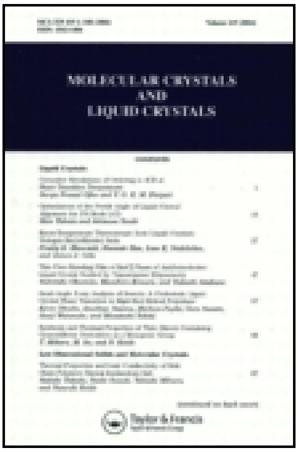

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ENANTIOSELECTIVE INCLUSION COMPLEXATION BY THE CHIRAL HOST AND PHOTOCYCLIZATION REACTION

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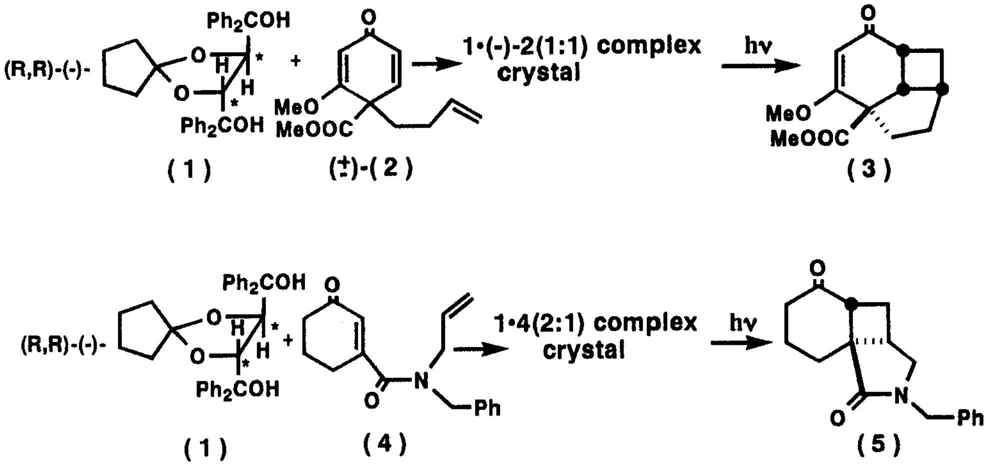
<u>Abstract</u> The chiral host **1** derived from tartaric acid formed the 1:1 inclusion complex with **2** by incorporating one of the enantiomers of **2** into the complex crystal. The irradiation of **2** gave optically pure product **3**. The host **1** formed the 2:1 inclusion complex with the prochiral guest **4**. The irradiation of this complex gave optically pure **5**. In order to elucidate the enantioselective inclusion complexation and the stereospecific control of the photocyclization reaction by host **1**, the X-ray crystallographic study of **1•2**, **1•4** and **5** have been undertaken. All structures were solved by direct methods and refined by full-matrix least-squares refinement to give final R values of 0.055 for **1•2**, 0.040 for **1•4** and 0.049 for **5**. Each host molecule has one O-H---O intramolecular hydrogen bond and the same conformation. The enantioselective complexation in **1•2** will be attained by the specific host-guest interactions observed in the complex crystal, allowing an easy and straightforward method to prepare the optically pure **3** with the determination of the absolute configuration of **3** by reference to the known chirality of **1**. The overall structure of the 2:1 inclusion complex of **1•4** clearly shows the stereochemical control, which forms the optically pure **5** from the prochiral **4**. The absolute configuration of **5** was deduced from the host-guest relative orientation in the **1•4** complex crystal and the known absolute configuration of **1**.

