

## Molecular movement and chiral arrangement in the solid state

F. Toda

Department of Applied Chemistry, Faculty of Engineering,  
Ehime University, Matsuyama, Ehime 790, Japan

Abstract: Under appropriate conditions, molecules move from crystal to crystal. When the molecular movement occurs between crystals of reactant and reagent, solid state reaction would be observed. Some such solid state reactions are described. Mixing of crystals of donor and acceptor in the solid state gave their charge-transfer complex crystal. By combination of enantioselective molecular movement and distillation procedure, enantiomers were separated by fractional distillation in the presence of an optically active host compound. Mixing of powdered crystalline chiral host and achiral guest compound in the solid state gave an inclusion complex crystal in which the latter molecules are arranged in a chiral form. In special case, host-guest inclusion complex was formed only by the mixing method, and the complex was not formed by recrystallization of both components from solvent.

### 1. Introduction

Most organic reactions have been studied in solution. One reason for this might be because of the famous Aristoteles's philosophy "No Coopora nisi Fluida" which means "no reaction occurs in the absence of solvent". This philosophy had a big influence on modern Sciences evolved in Europe. In the ancient period of Aristoteles, it was difficult to be aware that many reactions occur in the absence of solvent. Nevertheless, it is very curious that almost all reactions are still carried out in solution. We found that quite a few reaction proceeds in the solid state. In some cases, the solid state reaction occurs more efficiently and more selectively than does solution reaction. Efficient solid state reactions show that molecules of reactant and reagent move in the solid state. In fact, host-guest inclusion complexation occurs by mixing the both crystals in the solid state. Surprisingly, the solid state complexation occurs even selectively. For example, mixing of racemic guest and optically active host in the solid state gives an inclusion complex of one enantiomer of the guest with the host, from which optically active guest is obtained. By a combination of the enantioselective molecular movement in the solid state and distillation procedure, enantiomers of racemic compound were easily separated by fractional distillation in the presence of chiral host compound. The most exciting finding is that a mixing of chiral host and racemic guest in the solid state gave their inclusion complex crystal in which the latter molecules are arranged in a chiral form. By photoirradiation of the complex, the chirality of the achiral guest was frozen to give optically active photoreaction product. In some special cases, host-guest inclusion crystal in which achiral guest molecules are arranged in a chiral form was formed only by mixing both crystals in the solid state, although recrystallization of both from solvent did not give any inclusion complex. Some such interesting molecular movements in the solid state are described.

## 2. Organic Solid State Reactions

When a mixture of powdered methyl *m*-nitrobenzoate and NaOH was kept at room temperature for 3 h, sodium *m*-nitrobenzoate was obtained which upon acidification by dil HCl finally gave *m*-nitrobenzoic acid in quantitative yield. The solid state reaction can be followed by FT-IR spectroscopy, and ester absorption peak decreased and finally disappeared, and sodium benzoate absorption increased as the reaction proceeds.

When a 1:2 inclusion complex (**2**) of the acetylenic diol host **1**<sup>1</sup> and benzaldehyde was mixed with powdered Wittig-Horner reagent **3**, and the mixture was kept at room temperature for 2.5 h, Wittig-Horner reaction product **4** was obtained in quantitative yield. This solid state reaction can also be followed by FT-IR spectroscopy. As the reaction proceeds, C=O absorption peak of benzaldehyde decreased and finally disappeared, and ester and olefin absorption peaks of **4** appeared.

The solid state Wittig-Horner reaction also proceeds enantioselectively. Treatment of **3** of with a 1:1 inclusion crystal of 4-methylcyclohexanone (**5 a**) and the chiral host **6 a**<sup>2</sup> which had been derived from tartaric acid at 70 °C for 4 h gave (-)-**7 a** of 42.8% ee in 51% yield.<sup>3</sup> Similar treatments of 1:1 inclusion complexes of **5 b** with **6 b** and of **8** with **6 c** gave (-)-**7 b** of 45.2% ee in 73% yield and (-)-**9** of 56.9% ee in 58% yield, respectively.<sup>3</sup>

Acid-catalyzed etherification reaction of benzhydrol (**10**) in the solid state proceeded much faster than did in solution. Treatments of powdered **10** with powdered *p*-toluenesulfonic acid at 15 °C for 11 min in the solid state, and in benzene and MeOH solution gave the corresponding ether **11** in 95, 45 and 34% yields, respectively.<sup>4</sup> The same treatment of several benzhydrol derivatives gave similar results.<sup>4</sup> The very efficient etherification reaction in the solid state is due to a molecular packing pattern of **10** in crystal. X-ray crystal structure analysis showed that two molecules of **10** form a pair through hydrogen bond formation in crystal (Fig. 1).

