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Enantiomeric Recognition of Alkyl Phenyl Sulfoxides by Crystalline (*R*)-Phenylglycyl-(*R*)-phenylglycine

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Abstract: The inclusion compounds of several alkyl phenyl sulfoxides by (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**] were prepared by two different methods (sorption and crystallization). Alkyl phenyl sulfoxides entered crystalline (*R*,*R*)-**1** with high *S*-enantioselectivity except for methyl phenyl sulfoxide which was recognized with high and reverse enantioselectivity (*R*-form in 92% ee). From the X-ray crystallographic study of an inclusion compound of bis[(*o*-methylsulfinyl)benzyl]ether (**3**) and (*R*,*R*)-**1**, it is deduced that the reversal of enantioselectivity was achieved by the conformational change of phenyl groups on the dipeptide layer. © 1997 Elsevier Science Ltd.

INTRODUCTION

The chemistry of inclusion compounds has a long history, and one of the most useful applications is optical resolution using diastereomeric interaction which results from inclusion of racemic guest substances into the molecular cavity or crystal lattice of chiral hosts.[1]

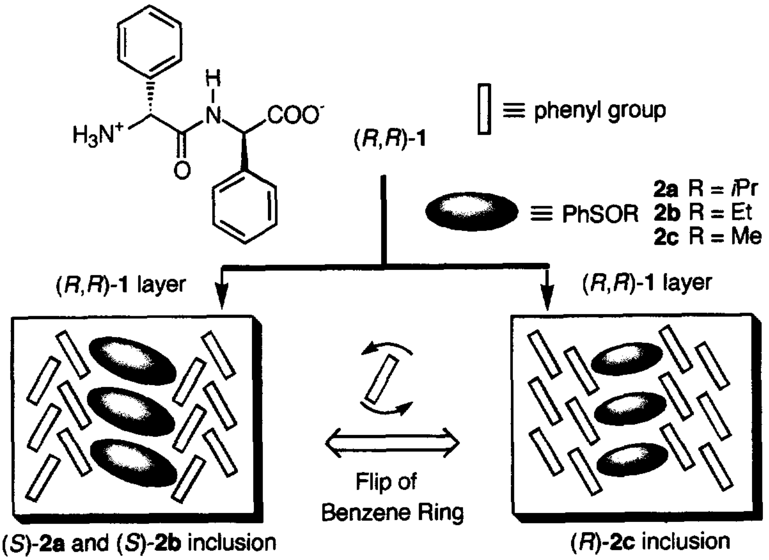


Fig. 1. Schematic representation of conformational change of phenyl groups induced by sulfoxide guest on the (*R*,*R*)-**1** layers.

Hitherto there have been a few reports on the optical resolution of alkyl phenyl sulfoxides by the formation of an inclusion complex,[2,3] but these inclusion phenomena were clarified to use the diastereomeric interaction between the sulfoxide and the host for the crucial driving force of enantiomeric recognition. In course of our studies on the inclusion phenomena of crystalline dipeptides, we revealed that (*R*)-phenylglycyl-(*R*)-phenylglycine molecules [(*R,R*)-**1**] self-assembled to form a layer structure and (*S*)-isopropyl phenyl sulfoxide molecules were stereospecifically included in the void between the layers.[4] Furthermore, it was found that some alkyl phenyl sulfoxides were included by the (*R,R*)-**1** crystals with a high enantioselectivity of (*S*)-enantiomer, while, in case of methyl phenyl sulfoxide, its (*R*)-enantiomer was recognized with a high efficiency. Now we wish to report the full detail of this drastic reverse of enantioselectivity which may be brought about by the conformational change of the phenyl groups located on the (*R,R*)-**1** layer to achieve the maximum contact with them (Fig. 1).