INTRODUCTION

The chiral host molecule, (*R*,*R*)-(–)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxa-spiro[4,4]nonane(**1**) (Scheme 1), has been reported to produce inclusion complexes with various kinds of guest molecules.[1] The complexes between the hosts **1** and photoreactive guest molecules have been used to control the regioselectivity and enantioselectivity of the reaction on the basis of the arrangement of the host molecules around the guest molecules in the solid state. In the case of the racemic guest, the photocyclization reaction after enantioselective inclusion complexation by host **1** may give the product with high e.e. by the irradiation of the inclusion crystal. In the case of the prochiral guest, the use of host **1** as a chiral handle may show asymmetric induction due to the irradiation of the inclusion crystal.. The host **1** formed the 1:1 and 2:1 inclusion complexes with 4-(3'-butenyl)-4-carbomethoxy-3-methoxy-2,5-cyclohexadien-1-one (**2**)[2] and N-allyl-N-benzyl-3-oxo-1-cyclohexenecarboxamide (**4**),[3] respectively. Irradiation of the inclusion crystals of **1**•**2**(1:1) and **1**•**4**(2:1) gave optically pure cycloaddition products **3** and **5**, respectively. In order to elucidate the host-guest interactions and enantioselective photocyclization in the crystals, X-ray crystallographic studies of **1**•**2**, **1**•**4** and **5** have been undertaken.



Scheme 1

EXPERIMENTAL

Preparation of Inclusion Crystals of 2 and 4 with the host 1

When a solution of **1** (2.9mmol) and **2** (5.9mmol) in ether-hexane (1:1,50ml) was kept at room temperature for 10h, a 1:1 inclusion compound of **1** with (-)-**2** (66.4% e.e.) was obtained (74% yield). Three recrystallizations of the inclusion compound from ether-hexane (1:1) gave pure inclusion compound (>99.9% e.e.) as colorless prismatic crystals.[2] A powdered 2:1 inclusion compound of host **1** with **4** was prepared by recrystallization of both components from diethyl ether. The slow evaporation of the diethyl ether solution of the inclusion compound gave colorless prismatic crystals.[3]

Solution and Refinement of the Structures

The inclusion complex crystal of **1•4** was sealed in a glass capillary to avoid crystal degradation. Diffraction intensities were measured on Rigaku automatic diffractometers (AFC-5A for **1•2** and **5**, and AFC-7R for **1•4**), using the $\omega/2\theta$-scan mode at room temperature. No correction was made for the absorption effect. Crystal data are listed in Table 1. All structures were solved by direct methods with use of SHELX86.[4] All hydrogen atoms except two hydrogens of **4** were located in the difference Fourier syntheses and isotropically refined. All structures were refined by full matrix least squares using anisotropic temperature factors for all atoms. All calculations except for the direct methods were performed using the teXsan crystallographic software package from the Molecular Structure Corporation.[5]

Table 1. Crystal data

	1•2(1:1)	**1•4**(2:1)	**5**
Formula	$C_{33}H_{32}O_4 \cdot C_{13}H_{16}O_4$	$2(C_{33}H_{32}O_4) \cdot C_{17}H_{17}O_2N$	$C_{17}H_{19}O_2N$
F.W.	728.84	1252.55	269.33
Crystal size (mm3)	1.2×1.0×1.0	0.3×0.2×0.1	1.0×0.5×0.3
Crystal system	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_1$	$P2_12_12_1$
Cell const.			
a(Å)	10.357(3)	9.743(2)	17.408(9)
b	18.818(9)	34.807(8)	10.412(3)
c	9.618(2)	9.764(2)	7.984(2)
β(°)	92.88(2)	93.96(2)	
V(Å^3)	1962(1)	3303(1)	1447(2)
Z	2	2	4
*D*calc.(g/cm3)	1.23	1.26	1.24
X-ray source	MoKα	CuKα	MoKα
No. of independent reflctns	3592	5431	1500
No. of reflctns used($I>3\sigma(I)$)	2691	4628	1192
R-factor	0.055	0.040	0.049
wR	0.079	0.055	0.070

RESULTS AND DISCUSSION

1•2 Inclusion complex

Figure 1 shows the crystal structure of the inclusion complex of **1•2** and the structure of the 1:1 host-guest complex in the crystal. The X-ray crystal structure of **1•2** clarified the host-guest interactions in the crystal and the absolute configuration of **2**. The host **1** takes a very similar conformation to those found in other inclusion complex crystals of the host **1** and its derivative,[6,7] mainly due to the formation of the intramolecular hydrogen bond (2.65Å) between O3 and O4 that fixes the rotation around C6-C7 and C8-C9. The cyclohexadienone ring of **2** fits the concavity formed by the two phenyl rings (C10~C15, and C28~C33) of host **1** with the C1=O1---H-O3 intermolecular hydrogen bond (2.64Å), giving a 1:1 host-guest complex. The dihedral angle of C7-C6-O3-H is 101°. The relative orientation of host **1** with guest **2** in this complex is different

