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REVIEW

Molecular Recognition

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INTRODUCTION

Precise molecular recognition is important in molecular assembly and reactions of biological substances. At the reaction between, for example, body and antibody, enzyme and substrate, any error should not occur in molecular recognition. We are interested in whether molecular recognition is special for biologically active substances or not. When usual organic molecules are found to be able to recognize other molecules in their molecular assembly and reaction, our understanding and interest in such molecules become more wide and deep.

Most biological reactions *in vivo* occur in the micelle formed by assembling hydrophobic moieties of substances. These reactions do not occur in aqueous solution, although these occur in aqueous media. In relating to the reaction in the hydrophobic micelle, we are interested in the reaction and molecular recognition in the solid state, and we studied molecular assembly of host and guest compounds and molecular recognition between them in the solid state.

MOLECULAR RECOGNITION AT ASSEMBLY OF HOST AND GUEST MOLECULES

In 1968, we first found that the diol host compounds (**1a–c**) form crystalline inclusion complexes with various guest compounds in a stoichiometric ratio (*1*). X-ray crystal structure analysis of these inclusion complexes showed that the host and guest molecules are assembling through hydrogen bond formation and van der Waals' interaction. In the complex, host and guest molecules recognize each other precisely. For example, **1a** recognizes the stereoisomerism of *m*- (**2a**) and *p*-methylbenzaldehyde (**2b**), and includes the latter selectively (*2*). By using the selective inclusion, a mixture of **2a** and **2b** can be separated to each in pure state.

The separation method can be applied to the isomer separation of not only benzene and naphthalene derivatives but also a wide variety of other compounds (*2–4*). Since the molecular recognition with **1a** is also applicable to the isolation of natural products, for example, caffeine from tea leaves, nicotine from tobacco

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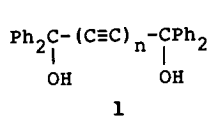
leaves, and cholesterol from bile stone (*5*), the molecular recognition ability of **1a** seems very high like that of an enzyme.



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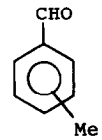
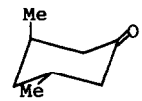
b: n=1

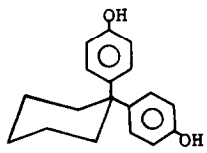


2

3a



3b



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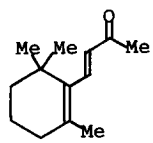
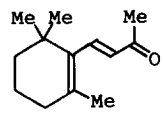
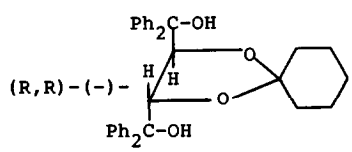


5a



5b

Stereoisomerism of cyclohexane derivatives can also be recognized with using simple host compounds. For example, since **1a** includes *cis*-3,5-dimethylcyclohexanone (**3a**) but not its *trans*-isomer (**3b**), these can be separated in pure state from a mixture (*6*). In this case, **1a** recognizes whether the Me group of **3** is axial or equatorial. In other words, less bulky **3a** molecules can be accommodated in the crystalline lattice of the inclusion complex with **1a**; however, more bulky **3b** molecules cannot be accommodated. This was clarified by X-ray crystal structure study (*6*). Interestingly, the host **4** includes *S-trans*-conformer of β-ionone (**5a**) selectively, although the β-ionone exists as *S-cis*-conformer (**5b**) in solution. On the other hand, the host **6** which is derived from tartaric acid includes **5b**. However, the hydrocarbon host **7** includes α-ionone exclusively in the boat form holding the enone moiety at axial position (**8**) (*7*). All the conformations of **5a, 5b,** and **8** have been studied by X-ray crystal structure study (*7*). The recognition of the conformer of **5a** and **5b** is interesting to the retinal chromophore, whose binding within rhodopsin is known to be conformationally dependent (*8*).



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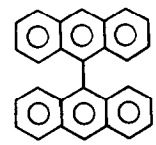

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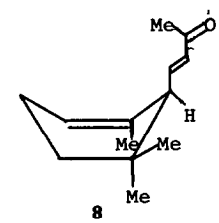
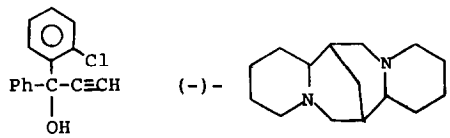


8

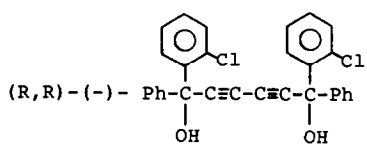
Chiral recognition is one of the most interesting molecular recognition. We first found that alkaloids such as brucine and sparteine form inclusion complexes with various alcohols such as secondary alcohols, halohydrins, propargyl alcohols, and cyanohydrins, and that precise chiral recognition occurs in these complexes and then the alcohols can be resolved (*4*). For example, complexation of **9** and (−)-sparteine (**10**) in acetone gives a 1 : 1 crystalline complex of (−)-**9** and **10**, which

upon distillation *in vacuo* gives optically pure (−)-**9** (*9, 10*). By using the mutual chiral recognition of alkaloid and alcohol, racemic alkaloid can be resolved by complexation with optically active alcohol (*9, 10*). Mechanism of the mutual chiral recognition between alkaloid and alcohol has been studied by X-ray analysis (*9, 10*).