RESULTS AND DISCUSSION

An inclusion compound was prepared by two methods: (a) insoluble (*R,R*)-**1** was simply stirred in the presence of an alkyl phenyl sulfoxide and water [Method A: "sorption"] and (b) (*R,R*)-**1** is recrystallized in the presence of the sulfoxide [Method B: "crystallization"]. The results are summarized in Table 1, which shows enantioselectivity and efficiency for the included alkyl phenyl sulfoxides. The efficiency means mol percentage of the guest molecule based on (*R,R*)-**1** molecule in the inclusion compound.

Table 1. Enantioseclective Inclusion of Alkyl Phenyl Sulfoxides by (*R,R*)-**1**.

Guest		Method A (Sorption)		Method B (Crystallization)	
PhSOR	R	ee (%)	Efficiency (%)[a]	ee (%)	Efficiency (%)[a]
2a	*i*Pr	86(*S*)	100	87(*S*)	100
2b	Et	Not Included		91(*S*)	95
2c	Me	92(*R*)	95	93(*R*)	100
2d	*t*Bu	37(*S*)	89	90(*S*)	100
2e	*c*Hex	Not Included		Not Included	

[a] Efficiency means mol% of the guest molecule based on (*R,R*)-**1** molecule in the inclusion compound.

By Methods A and B, isopropyl phenyl sulfoxide (**2a**) was included in crystalline (*R,R*)-**1** with high (*S*)-enantioselectivity (86 and 87% ee, respectively).[4] Ethyl phenyl sulfoxide (**2b**) formed no inclusion compound by Method A, but the inclusion compound of (*S*)-**2b** was obtained by Method B. These are in sharp contrast with the behavior of methyl phenyl sulfoxide (**2c**): it was absorbed into crystalline (*R,R*)-**1** by Methods A and B to give the inclusion compound with high (*R*)-enantioselectivity (92 and 93% ee, respectively). *tert*-Butyl phenyl sulfoxide (**2d**) was recognized with high (*S*)-enantioselectivity only by

Method B. Cyclohexyl phenyl sulfoxide (**2e**), which has a larger alkyl group, was not included at all by both of Methods A and B.

Single-crystal X-ray crystallography of the inclusion compounds of (*S*)-**2a** and (*S*)-**2b** revealed that (*R*,*R*)-**1** molecules form a layer structure as shown in Figure 2a and 2b.

