 3435 cm\(^{-1}\) can be assigned to the stretching of the two OH groups which act as hydrogen acceptor and donor, respectively (Fig. 2). Similarly, the two OH absorptions of 1c at 3470 and 3430 cm\(^{-1}\) are assignable to the two OH groups which are a hydrogen acceptor and a hydrogen donor, respectively (Fig. 2).

The difference in the heat of melting of 1c (AH 32 k mol\(^{-1}\)) and 1a, 1b (AH 29 k mol\(^{-1}\)) recorded by DSC measurements also indicates that 1c crystals are more stable than 1a and 1b crystals. The more stable structure of 1c would be a driving force to cause molecular movement between 1a and 1b and the formation of 1c in the solid state. Nevertheless, it is very interesting that the two chiral crystals in which 1a and 1b molecules are arranged so as to form a three-fold screw axis (clockwise and anti-clockwise, respectively) give racemic crystals 1c in which two kinds of two-fold screw axes with alternate clockwise and anti-clockwise arrangements are produced just by mixing 1a and 1b crystals for a short time in the solid state.

Formation of 5c, 6c, 7c and 8c in the solid state

By successive IR spectral measurements of a 1:1 mixture of 5a and 5b in Nujol mulls every 5 min for 30 min, the original OH absorptions at 3480 and 3420 cm\(^{-1}\) turned into those of 5c at 3480 and 3420 cm\(^{-1}\). By similar measurements of a 1:1 mixture of 6a and 6b (3530, 3510 and 3460 cm\(^{-1}\)) for 30 min and of 7a and 7b (3495 and 3450 cm\(^{-1}\)) for 3 h, the OH absorptions indicated turned into those of 6c at 3520, 3468 and 3420 cm\(^{-1}\) and those of 7c at 3490 and 3430 cm\(^{-1}\), respectively. The formation of 6c is extremely fast. However, the formation of 8c from 8a and 8b is relatively slow. When successive IR spectra of a 1:1 mixture of 8a and 8b were measured, the original OH absorptions at 3270 cm\(^{-1}\) disappeared after 5 h and the new absorption of 8c at 3185 cm\(^{-1}\) appeared.

X-ray structures of 5b and 5c crystals are shown in Fig. 3. In 5b crystals, a 2\(_1\) helical structure similar to that consisting of 1c molecules in 1c crystals is created along the c-axis by the O···H···O hydrogen bonds (2.910 Å) between the neighboring 5b molecules. The dihedral angle between the two phenyl rings of 5b is 81.5°. The crystal structure of 5c consists of an alternating arrangement of the 2\(_1\) helical structures of opposite chirality. The stacking of the helical structures along the \(b\)-axis in 5c crystals is identical to that in the 5b crystals. The dihedral angle between the two phenyl rings is 86.4° and the hydrogen bond distance is 2.878 Å.

In 5b and 5c crystals, the hydrophilic parts (two OH groups) of the molecules are located in the center of the helical column and encircled by the large hydrophobic moieties, resulting in no participation of one of the two hydroxy hydrogens of the molecule in hydrogen bonding. This hydrogen is sandwiched between two benzene rings of the molecule and the neighboring one in the column. Only van der Waals interactions are observed between the helical structures. The 5c crystal is modeled by replacing alternately the 2\(_1\) helical structures in 5b crystals by the 2\(_1\) helical structures in 5a crystals. The hydrogen bond is shorter in 5c than in 5b, the dihedral angle in 5c is closer to a right angle than that in 5b, and the density of 5c is slightly larger than that of 5b, suggesting that the molecular packing of 5c will be more favorable than that of 5b.

X-Ray crystal structures of 7b and 7c are shown in Fig. 4. The crystal structure of 7b is complicated compared with that of 5b, because the asymmetric unit contains two independent molecules. However, the independent 7b molecules form similar 2\(_1\) helical structures along the \(b\)-axis. The stacking of the helical structures along the \(b\)-axis is the same as that in 7b crystals. The dihedral angle between the two phenyl rings is 76.4° and the hydrogen bond length is 2.838 Å.

In 7b and 7c crystals, there are no special interactions between the helical structures except van der Waals interactions and one of the two hydroxy hydrogens of the molecule is free from hydrogen bonding as is observed in the crystal structures of 5b and 5c. The stacking of the helical structures along the \(b\)-axis of the 7c crystals mimics those along the \(a\)- or \(b\)-axis of 7b. As far as the hydrogen bond distances and the dihedral angles are concerned, the molecular packing of 7c will be favorable compared with that of 7b. The slow transformation from enantiomeric crystals of 7a and 7b to 7c crystals might be at least in part due to the rectangular arrangements of the helical structure in the chiral crystal and the slightly larger density of 7b than that of 7c.