9 **10**

The optically active host (**11**) which was prepared by coupling of (−)-**9** is very useful for resolution of various guest compounds such as ketone, epoxide, halide, alcohol, and amine (*2, 11, 12*). One of the most important resolution with **11** is that of **12a** which upon hydrolysis gives the important starting material (**13b**) of prostaglandin synthesis (*13*).



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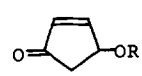


12

a: R=COMe

b: R=H

Many resolutions by complexation with some other hosts have been reported (*2*). In all cases, precise mutual chiral recognition is working in between the host and guest.

MOLECULAR RECOGNITION AT REACTION

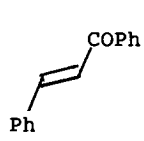
The most interesting molecular recognition for bioorganic and organic chemists is that appears at reaction. Studies on the role of molecular recognition at photochemical and usual organic reactions in the solid state are reviewed in this chapter.

Molecular Recognition at Photochemical Reaction

Photochemical conversion of ergosterol into vitamin D_2 in the skin is an important biochemical process for human being. In relating to such the biological reaction, studies of selective solid-state photochemistry of guest compounds in host–guest complex is interesting.

Photodimerization of chalcone (**13**) does not occur efficiently neither in solution nor in crystalline state. Irradiation of, however, a 1 : 2 complex of **1a** and **13** for 6

h in the solid state gave the dimer **14** in 80% yield (*14, 15*). X-ray crystal structure study of the complex showed that the two **13** molecules are arranged in close positions (distance between double bonds, 3.862 Å) in a manner parallel to each other (*15, 16*). It has been clarified that **13** molecules are not arranged in appropriate positions for photodimerization in its own crystal (*17*). In similar way, photodimerization of dibenzalacetone, 9-formyl- and 9-acetylnaphthalene, and pyridone was also achieved by irradiation of their inclusion complex with host in the solid state (*15*). In all complexes, each two guest molecules are arranged in appropriate positions for the photodimerization (*15*).



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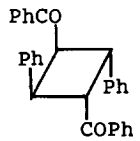

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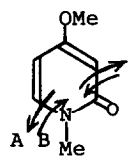

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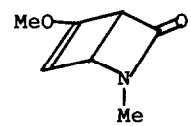

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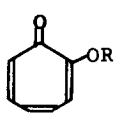
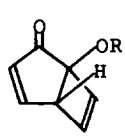
Enantioselective photoreaction of achiral guest can be carried out by using chiral recognition with chiral host. Irradiation of a 1 : 1 inclusion complex of **11** and 1-methyl-4-methoxypyridone (**15**) in the solid state gave optically pure β-lactam derivative **16** (*15, 18*). Reason for the high enantiocontrol was studied by X-ray crystal structure analysis of the complex (*15, 18*). Owing to a steric repulsion between the phenyl group of **11** and the methoxy group of **15**, disrotatory ring closure of **15** is forced to occur only to one direction, for example, A but not B direction as shown in **15**. In a similar manner, enantioselective photocyclizations of tropolone alkyl ether **17** into the bicyclic enone **18** (*15, 19*), imine oxide **19** into the oxaziridine **20** (*20*), and oxoamide **21** into β-lactam (**22**) (*15, 19*) were as also achieved efficiently. The latter one is especially efficient and optically pure **22** was obtained in 92% yield by 6 h irradiation of a 1 : 1 inclusion complex of **21** and **11**. The efficient enantiocontrol was studied by X-ray crystal structure analysis of the complex (*19*). In the complex of **11** and **21**, the CO–CO bond is twisted as shown as A in Fig. 1, and irradiation of the complex gives (−)-**22**. In the complex of (S,S)-(−)-enantiomer of **11** and **21**, the twisting of the CO–CO bond (B) is enantiomeric to A, and irradiation of the complex gives (+)-**22**. It is interesting that the achiral **21** is forced to be twisted and arranged in a chiral form by complexing with chiral host (Fig. 1).