Various organic reactions such as pinacol rearrangement,<sup>5</sup> benzilic acid rearrangement,<sup>6</sup> Beckmann rearrangement,<sup>7</sup> epoxidation,<sup>7</sup> Baeyer-Villiger oxidation,<sup>8</sup> NaBH<sub>4</sub> reduction,<sup>9</sup> aldol condensation,<sup>10</sup> Reformasky and Luche reactions,<sup>11</sup> Michael addition reaction,<sup>12</sup> ylide addition reaction,<sup>13</sup> FeCl<sub>3</sub>-catalyzed coupling reaction of phenol derivatives,<sup>14</sup> Zn-ZnCl<sub>2</sub>-catalyzed coupling reactions of aldehydes and ketones,<sup>15</sup> and copper ion-catalyzed coupling reaction of acetylenic compounds<sup>16</sup> have also been found to proceed efficiently and selectively in the solid state.

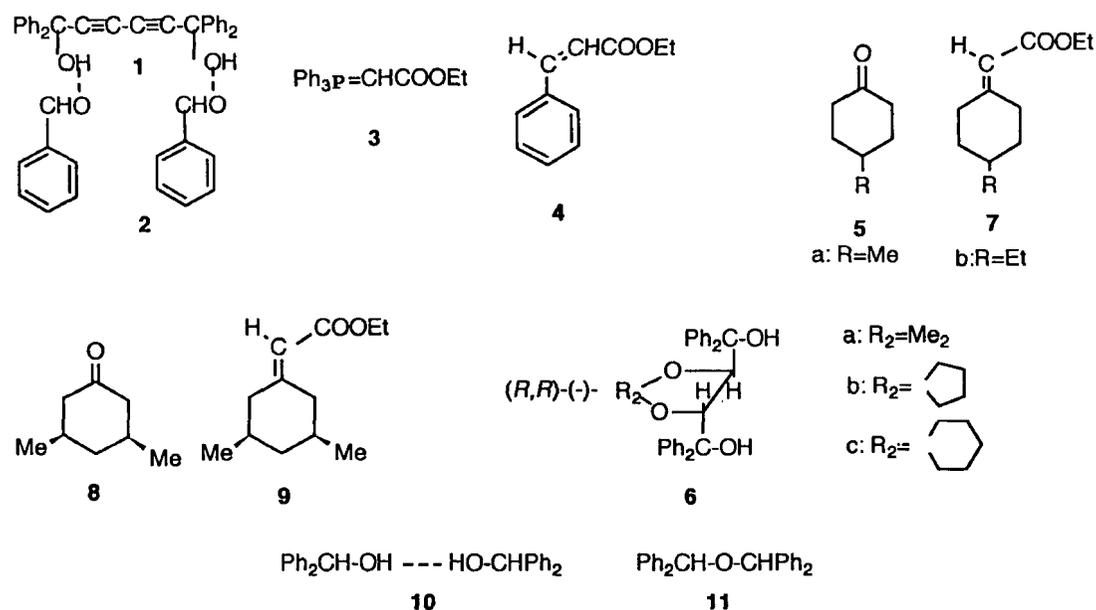


Fig. 1. A pair of **10** in crystal

### 3. Design of Host Compounds

Nevertheless, molecules in crystal are not always arranged at an appropriate position for solid state reaction. In such cases, some special techniques are necessary in order to arrange molecules in a suitable form for solid state reaction. For this purpose, host-guest technique was used. In a host-guest inclusion complex crystal, arrangement of guest molecule can be controlled by the host molecule used.