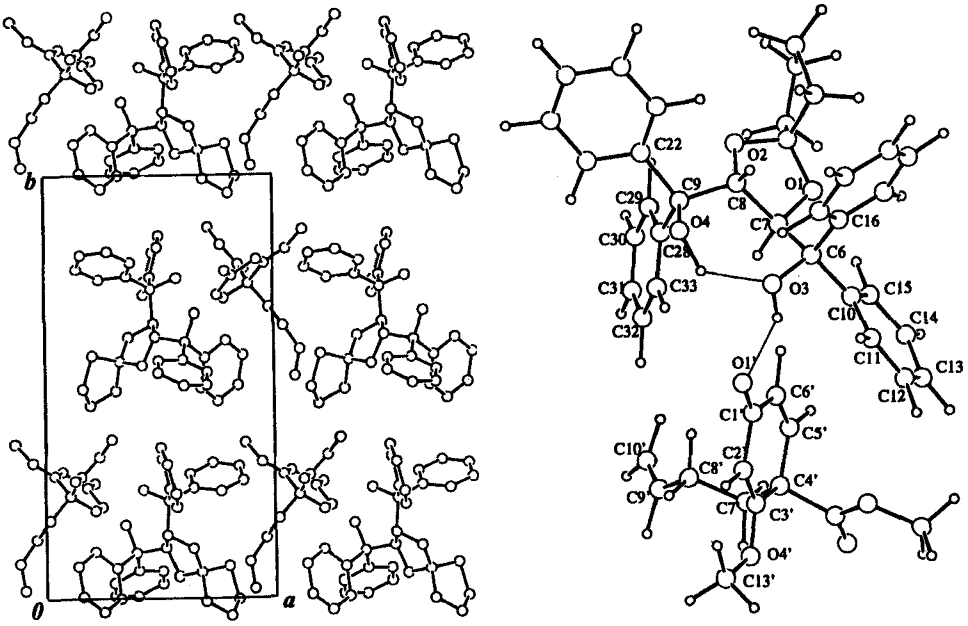


FIGURE 1 Crystal(left) and molecular(right) structure of **1•2**(1:1) inclusion complex.

from those found in the 1:1 complexes of host **1** and its derivative with other guests.[6,7] where the atoms acting as hydrogen bond acceptors of the guest molecules do not approach the hydrophilic part of the host molecules from the direction perpendicular to the plane defined by O3, C6, C9 and O4, but from the direction parallel to the corresponding plane with the dihedral angles (C7-C6-O3-H) of about 180°. The guest molecule **1** is surrounded by many other host molecules in the crystal, and has many van der Waals contacts with the hydrophobic parts of these host molecules. Thus, the enantioselective inclusion complexation will be attained by the specific interactions between the host **1** and guest **2** in the 1:1 complex and the asymmetric environment around the guest molecule. The absolute configuration of **2** was unambiguously determined by reference to the known configuration of **1**, resulting in the determination of the absolute configuration of **3** as is shown in Scheme 1. The photocyclization reaction in the solution of the optically pure enantiomer of **2** producing the optically pure **3** has also been reported.[8] However, the enantioselective inclusion complexation followed by the photocyclization reaction in the solid state is not only a simple and easy method to prepare the optically pure **3**, but also a straightforward way to determine the absolute configuration of **2** and **3**, since the absolute configuration of host **1** is known.

1•4 Inclusion Complex

The crystal structure of inclusion complex **1•4** and the structure of the 2:1 host-guest complex in the crystal are shown in Figure 2. There are two independent host molecules (A and B in Figure 2) and one guest molecule (G in Figure 2) in the asymmetric unit of the **1•4** inclusion complex crystal. Molecule A stacks along the *a*-axis to make the molecular layer [A] parallel to the *ab*-plane. Similarly, the molecules B and G make the molecular layers [B] and [G] parallel to the *ab*-plane, respectively. The crystal structure of the **1•4** inclusion complex is characterized by $([A]\cdot[G]\cdot[B])_n$, since [G] is located between [A] and [B]. This crystal structure is similar to those observed in **1**•N-isopropyl-N-methylphenylglyoxylamide and its related complex.[9] The conformation of the two independent host molecules with O-H---O intramolecular hydrogen bonds is quite similar to that of **1•2** and those found in other inclusion complexes of host **1**.[6,7,9] The two independent host molecules A and B of the **1•4** inclusion complex interact with