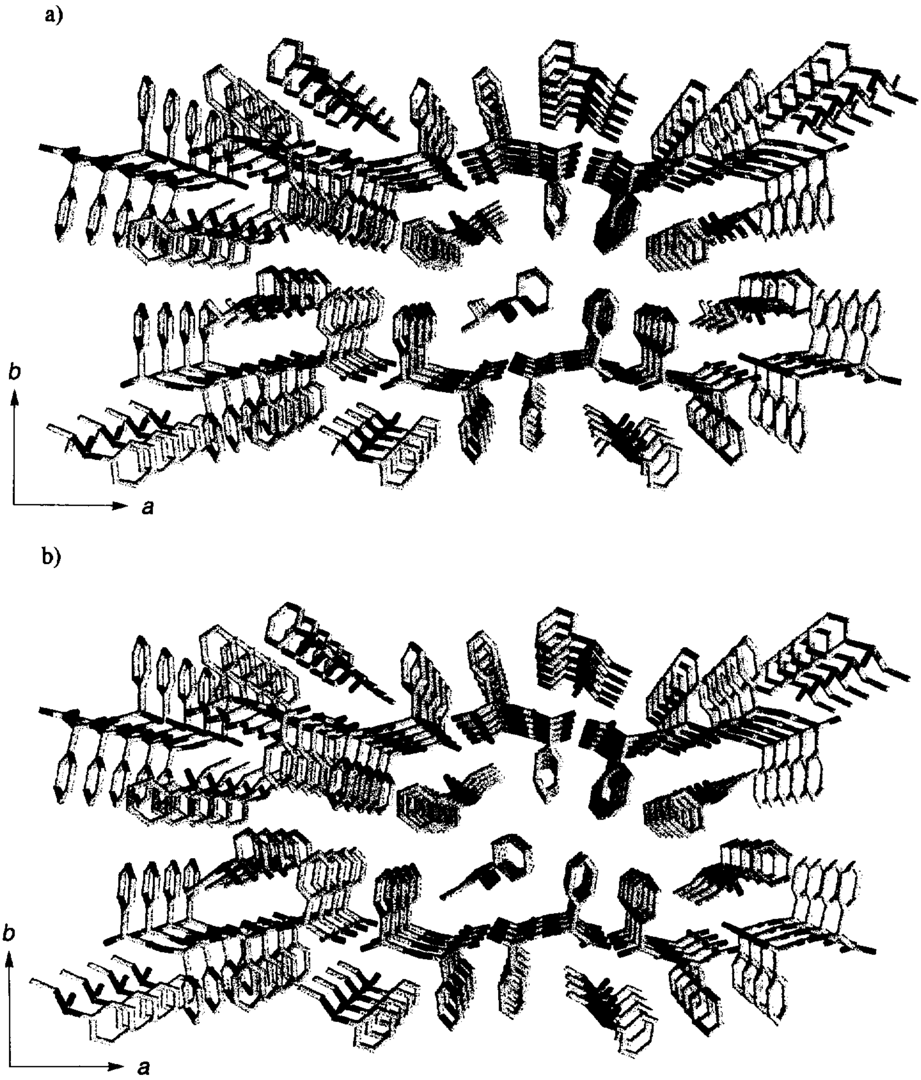


Fig. 2. Perspective views from *a*-*b* plane. a) The inclusion compound of (*S*)-**2a**. b) The inclusion compound of (*S*)-**2b**.

In the layer, the glycylglycine backbones self-assemble via the alternating salt formation between NH_2 and COOH groups to form a sheet (Figure 3a) and the phenyl groups are located perpendicular to the sheet to stack each other in an edge-to-face fashion (namely, "tilted T"-shaped structure) (Figure 3b).[5] The inclusion compound of (*S*)-**2b** is isostructural with that of (*S*)-**2a**. In both cases, the sulfoxide molecules are accommodated in the void between the layers via three-point interaction: hydrogen bonding between $^+NH_3$ and the sulfinyl group,[6] the "tilted T"-shaped interaction between two phenyl groups,[5,7] and the CH/π interaction of the phenyl and alkyl groups.[8] As mentioned above, (*S*)-**2b** was not included by Method A. Method A is free from crystallization process (Method B) and a strong interaction between sulfoxide molecules and the crystals of (*R*,*R*)-**1** is required in order to complete the inclusion via Method A. However, the lack of one methyl group may make enthalpy (interaction with the inclusion cavity) and entropy disadvantageous in crystal packing to result in no inclusion of **2b** via Method A.