Since neither 8b (nor 8a) nor 8c formed suitable crystals for a single X-ray crystal analysis, the 1:1 inclusion crystal of 8b and optically pure (+)-methyl phenyl sulfoxide (10b)\(^{19}\) was subjected to X-ray analysis. The packing of the 1:1 complex is shown in Fig. 5, from which the absolute configuration of 8b was elucidated to be (S), because the configuration of 10b is known as R.\(^{19}\) The packing of 8b itself is also shown in Fig. 5, by excluding 10b molecules for clarity. The molecules of 8b are linked by hydrogen bonds to give a linear arrangement of 8b
molecules along the b-axis. The same type of linear arrangement of 8b probably would be formed in chiral and racemic crystals of 8, although no direct structure analysis is available for either 8b or 8c crystals.

Formation of 11c, 12c and 14c in the solid state
When IR spectra of a 1:1 mixture of 11a and 11b were measured every 30 min for 3 h, the original OH absorption at 3275 cm$^{-1}$ turned into that of 11c at 3410 cm$^{-1}$. Interestingly, mixing of 11b and 12a in a 1:1 ratio in the solid state gave a mixed racemic compound of 11b and 12a. By measurement of IR spectra of a 1:1 mixture of 11b (3275 cm$^{-1}$) and 12a (3275 cm$^{-1}$) every 15 min for 1.5 h, the original OH absorptions changed into those of the mixed racemic compound at 3400 cm$^{-1}$. The IR spectrum of the 1:1 mixed racemic compound (mp 1918 C) of 11b (mp 1278 C) and 12a (mp 1388 C) was identical to that prepared by crystallization of 11b and 12a from toluene and the mp of the racemic compound was rather higher than that of each component as indicated. By similar IR spectral measurement of a 1:1 mixture of 11b and 14a every 15 min for 2 h, OH absorptions of 11b (3275 cm$^{-1}$) and 14a (3255 cm$^{-1}$) turned into those of their mixed racemic compound (3410 cm$^{-1}$). The mp of the racemic compound (mp 1938 C) was also much higher than that of 11a (mp 1278 C) or 14a (mp 1008 C). However, the acetylenic diol 16c, which has tert-butyl substituents instead of the aryl groups present in 11, 12 and 14, did not show any tendency towards molecular movement in the solid state. This is not due to the bulk of the tert-butyl group, because 15 which has hydrogen substituents also did not show any such behavior. In order to study the mechanism of this molecular movement in the solid state, X-ray structural study of these crystals was carried out.

In 11b crystals, two independent molecules A and B (see Fig. 6) stack along the c-axis to form a molecular column with a hydrophilic interior and hydrophobic exterior. The center of the column is penetrated by a non-crystallographic two-fold axis. In racemic crystals of 11c, the molecules related by centers of
The side view of the molecular columns in 11b and 11c crystals is shown in Fig. 6. These two molecular columns look quite different from each other but have similar structural components. The columns in 11b crystals are separated into two identical zigzag chains by breaking the hydrogen bonds between molecules A and B. One of these chains is labelled X in Fig. 6 and the other is unlabelled. These zigzag chains are formed by the repetition of head-to-tail hydrogen bonds. Similarly, the columns in 11c crystals consist of two zigzag chains with opposite chirality, by breaking the hydrogen bond between 11a and 11b molecules. The zigzag chain (labelled X) of 11b in the 11c crystals is similar to that (labelled X) in the 11b crystals. The molecular column in 11b crystals is modelled by combining two zigzag chains of the same chirality so that a cyclic hydrogen bond may be formed. The molecular column in 11c crystals is modelled by combining (+)- and (−)- zigzag chains so that a continuous hydrogen bond chain, ⋯−OH⋯O−⋯O−H⋯, may be formed.

The construction of the hydrophobic columns in 11c crystals can be imagined by mixing the columns in 11a and 11b, separating each column into two zigzag chains, pairing the (+) and (−) chains to make new columns and rearranging them. The structure solution of 11b is poor because of severe crystal decay during data collection and therefore detailed comparison of hydrogen bonds between 11b and 11c is meaningless. However, the density of 11b crystals is much smaller than that of 11c crystals, implying that the intercolumn packing in 11c will be more favorable than that in 11b.