Principle of the design of host molecules which have been used in our research group is shown in Fig. 2. Sterically hindered alcohol molecules can not form hydrogen bond. However, hydrogen bond is formed by an accommodation of a guest molecule. According to this simple idea, various kinds of useful host compounds such as **1** and **6** have been synthesized.<sup>17-19</sup> Most of them are achiral but some are chiral.

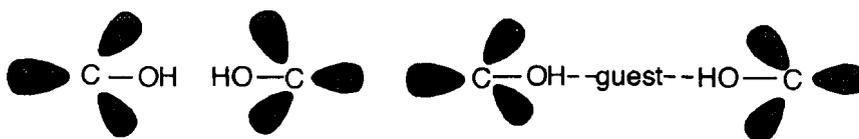


Fig. 2. Principle of the design of host molecule

### 4. Molecular Movement

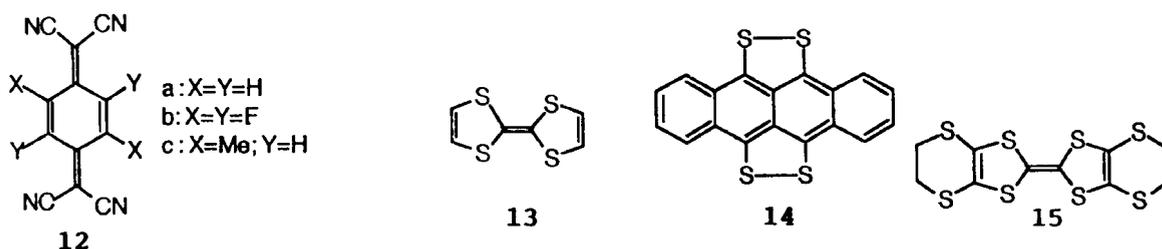
It has been disclosed that host-guest inclusion complexation can be achieved by mixing powdered crystalline host and guest compound with using mortar and pestle.<sup>20</sup> Recently we found that this inclusion complexation method is applicable to a preparation of charge-transfer complex in the solid state. Since molecular movement in the solid state occurs even enantioselectively, a combination of the enantioselective molecular movement and distillation procedure can establish a new separation method of enantiomers by fractional distillation. We further found that achiral guest molecules are forced to be arranged in a chiral form in the inclusion crystal formed by mixing with chiral host in the solid state. By combination of the complexation of achiral guest and chiral host in the solid state with photoirradiation, a new simple procedure of enantioselective photoreactions in the solid state was developed.

#### 4.1. Charge-Transfer Complex Formation in the Solid State

When a mixture of yellow crystals of tetracyanoquinodimethane (**12a**) (0.204 g, 1 mmol) and orange crystals of tetrathiafulvalene (**13**) (0.204 g, 1 mmol) was ground occasionally for 1 h by using an agate mortar and pestle, the charge-transfer (CT) complex of **12a-13** was formed as a black crystalline powder.<sup>21</sup> The IR spectrum of the complex was identical to that of an authentic sample prepared by recrystallization of the both components from MeCN. The electric conductivity measured at room temperature for the complex,  $0.70 \text{ S cm}^{-1}$ , is comparable to that reported for the authentic sample,  $21 \text{ S cm}^{-1}$ .<sup>22</sup>

By a similar grinding method, the CT complex of **12a** and tetrathianaphthacene (**14**) was formed as dark green crystals and its electric conductivity at room temperature,  $0.024 \text{ S cm}^{-1}$  is comparable to that of the authentic sample prepared by recrystallization procedure,  $1.3 \text{ S cm}^{-1}$ .<sup>22</sup>

Both the acceptors 2,3,5,6-tetrafluoro-7,7,8,8-tetracyanoquinodimethane (**12b**) and 2,5-dimethyl-7,7,8,8-tetracyanoquinodimethane (**12c**) also formed CT-complexes with the donors **13**, **14**, and **15**, although **12a** did not form CT complex with **15**.<sup>21</sup>