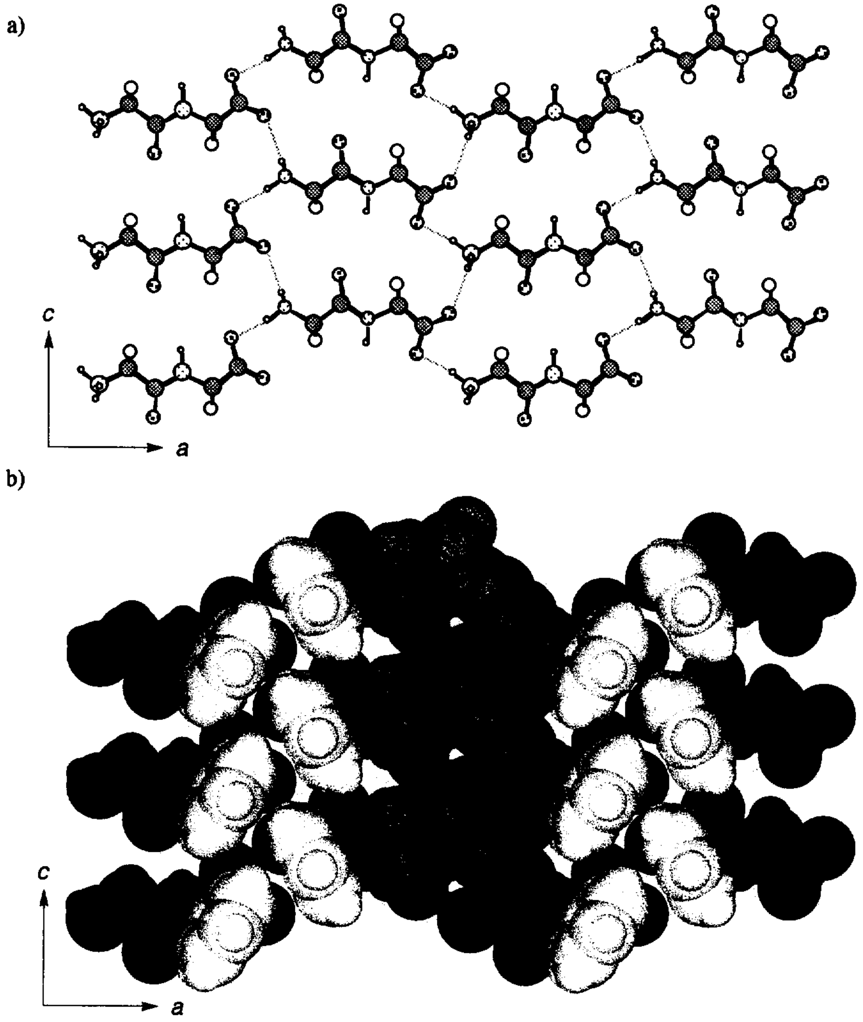
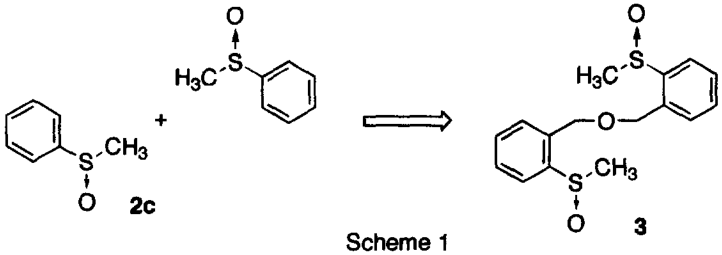


Fig. 3. Views from *a-c* plane of the inclusion compound of (*S*)-**2a**. a) Sheet structure of the glycylglycine backbones of (*R*,*R*)-**1**. For clarity, (*S*)-**2a** and phenyl groups of (*R*,*R*)-**1** are omitted. b) Top view of CPK model of the inclusion compound. For clarity, phenyl groups of (*R*,*R*)-**1** and (*S*)-**2a** are colored white and gray, respectively.

Another question remained unsolved: why is (*R*)-methyl phenyl sulfoxide (**2c**) included in crystalline (*R*,*R*)-**1**? Since a suitable single crystal of the (*R*)-**2c** inclusion compound could not be obtained, we designed a new guest molecule (**3**) that has two (*R*)-**2c** units linked by a -CH_2OCH_2- bridge (Scheme 1).



