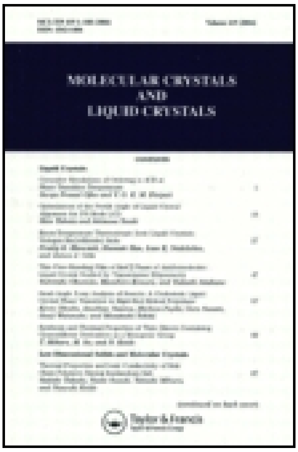

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Enantioselective Transfer of Molecules from Crystal to Crystal

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ENANTIOSELECTIVE TRANSFER OF MOLECULES FROM CRYSTAL TO CRYSTAL

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Abstract When a mixture of powdered optically active host and racemic guest crystals is kept at room temperature, enantioselective transfer of guest molecule occurred from the racemic guest crystal to the host crystal and an inclusion crystal of the host and optically active guest molecules. When powdered inclusion crystal of an optically active host and a prochiral guest is mixed with powdered crystalline reagent and the mixture is kept at room temperature, enantioselective approach of the reagent to the prochiral quest molecule was occurred and optically active product was obtained.

INTRODUCTION

Most organic reactions have been studied in solution, since most chemists believe that molecules freely move in liquid and solution but not in the solid state. One reason for this might be because of the famous Aristtales's philosophy "No Coopora nisi Fluida" which means "no molecular movement and then no reaction occur in the absence of solvent". This philosophy had a big influence on modern Sciences evolved in Europe. By this influence, almost all reactions are still carried out in solution, even when a special reason for the use of solvent cannot be found.

We have found that molecules move quite eaily in the solid state under some conditions and that organic reactions also occur in the solid state. For example, when a mixture of powdered diacetylenediol host (**1**) and chalcone guest (**2**) in a 1:2 molar ratio is kept at room temperature, inclusion complexation between them occurs and a 1:2 inclusion crystal (**3**) of **1** and **2** is formed efficiently.[1] The complexation can be followed by measurement of the UV spctrum in the solid

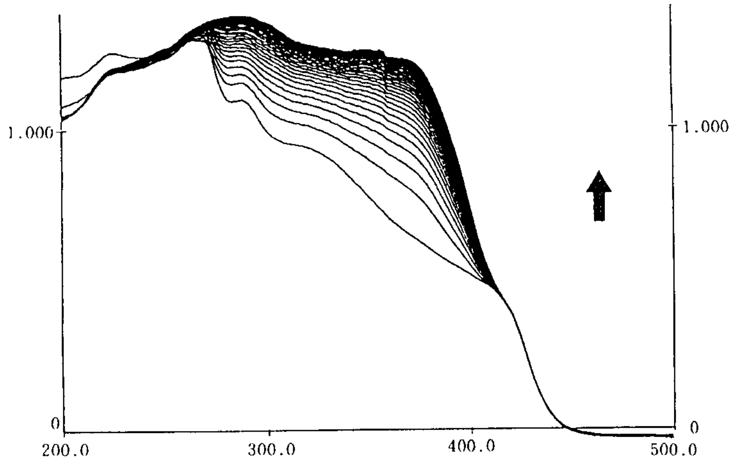


FIGURE 1 UV Spectrum of a mixture of powdered **1** and **2** in the solid state (measured every 10 min for 6 h)

state (Figure 1). As the inclusion crystallization proceeds, population of planar molecules of **2** in **3** increases and molecular coefficent in the UV spectrum increases as shown in Figure 1. The planar structure of **2** in **3** has been studied by X-ray crystal structure analysis of **3**.[2]

When the inclusion crystallization experiment by mixing powdered **1** and excess **2** in the solid state is combined with photoirradiation of the mixture, successive photodimerization of **2** can be achieved. By this procedure, excess **2** is converted to the syn-head-to-tail dimer (**4**) selectively, although possiblity of the formation of three other isomeric dimers is present. X-ray crystal structure study of **3** showed that two molecules of **2** are arranged as shown in Figure 2, in which **2** should give **4** upon irradiation. By mixing powdered **1** and **2**, inclusion complex **3** is formed and the complex gives **4** upon photoirradiation. By further mixing, excess **2** forms complex with **1** and gives **4** by photoirradiation, and finally all **2** is converted to **4**. This shows that **1** is used as a catalyst.

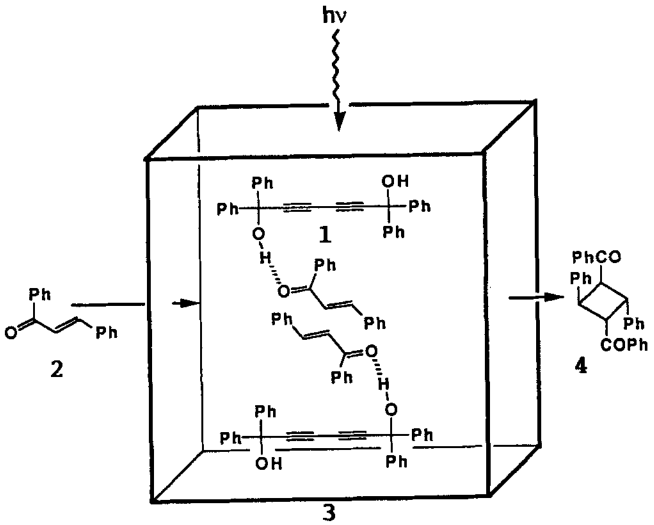
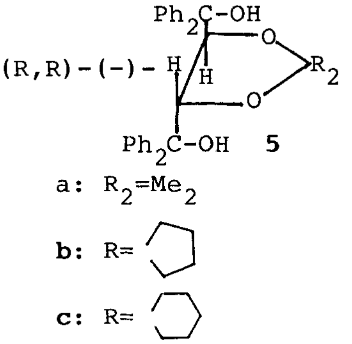