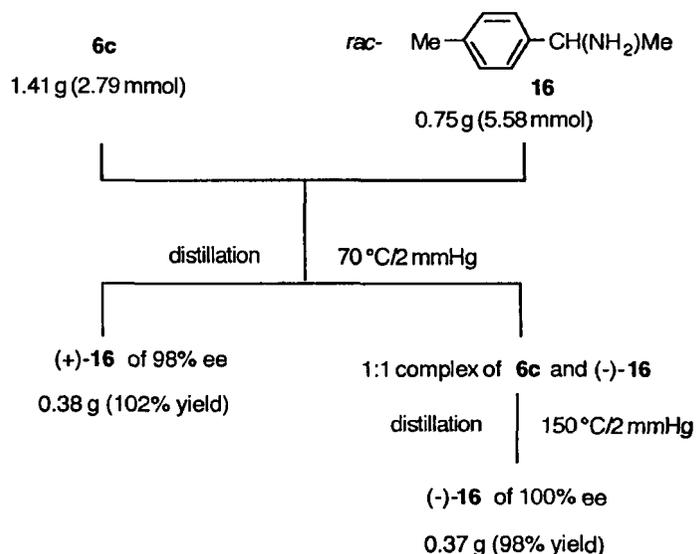


#### 4.2. Separation of Enantiomers by Fractional Distillation

Heating of a mixture of powdered **6c** (1.41 g, 1.79 mmol) and *rac-p*-methyphenethyl amine (**16**) (0.75 g, 5.58 mmol) at 70 °C/2 mmHg in a Kugerohr apparatus gave (+)-**16** of 98% ee (0.38 g, 102% yield) by distillation. Further heating at 150 °C/2 mmHg gave (-)-**16** of 100% ee (0.37 g, 98% yield) by distillation. By the distillation in the presence of the chiral host **6c**, enantiomers of *rac*-amine **16** were separated almost perfectly. By mixing of **6c** and **16**, (-)-**16** moves to the chiral host and forms inclusion complex. By heating the mixture in vacuo, the uncomplexed (+)-**16** distils at relatively low temperature, and the complexed (-)-**16** distils at relatively high temperature. This is the mechanism of the separation of enantiomers by distillation.<sup>23</sup>

This simple resolution method is applicable to various kinds of racemic compounds, such as alcohols, diols, amino alcohols, alkyl hydroxycarboxylates, epoxides, amines. Since chiral host compound is recovered unchanged and can be used again, this resolution method is economical and useful in industry.

Of course, this separation method of enantiomers by distillation can be applied to a separation of isomers which can not be separated by simple fractional distillation because of the same or close boiling point.



#### 4.3. Achiral Molecules Move and Arrange in a Chiral Form in the Solid State

We have reported that irradiation of powdered 2:1 inclusion crystals of **6b** and *N*-allyl-*N*-benzyl-3-oxo-1-cyclohexenecarboxamide (**17**) which had been prepared by recrystallization of these from ether, in a water suspension which contains alkylsulfate as a surfactant at room temperature for 10 h gave (-)-**18** of 100% ee in 90% yield.<sup>24</sup> Similar treatment of 2:1 inclusion crystals of **6c** and **17** prepared by recrystallization from benzene gave (-)-**18** of 100% ee in 87% yield.<sup>21</sup> Since the photoreaction of **17** itself in MeCN gives a mixture of *rac*-**18** and an isomeric photocycloaddition product,<sup>25</sup> it is clear that the steric course of the photoreaction is controlled efficiently by the chiral host **6**. It is probable that molecules of **17** are arranged in a chiral form in the inclusion complex with **6**.

Interestingly, however, we found that the same inclusion complex of **6** and **17** as that prepared by recrystallization can be obtained just by mixing **6** and **17** in the solid state and that photoirradiation of the inclusion crystals obtained by mixing gives optically active photoreaction product. For example, an occasional mixing of powdered **6b** of about 50-100  $\mu\text{m}$  diameter and a half molar amount of oily **17** using an agate mortar and pestle for 1 h in order to avoid solidification gave the IR spectroscopically identical 2:1 inclusion complex crystal of **6b** and **17** with that obtained by the recrystallization