Scheme 1

Consideration using CPK molecular model suggested that **3** is enough large in size to spread over two continuous cavities between the (*R*,*R*)-**1** layers. This may make it easier for the inclusion compound of **3** to crystallize. Indeed, stirring of crystalline (*R*,*R*)-**1** and *dl*-**3** in the presence of water (Method A) gave an inclusion compound, in which (*R*,*R*)-**3** was included with an enantioselectivity of 91% ee and inclusion efficiency of 97%. Fortunately, a single crystal of the inclusion compound of (*R*,*R*)-**3** was obtained by Method B and subjected to X-ray crystallographic analysis. As expected, (*R*,*R*)-**3** molecules were intercalated between two (*R*,*R*)-**1** layers. From a perspective side view (Figure 4) and a top view (Figure 5) of its crystal structure, the following distinct features became apparent: (1) the layer structure is same to those of the inclusion compound of (*S*)-**2a** and (*S*)-**2b** *except for the phenyl-phenyl stacking mode.* The phenyl groups on the dipeptide layer change their conformation from the "tilted T"-shaped mode to "parallel stacking and displaced" mode.[5] (2) (*R*,*R*)-**3** is anchored at two sulfinyl oxygens to two neighboring layers by means of hydrogen bonding ($S{=}O\cdots H_3N^+$).[6]

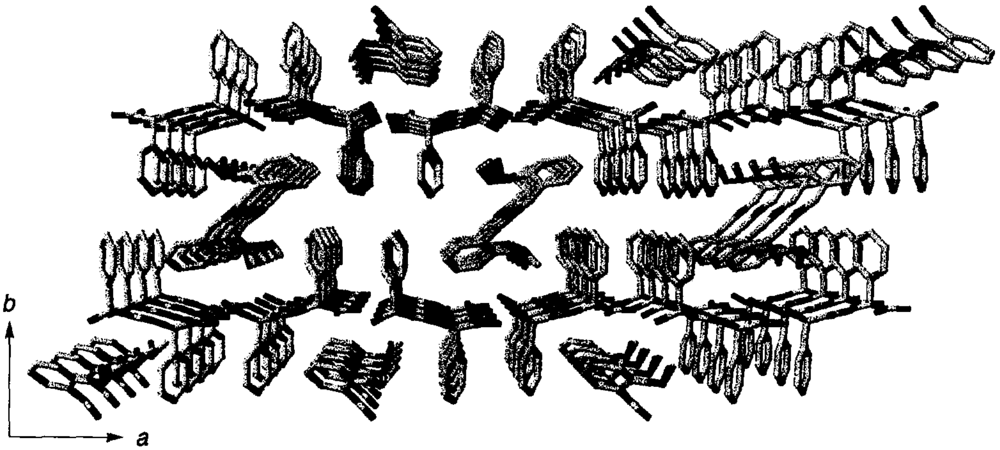


Fig. 4. Perspective views from *a-b* plane of the inclusion compound of (*R*,*R*)-**3**.

(3) (*R*)-(Methylsulfinyl)phenyl moiety interacted with two phenyl groups of the layer. One interaction is "T"-mode phenyl-phenyl stacking[5] (the distance between *p*-H of phenyl group of (*R*,*R*)-**3** and the center of one phenyl ring of (*R*,*R*)-**1** is 2.54 Å) and a CH/π interaction[8] works between methyl and phenyl groups (the distance between one hydrogen of methyl group of (*R*,*R*)-**3** and the center of another phenyl ring of (*R*,*R*)-**1** is 2.92 Å). For the interaction with phenyl group, the methyl group that binds directly to a highly polarized sulfinyl group seems to have advantage of the corresponding ethyl group in entropy and enthalpy. In fact, strong CH/π interaction was observed between a benzene ring and the methyl group on a cationic nitrogen.[9] Therefore, it is reasonably assumed that the present conformation change makes it possible for the guest (*R*,*R*)-**3** to contact fully with the phenyl groups on the (*R*,*R*)-**1** layer.