FIGURE 2 Photoirradiation of a mixture of **1** and excess **2** in the solid state

The above data clearly show that molecules move quite freely from crystal to crystal. We finally found that such a molecular transfer from crystal to crystal occurs even enantioselectively. For example, one enantiomer of racemic guest crystal transfer to optically active host crystal selectively. Furthermore, reagent molecule moves and attacks in the solid state one side of prochiral molecule which is included with optically active host molecule. We report these new findings on enantioselective molecular transfers in the solid state.

ENANTIOSELECTIVE TRANSFER OF MOLECULES IN THE SOLID STATE

When a suspension of powdered optically active host, trans-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**5a**) (1.0 g, 2.14 mmol) in hexane (10 ml) was mixed with rac-1-phenylethanol (**6a**) (0.262 g, 2.14 mmol) and the mixture was kept at room temperature for 6 h, a 2:1 inclusion crystal of **5a** and (-)-**6a** (1.12 g) was obtained. Heating in vacuo of the inclusion crystal which has been separated from uncomplexed (+)-**6a** by filtration gave (-)-**6a** of 95% ee (0.112 g, 85% yield). By similar procedure, **6b-c**, **7a-b**, **8a-c**, and **9a-d** were resolved efficiently (Table 1). In some cases, the host **5b**, **5c** or optically active 1,6-(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**10**) is more effective than **5a** as shown in Table 1.

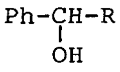


5

a: R_2=Me_2

b: R=

c: R=



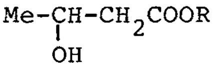
$\mathrm{Ph{-}\underset{OH}{\underset{|}{C}}H{-}R}$

6

a: R=Me

b: R=Et

c: R=C≡CH

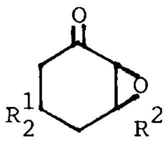


$\mathrm{Me{-}\underset{OH}{\underset{|}{C}}H{-}CH_2COOR}$

7

a: R=Me

b: R=Et

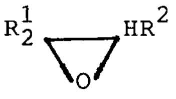


8

a: R^1=H; R^2=Me

b: R^1=R^2=H

c: R^1=R^2=Me



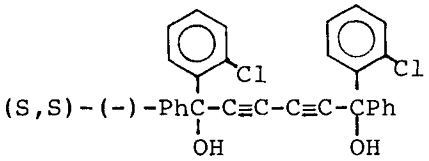
9

a: R^1=Et; R^2=COOEt

b: R^1=Me; R^2=COOEt

c: R^1=Me; R^2=COOMe

d: R^1=H; R^2=Ph



10

$\mathrm{Me(CH_2)_{15}N^+Me_4\cdot Br^-}$

11

Since the host **5** and **10** are insoluble in hexane although the guest compounds **6-9** are soluble in hexane, the inclusion crystallization may proceed in the solid state. The enantioselective inclusion crystallization was also found to proceed in a water suspension efficiently. For example, when a suspension of powdered **5a** (1.0 g, 2.14 mmol) and rac-**6a** (0.26 g, 2.14 mmol) in water (10 ml) containing N-hexadecyltrimethylammonium bromide (**11**) (0.1 g) as a surfactant was stirred at room temperature for 24 h, a 2:1 inclusion crystal of **5a** and (-)-**6a** was obtained. Heating in vacuo of the inclusion crystal separated from uncomplexed (+)-**6a** by filtration gave (-)-**6a** of 98% ee (0.11 g, 85% yield). This result clearly shows that the enantioselective inclusion crystallization occurs efficiently in the solid state. By similar procedure,

TABLE I Result of optical resolution by inclusion crystallization by suspension method