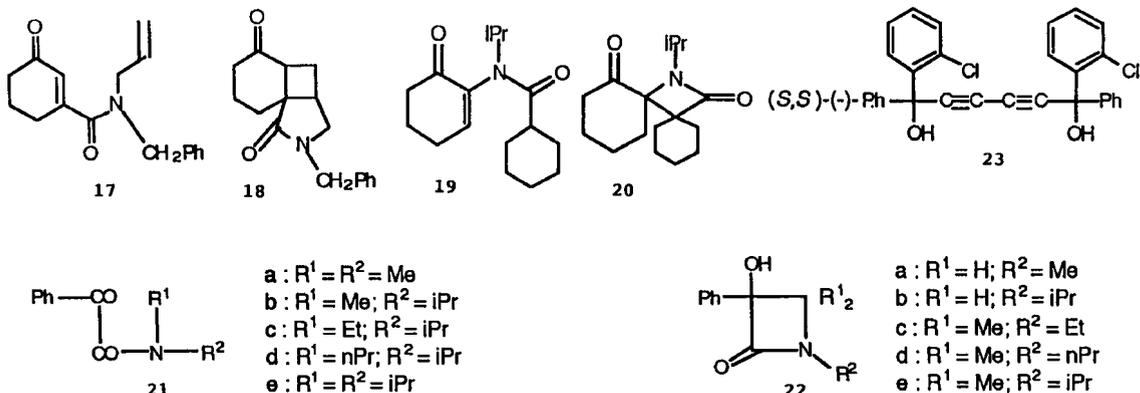
method. Photoirradiation of the complex in a water suspension for 10 h gave (-)-**18** of 99% ee in 48% yield. Similar mixing of **6c** and **17** in the absence of solvent for 1 h followed by irradiation for 10 h gave (-)-**18** of 87% ee in 40% yield. These data clearly show that inclusion crystals of **6** and **17** in which achiral molecules of **17** are arranged in a chiral form produced just by mixing both components. Such molecular movement in the solid state and arrangement in a chiral form are not special for **16** but rather common. For example, mixing of powdered **6b** and an equimolar amount of powdered *N*-isopropyl-*N*-2-(1-oxocyclohex-2-enyl)cyclohexanecarboxamide (**19**) followed by irradiation gave the photocyclization product (-)-**20** of 81% ee in 37% yield.<sup>26</sup> Photoirradiation of **19** in acetone gives *rac*-**20** together with an isomeric photocycloaddition product.<sup>27</sup>

*N,N*-Dialkylphenylglyoxylamide (**21**) also forms an inclusion complex on mixing with **6** and the achiral molecules of **21** are arranged in a chiral form in the inclusion crystal. Occasional mixing of oily **21a** with an equimolar amount of powdered **6b** for 1 h followed by irradiation in a water suspension for 10 h gave (-)-**22** of 78% ee in 54% yield.<sup>21</sup> Similar treatments of oily **21b** with **6b** or of oily **21d** with **6c** followed by photoirradiation gave (-)-**22b** of 87% ee (45% yield) of (-)-**22d** of 93% ee (39% yield), respectively in the yields indicated.<sup>26</sup>

The inclusion complex of **6a** and **21a** could not be obtained by recrystallization, although more than 15 organic solvents were tested. In all cases **6a** crystallized out separately. However, when powdered **6a** and oily **21a** were mixed for 1 h using an agate mortar and pestle, the mixture solidified to give a 2:1 inclusion complex crystal of **6a** and **21a**. Photoirradiation of powdered complex crystal in a water suspension gave **22a** of 61% ee in 70% yield.

Very interestingly, irradiation of the 1:1 inclusion complex of **6c** and **21a** which had been prepared by mixing both components in the absence of solvent gave (+)-**22a** of 45% ee in 42% yield, although the same irradiation of the complex prepared by recrystallization of **6c** and **21a** from toluene gave the other enantiomer (-)-**22a** of 100% ee in 40% yield.<sup>26</sup> The type of chiral arrangement of **21a** molecules varies depending on the conditions of the inclusion complexation experiment.