The structure of the mixed racemic crystals of 11b and 12a was determined by X-ray analysis. The structure was isomorphous with that of 11c. The replacement of 11a molecules in 11c crystals by 12a molecules gives the mixed racemic crystals consisting of 11b and 12a molecules. The 12a crystals will be isomorphous with those of 11a. The transformation of a powdered mixture of 11b and 12a into the mixed racemic crystals will be essentially the same as that in 11.

The crystal structures of 16b and 16c are shown in Fig. 7. The powdered enantiomer crystals of 16a and 16b are not transformed into the racemic crystals. The racemic crystals of 16c were formed by recrystallization of 16a and 16b from toluene. Interestingly, no intermolecular hydrogen bond is observed in 16b crystals, while cyclic dimers are formed around the centers of symmetry by hydrogen bonding in 16c crystals. There is no common packing mode between 16b and 16c. Since the density of 16b is quite large compared with that of 16c and the diacetylenic rod of 16a or 16b in the racemic crystal is not straight but curved due to steric strain, possibly, because of the formation of a cyclic dimer by hydrogen bonding, the molecular packing in the chiral crystals of 16b would be more favorable than that in the racemic crystals of 16c. It is possible that the packing of the chiral crystal is so good that the formation of the cyclic hydrogen-bonded dimer might not induce transformation from the mixture of enantiomeric crystals to racemic crystals.

Formation of 17c, 18c and 19c in the solid state

When IR spectra of a 1:1 mixture of 18a and 18b were measured in a Nujol mull every 10 min for 1 h, the original OH absorptions at 3395 and 3590 cm⁻¹ disappeared and new absorptions at 3530 and 3340 cm⁻¹ appeared (Fig. 8). By similar measurement of a 1:1 mixture of 17a and 17b for 2 h, the original absorptions at 3445 and 3210 cm⁻¹ turned into those of 17c at 3425 and 3230 cm⁻¹. By similar measurement of a 1:1 mixture of 19a and 19b for 2.5 h, the original OH absorptions at 3530 and 3340 cm⁻¹ turned into those of 19c at 3370 and 3215 cm⁻¹.

The crystal structures of 17a and 17c, 18a and 18c, and 19a and 19c are displayed in Figs. 9, 10 and 11, respectively. The
molecules in these crystals have intramolecular hydrogen bonds between two hydroxy groups. In all such crystals, 17a, 18c, and 19c, the two molecules related by a center of symmetry form a hydrogen bonded dimer. The hydrophilic groups are concentrated in the interior of the dimer to make a closed hydrogen bonded loop while the exterior of the dimer is hydrophobic and no inter-dimer hydrogen bond is formed.

In 17a crystals, there are two independent molecules per unit cell (Fig. 9). These two molecules related by a pseudo two-fold axis are hydrogen bonded to give a dimeric structure with a hydrophilic interior and a hydrophobic exterior. There is no hydrogen bond between the dimers. The distances of intra- and inter-molecular hydrogen bonds are 2.611 and 2.620 Å, respectively. In 17c crystals, the distances and angles of intra- and inter-molecular hydrogen bonds are 173 and 170°, while the angles of intermolecular hydrogen bonds are 137 and 133° (which deviate considerably from 180°). In 17c crystals, the distances of intra- and inter-molecular hydrogen bonds are 2.616 and 2.722 Å, and 165 and 147°, respectively. The intermolecular hydrogen bond in 17c crystals is shorter in length and geometrically more favorable than that in 17a, and the density of 17c is significantly larger than that of 17a.

In 18a crystals, no intermolecular hydrogen bond is observed (Fig. 10). The distance and angle of the intramolecular hydrogen bond are 2.706 Å and 155°, respectively. A subtle competition between van der Waals interactions and hydrogen bonding interactions determines whether the hydrogen bonded dimer is formed or not. The formation of the closed hydrogen bonded loop is geometrically strained as observed in 17a crystals and the molecular is mostly hydrophobic. Suggesting that the sum of the dispersion forces is fairly large. In 18c crystals, the distances and angles of intra- and inter-molecular hydrogen bonds are 2.639 and 2.723 Å, and 174 and 149°, respectively. The conversion of the mixed crystals of 18a and 18b into 18c crystals is at least in part due to the formation of the hydrogen bonded dimer in 18c crystals, although the density of 18c is slightly smaller than that of 18a.