			result of resolution		
Host	Guest	Medium	Product	Yield(%)	Purity(%ee)
5a	**6a**	hexane	(-)-**6a**	85	95[b]
5a	**6a**	H_2O	(-)-**6a**	85	98[b]
5a	**6b**	hexane	(-)-**6b**	75	100[c]
5a	**6b**	H_2O	(-)-**6b**	75	98[c]
5a	**6c**	hexane	(+)-**6c**	89	92[c]
5a	**6c**	H_2O	(+)-**6c**	76	100[b]
5b	**7a**[a]	hexane	(+)-**7a**	80	80[d]
5b	**7b**[a]	hexane	(+)-**7b**	93	78[d]
5b	**8a**	hexane	(-)-**8a**	82	100[e]
5a	**8a**	H_2O	(-)-**8a**	73	100[e]
5a	**8b**[a]	hexane	(+)-**8b**	78	75[e]
10	**8c**	hexane	(+)-**8c**	57	98[e]
10	**8c**	H_2O	(+)-**8c**	85	97[e]
5b	**9a**	hexane	(+)-**9a**	75	100[d]
5b	**9a**	H_2O	(+)-**9a**	89	100[d]
5c	**9b**	hexane	(+)-**9b**	78	100[d]
5c	**9b**	H_2O	(+)-**9b**	80	100[d]
5b	**9c**	hexane	(+)-**9c**	59	70[d]
5b	**9c**	H_2O	(+)-**9c**	52	86[d]
5c	**9d**	hexane	(+)-**9d**	76	75[f]
5c	**9d**	H_2O	(+)-**9d**	74	47[f]

[a] No inclusion crystallization occurred in water suspension. [b,c] Determined by HPLC using a column containing optically active solid phase, Chiralcel OJ and OB, respectively. [d] Determined by measurement of ^1H NMR in the presence of chiral shift reagent, $Eu(hfc)_3$. [e] Determined by HPLC using the column containing optically active solid phase, Chiralpak As. [f] Determined by comparison of the $[\alpha]_D$ value with that reported.

6b-c, 7a-b, 8a-c, and **9a-d** were also resolved efficiently (Table I). In the cases of **7a, 7b,** and **8b,** however, no inclusion crystallization occurred in water suspension.

Efficiency of the resolution by the suspension method is sometime higher than that by recrystallization method. For example, **8c** has been resolved by an inclusion crystallization with **10** in ether solution followed by two recrystallizations of the inclusion crystal, and (-)-**8c** of 100% ee has been obtained in 35% yield from the purified inclusion crystal by distillation.[3]

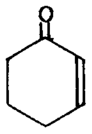
When the resolution by the suspension method is combined with distillation, both enantiomers can be separated easily by fractional distillation. For example, after a suspension of **5a** (1.0 g, 2.14 mmol) and **6a** (0.26 g, 2,14 mmol) in hexane (1 ml) was kept at room temperature for 1 h, the mixture was distilled in vacuo to give initially uncomplexed (+)-**6a** of 59% ee (0.16 g, 125% yield) at lower boiling temperature. The residue was continued to distil at elevated temperature and (-)-**6a** of 97% ee (0.09 g, 69% yield) was obtained at higher boiling temperature. By the same combination method, rac-**8c** was separated to enantiomers by fractional distillation in the presence of **10**, and (-)-**8c** of 68% ee (121% yield) and (+)-**8c** of 95% ee (63% yield) were obtained at lower and higher boiling temperature, respectively.

ENANTIOSELECTIVE REACTION IN THE SOLID STATE

We have been studying enantioselective solid state reactions such as ketone reduction[4] and Wittig-Horner reaction[5] in inclusion crystals with optically active host compounds. We have applied enantioselective reaction to Michael addition reactions and have found that Michael addition reaction of thiols to 2-cyclohexeneone (**12**) included in **5c** in the presence of a catalytic amount of aqueous solution of benzyltrimethylammonium hydroxide (**13**) gives optically active addition product of high optical purity. We have also found that thiols (**14**) adds enantioselectively to 3-methyl-3-buten-2-one (**15**) in its inclusion crystal with **5c**.

A 1:1 inclusion crystal of **5c** and **12** was mixed with powdered 2-mercaptopyridine (**14a**) and 40% aqueous solution of **13**, and the mixture was irradiated with ultrasound for 1 h at room temperature, and then kept for 24 h. The reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was chromatographed on silica gel to give (+)-**16a** as an oil in 80% ee and 51% yield. The same reaction of **12** in the inclusion crystal with 2-mercaptopyrimidine (**14b**), 4,6-dimethyl-2-mercaptopyrimidine (**14c**), and 2-mercaptothiazoline (**14d**) gave (+)-**16b** in 78% ee, (+)-**16c** in 74% ee, and (+)-**16d** of unknown optical purity, respectively in good yields.

Michael addition of **14** to **15** in its inclusion crystal with **5c** also occurred enantioselectively. When a mixture of powdered inclusion crystal of **15** and **5c** and **13** was treated with **14a**, (+)-**17a** of 49% ee was obtained in 76% yield. By the same procedure, **14c** reacted with **12** and (+)-**17c** of 53% ee was obtained in 78% yield.[6]



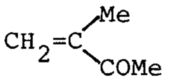
12

$PhCH_2NMe_3^{+}\cdot OH^{-}$

13

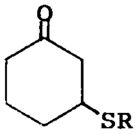
RSH

14

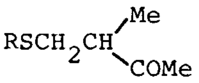


$CH_2=C(Me)COMe$

15



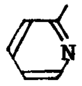
16



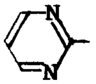
$RSCH_2CH(Me)COMe$

17

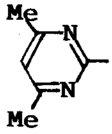
a: R=



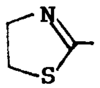
b: R=



c: R=



d: R=



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