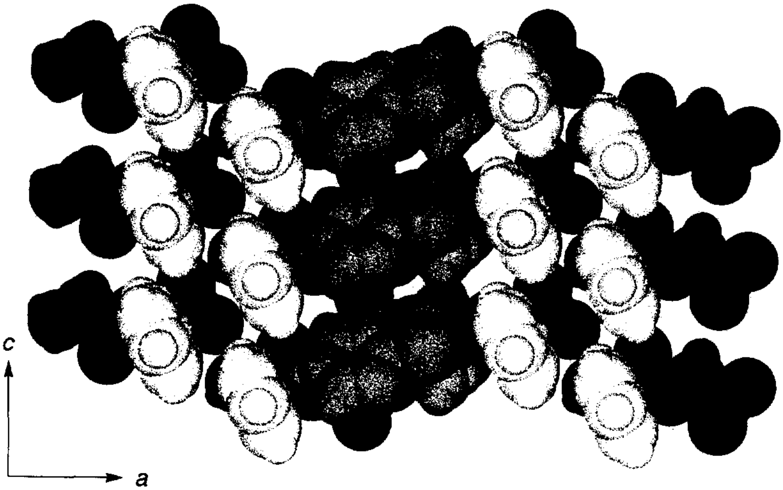


Fig. 5. Top view of CPK model from *a*-*c* plane of the inclusion compound of (*R*,*R*)-**3** (the half of (*R*,*R*)-**3** molecule is shown). For clarity, phenyl groups of (*R*,*R*)-**1** and (*R*,*R*)-**3** are colored white and gray, respectively.

In conclusion, (*R*)-phenylglycyl-(*R*)-phenylglycine [(*R*,*R*)-**1**] molecules self-assemble to form layers, between which alkyl phenyl sulfoxides are accommodated. In the inclusion compounds of **2a** and **2b**, the (*R*,*R*)-**1** layer is constructed by intermolecular salt formation and phenyl-phenyl "tilted T"-shaped stacking to attain three-point interaction with high (*S*)-enantioselectivity. The structure of the (*R*,*R*)-**3** inclusion compound allows us to deduce that, in the inclusion of **2c**, phenyl groups of the C-terminal of the dipeptide flip to stack each other in the "parallel stacking and displaced" mode which gives rise to three-point interaction of the layer with **2c**. Thus, the shape of the sulfoxide guest was shown to induce the conformational change of the phenyl groups on the dipeptide layer. These behavior, which is analogous to induced-fit phenomena at the active site of enzymes, seems to be based on a allostreric character of the crystalline dipeptide host.

EXPERIMENTAL SECTION

Preparation of inclusion compounds of alkyl phenyl sulfoxide and (*R*,*R*)-1.

[Method A] Crystals of (*R*,*R*)-**1** are essentially insoluble in organic solvents and water. A suspension of (*R*,*R*)-**1** (1.0 mmol) in water (2 ml) was stirred together with racemic alkyl phenyl sulfoxide **2** (2.0 mmol) at ambient temperature for 1 day. The formed inclusion compound was collected by filtration and washed with water (20 ml) and CH_2Cl_2 (20 mL).

[Method B] (*R*,*R*)-**1** was dissolved in 0.1 N HCl aq, then the pH was adjusted to about 6.5 by the addition of 0.1 N NaOH aq.[10] After the addition of an alkyl phenyl sulfoxide (**2**) to the aqueous solution of (*R*,*R*)-**1**, the resulting mixture was allowed to stand at an ambient temperature for several days. The deposited inclusion compound was collected by filtration and washed with water and CH_2Cl_2.

After decomposition of the inclusion compound with diluted DCl in D_2O, the inclusion efficiency was determined by NMR measurement. The included sulfoxide was isolated by dissolution of the inclusion compound in 0.1 N HCl aq (40 mL) and extraction with CH_2Cl_2. The enantiomeric purity were obtained by HPLC using a DAICEL CHIRALCEL OB (4:1 = hexane-IPA) for **2b**, (9:1 = hexane-IPA) for **2a** and **2c**, and (30:1 = hexane-IPA) for **2d**. A DAICEL CHIRALCEL OD (4:1 = hexane-IPA) for *dl*-**3** was used.

Crystallographic data for the inclusion compounds.