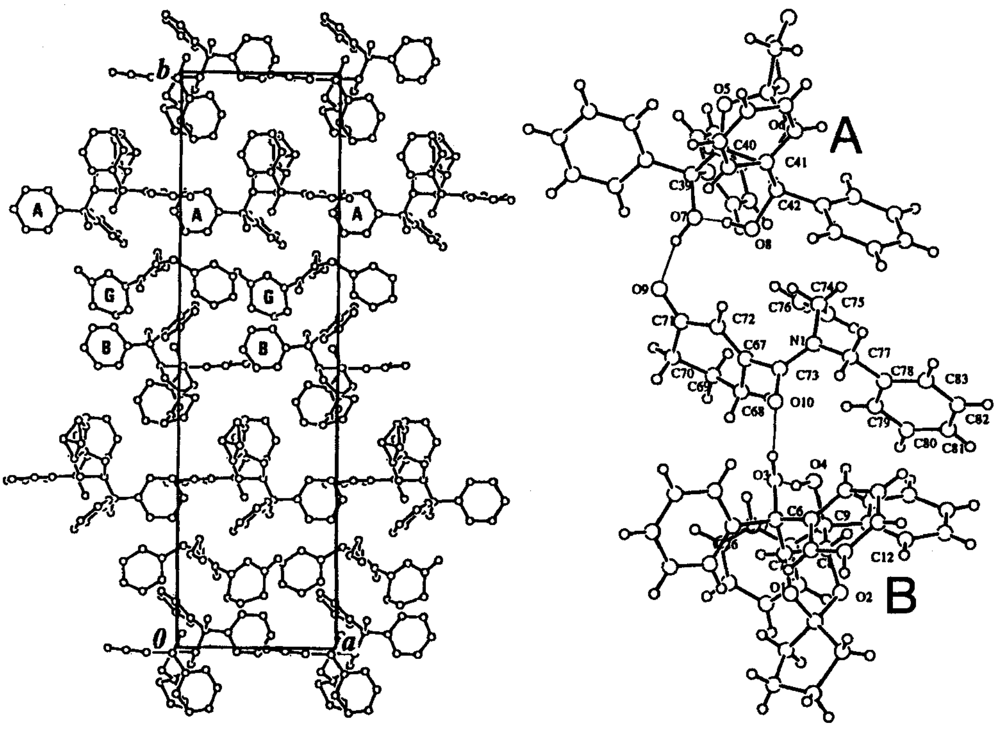


FIGURE 2 Crystal(left) and molecular(right) structure of **1•4**(2:1) inclusion complex.

the guest molecule from both sides to make two intermolecular hydrogen bonds. One (2.72Å) is between the O7-H group of one host molecule and the carbonyl oxygen of the cyclohexenone ring, and the other(2.69Å) is between the O10-H group of the other host molecule and the carbonyl oxygen of the amide group. The dihedral angles of C7-C6-O3-H and C40-C39-O7-H are -174° and 179°, respectively, which are in contrast to 101° observed in the 1:1 inclusion complex **1•2**. In addition to these hydrogen bond interactions, the guest molecule makes van der Waals contacts with the phenyl rings of the host molecules. The cyclohexenone ring makes an angle of 74° with the amide plane in 4, and the propenyl group (C75 and C76) is situated on the side of host A with respect to the cyclohexenone plane, indicating that 2+2 cyclo-addition occurs on this side. The distances between C67 and C75 and between C72 and C76 are 3.18 and 3.64Å, respectively. Thus, the absolute configuration was determined to be **5** (see scheme 1). This results shows that the host molecules produce an asymmetric induction during the formation of **5** by acting as a chiral handle through the specific intermolecular hydrogen bonds to the guest and the stereochemical control of the guest in the asymmetric environment.

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