Chiral arrangement of **21a** molecules in an inclusion crystal with (*S,S*)-(-)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**23**)<sup>28</sup> also depends on the conditions of the inclusion complexation experiment. Recrystallization of **23** and **21a** from ether gives a 1:1 inclusion complex, which upon irradiation affords (-)-**22a** of 100% ee in quantitative yield.<sup>29</sup> However, irradiation of the inclusion crystal prepared by mixing **23** and **21a** gave *rac*-**22a**. In the latter crystal, **21a** molecules would not be arranged in a chiral form. Interestingly, however, both inclusion crystals are thermally interconvertible. After melting (mp 126-127 °C), the former is solidified by cooling to give the latter, but the latter is converted to the former by heating gradually and melts again at 126-127 °C.



## REFERENCES

1. F. Toda and K. Akagi, *Tetrahedron Lett.* 3695 (1968).
2. F. Toda and K. Tanaka, *Tetrahedron Lett.* **29**, 551 (1988); D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, *Helv. Chim. Acta*, **70**, 954 (1987).
3. F. Toda and H. Akai, *J. Org. Chem.* **55**, 3446 (1990).
4. F. Toda, H. Takumi and H. Akehi, *J. Org. Chem.* **55**, 3446 (1990).
5. F. Toda and T. Shigemasa, *J. Chem. Soc. Perkin Trans. 1*, 209 (1989).
6. F. Toda, K. Tanaka, Y. Kagawa and Y. Sakaino, *Chem. Lett.* 373 (1990).
7. F. Toda, K. Mori, Y. Matsuura and H. Akai, *J. Chem. Soc., Chem. Commun.* 1591 (1990).
8. F. Toda, H. Yagi and K. Kiyoshige, *J. Chem. Soc., Chem. Commun.* 958 (1988).
9. F. Toda and K. Mori, *J. Chem. Soc., Chem. Commun.* 1245 (1989); F. Toda, K. Kiyoshige and M. Yagi, *Angew. Chem. Int. Ed. Engl.* **28**, 320 (1989); F. Toda and T. Shigemasa, *Carbohydr. Res.* **192**, 363 (1989).
10. F. Toda, K. Tanaka and K. Hamai, *J. Chem. Soc. Perkin Trans. 1*, 3207 (1990).
11. K. Tanaka, S. Kishigami and F. Toda, *J. Org. Chem.* **56**, 4333 (1991).
12. F. Toda, K. Tanaka and J. Sato, *Tetrahedron Asymm.* **4**, 1771 (1993).
13. F. Toda and N. Imai, *J. Chem. Soc. Perkin Trans. 1*, 2673 (1994).
14. F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.* **54**, 3007 (1989).
15. S. Kishigami, K. Tanaka and F. Toda, *J. Org. Chem.* **55**, 2981 (1990).
16. F. Toda and Y. Tokumaru, *Chem. Lett.* 987 (1990).
17. F. Toda, *Top. Curr. Chem.* **140**, 43 (1987).
18. F. Toda, *Top. Curr. Chem.* **149**, 211 (1988).
19. F. Toda, *Synlett.* 303 (1993).
20. F. Toda, K. Tanaka and A. Sekikawa, *J. Chem. Soc., Chem. Commun.* 279 (1987).
21. F. Toda and H. Miyamoto, *Chem. Lett.* in press.
22. J. Ferrgris, D. O. Cowan, V. Walatka and H. Perlstein, *J. Am. Chem. Soc.* **95**, 948 (1973); R. C. Wheland and J. L. Gillson, *J. Am. Chem. Soc.* **98**, 3916 (1976).
23. F. Toda and Y. Tohi, *J. Chem. Soc., Chem. Commun.* 1238 (1993).
24. F. Toda, H. Miyamoto and S. Kikuchi, *J. Chem. Soc. Perkin Trans. 1*, 621 (1995).
25. S. L. Blanc, J.-P. Pete and O. Piva, *Tetrahedron Lett.* **34**, 635 (1993).
26. F. Toda and H. Miyamoto, *Chem. Lett.* in press.
27. M. Ikeda, T. Uchino, M. Yamano, Y. Watanabe, H. Ishibashi and M. Kido, *Chem. Pharm. Bull.* **34**, 4997 (1986).
28. F. Toda, K. Tanaka, K. Nakamura, H. Ueda and T. Oshima, *J. Am. Chem. Soc.* **105** 5151 (1983).
29. M. Kaftory, K. Tanaka and F. Toda, *J. Org. Chem.* **50**, 2154 (1985).