To the solution of (*R*,*R*)-**1**, a methanol solution of the guest was added directly in a vial, then a lid of the vial was loosely closed for evaporation of the solvent. The samples were allowed to stand for several days to form the desirable single crystals. A Mac Science MXC18 four-circle diffractometer with graphite monochromated Cu Kα (λ = 1.54178) radiation was used. The structures were solved and refined by a computer program package; CRYSTAN-GM ver. 6.2.1 from MAC Science Co. Ltd.

Single crystals of inclusion complexes were obtained by crystallization (*R*,*R*)-**1** with (*S*)-**2a** (87% ee) or racemic **2b**. Crystallization (*R*,*R*)-**1** with (*R*,*R*)-**3** of 92% ee (enantiomerically enriched by Method A) afforded the single crystal of the inclusion complex.

The inclusion compound of (*S*)-2a: crystal dimensions 0.35 x 0.20 x 0.20 mm, orthorhombic, $P2_12_12_1$, a = 15.853(5) Å b= 26.315(6) Å c = 5.564(2) Å, V = 2321(1) Å^3, Z = 4, ρ_{calcd} = 1.29 gcm^{-3}, $2\theta_{max}$ 140°, temperature 298 K, 2673 reflections measured, 2566 independent, R = 0.049 (2028 reflections with $|Fo| > 3\sigma(|Fo|)$); Rw = 0.047, structure solved by direct methods (SIR 92 on a computer program package; CRYSTAN-GM), 383 parameters, with heavy atoms refined anisotropically, residual electron density 0.69/-0.26. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre.[11]

The inclusion compound of (*S*)-2b: crystal dimensions 0.30 x 0.40 x 0.20 mm, orthorhombic, $P2_12_12_1$, a = 15.934(4) Å b= 26.615(7) Å c = 5.345(2) Å, V = 2267(1) Å^3 Z = 4, ρ_{calcd} = 1.28 gcm^{-3}, $2\theta_{max}$ 140°, temperature 298 K, 2636 reflections measured, 2529 independent, R = 0.058 (2084 reflections with $|Fo| > 3\sigma(|Fo|)$); Rw = 0.062, structure solved by direct methods (SIR 92 on a computer program package; CRYSTAN-GM), 357 parameters, with heavy atoms refined anisotropically, residual electron density 0.27/-0.55. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre.[11]

The inclusion compound of (*R*,*R*)-3: crystal dimensions 0.45 x 0.20 x 0.10 mm, orthorhombic, $P2_12_12$, a = 16.287(6) Å b = 24.018(9) Å c = 5.676(3) Å, V = 2220(2) Å^3, Z = 4, ρ_{calcd} = 1.33 gcm^{-3}, $2\theta_{max}$ 140°, temperature 298 K, 2545 reflections measured, 2445 independent, R = 0.061 (2087 reflections with $|Fo| > 3\sigma(|Fo|)$); Rw = 0.070, structure solved by direct methods (SIR 92 on a computer program package;

CRYSTAN-GM), 328 parameters, with heavy atoms refined anisotropically, residual electron density 0.31/-0.69. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre.[11]

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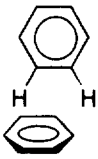
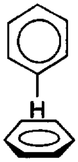
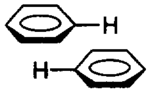


"tilted T"



"T"



"parallel stacked and displaced"

6. The distance and angle of S=O···H-N hydrogen bonding: O···N 2.748(5) Å, O···H 1.98 Å, O···H-N 160.6° for the inclusion compound of (*S*)-**2a**; O···N 2.743(4) Å, O···H 1.81 Å, O···H-N 167.4° for the inclusion compound of (*S*)-**2b**; O···N 2.782(7) Å, O···H 1.84 Å, O···H-N 165.8° for the inclusion compound of (*R,R*)-**3**. These values are almost same to the reported distances: 2.758(2) and 2.781(1) Å for SO···O of binaphthol;[3] 2.85(2) Å for SO(sulfinyl)···N(amide).[4]
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