Also in 19a crystals, no intermolecular hydrogen bond is observed (Fig. 11). The distance and angle of the intramolecular hydrogen bond are 2.681 Å and 169°, respectively. In 19c crystals, the distances and angles of intra- and intermolecular hydrogen bonds are 2.612 and 2.733 Å, and 163 and 159°, respectively. Since the hydrogen bonded dimers are formed in 19c and the density of 19c crystals is significantly larger than that of 19a crystals, the molecular assembly in 19c will be more favorable than that in 19a crystal.

It is clear that the molecular movement in the solid state is accelerated in Nujol mulls, since the formation of 18c from 18a and 18b in the absence of Nujol takes 20 days. The molecular movement of 17-19 in the solid state occurs much faster in the presence of liquid hosts such as silicone oil. In the presence of liquid, the dispersion forces is relatively small. In the absence of Nujol, the OH absorptions of a 1 : 1 mixture of isomeric enantiomers appeared at 3395 cm⁻¹, while in the presence of Nujol within 7 days, the OH absorptions are 3405 and 3335 cm⁻¹ occurred at 3410 and 3360 cm⁻¹. However, molecular movement of the dimethyl ester of 20 (21) occurred much faster. Within 3 h, the OH absorptions of 21a and 21b at 3475, 3415 and 3370 cm⁻¹ turned into those of 21c at 3530 and 3460 cm⁻¹. M onohydroxycarboxylic acids 22 and 23 also showed similar behaviour in the solid state. Within 24 h, OH absorptions of a 1 : 1 mixture of 22a and 22b at 3530 and 3385 cm⁻¹ turned into those of 22c at 3440 cm⁻¹. Similarly, within 2 h, the OH absorption of a 1 : 1 mixture of 23a and 23b turned into that of 23c at 3395 cm⁻¹. The molecular movement occurs more rapidly in a 1 : 1 mixture of norephedrine enantiomers 24a and 24b, and their OH absorptions at 3335 and 3270 cm⁻¹ turned into those of 24c at 3330 and 3270 cm⁻¹ within 3 min.

Conclusion

By mixing powdered (−)- and (+)-enantiomer crystals in the solid state, new crystals of the racemic compound were formed quite easily by molecular movement between the two enantiomcrystals. When the mixing was carried out in the presence of liquid hosts such as liquid paraffin, seed oils, silicone oil or water, the molecular movement occurred very fast and sometimes the formation of the racemic crystal was completed within a few minutes. It will be an extremely interesting and important research topic to investigate how these liquids carry such molecules in the solid state. X-Ray structural study of crystals of both the enantiomeric and racemic compound showed that a complex blending and accurate arrangement of molecules are necessary in order to form a new racemic compound crystal. Helical structures or molecular columns with a hydrophobic...
exterior are observed in the chiral crystals of 1, 5, 7 and 11. When powdered (−) - and (+)-enantioomer crystals are mixed, these hydrophobic structural units might diffuse to each other through the interface between the enantiomer crystals and be rearranged to make the corresponding racemic crystals. The energy required to separate the molecular column into the zig-zag chains will be compensated by the formation of new hydrogen bonds between the (−) - and (+)-chains. Because there is no intermolecular hydrogen bond in the chiral crystals of 18 and 19, the racemic crystals might be created just by the diffusion of the enantiomer molecules through the interface, followed by the formation of the centrosymmetric dimers. The dimers in the chiral crystals of 17 might easily migrate through the interface because only van der Waals interactions exist between the dimers. Thus, it is speculated that whenever the free energy of a chiral crystal is larger than that of the racemic crystal and the energy barrier of molecular movement through the interface is low, the powdered enantiomer crystals are transformed into the racemic crystals. It is surprising that such accurate blending and arrangement of molecules occur so fast in the solid state.

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Supporting information available: complete tables of the atomic coordinates, thermal parameters, bond angles, and bond distances for 1a, 1c, 5b, 5c, 7b, 7c, 8b, 10b, 11b, 11c, 12a, 16b, 16c, 17a, 17c, 18a, 18c, 19a and 19c have been deposited with the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', J. Chem. Soc., Perkin Trans. 2, 1997, Issue 1. A ny request to the CCDC for this material should quote the full literature citation and the reference number 188/83.

References
21 Chirpalak AS is available from Dacel Chemical Industries Co. Ltd., Himeji, Japan.