17

a: R=Me

b: R=Et



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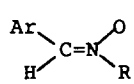

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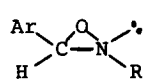

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If oxoamide molecule can be arranged in its own crystal as that of Fig. 1 without using any chiral host, irradiation of the crystal gives chiral product. This is a

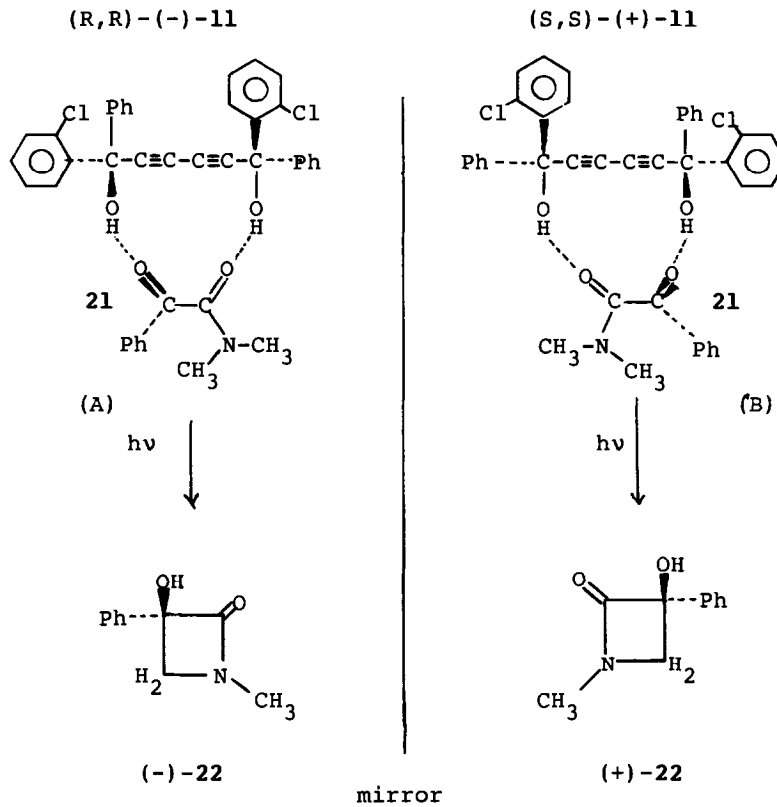


FIG. 1. Enantioselective photocyclization of **21** to β-lactam (**22**) in the inclusion complex with **11**.

generation of chirality. Fortunately, we found such the case for the oxoamide **23**. It was disclosed that one piece of crystal of **23** consists of (+)-twisted molecules, and the other one consists of (−)-twisted molecules, and irradiation of these crystals gave (+)- and (−)-**24**, respectively (*21*). We tentatively named the crystals as (+)- and (−)-crystals. Large amounts of the chiral crystal can easily be obtained by adding one piece of the chiral crystal as a seed during recrystallization of **23**. X-ray crystal structure analysis showed that **23** molecules are arranged like as that schematically shown in Fig. 2 (*22*).

This method is useful as a new preparative technique of chiral compound. Furthermore, the result might be a persuasive way of interpreting the generation of chirality on Earth, since the photocyclization of **23** to **24** occurs by sunlight and hydrolysis of **24** gives β-amino acid.

Molecular Recognition at Usual Organic Reaction

First we found that host–guest complexation between crystalline host and guest compounds occurs by mixing the both in the solid state (*23*). For example, grinding crystals of **1a** and benzophenone by agate motar and pestle for 5 min gave the

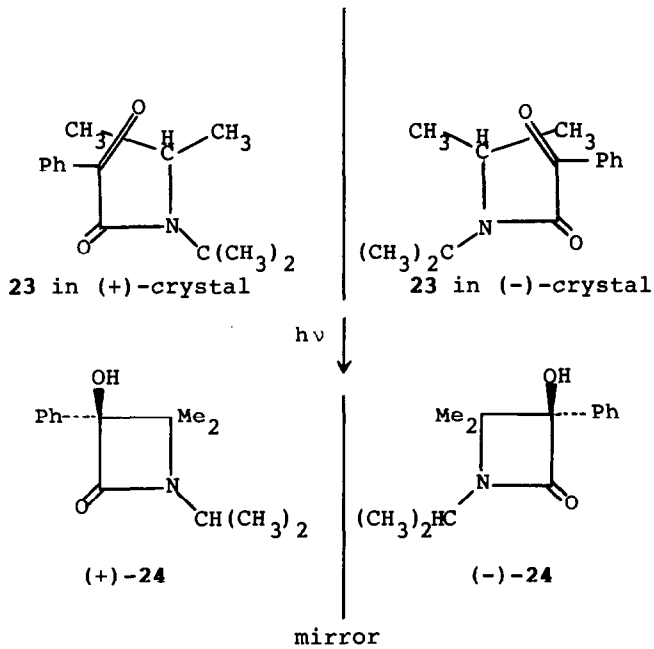


FIG. 2. Generation of chirality.

1 : 2 complex. Similar solid-state complexation can be carried out for various combinations of many host and guest compounds (*23*). The solid-state complexation can also be followed by spectroscopy. For example, by measuring of uv spectrum of a 1 : 2 molar mixture of powdered **1a** and **13** every 10 min for 6 h, progress of the complexation can well be observed (Fig. 3). As the complexation proceeds, population of coplanar **13** molecules increases and then molecular coefficient of the uv spectrum increases.

By combination of the complexation and photoreaction in the solid state, an enzyme model reaction could be carried out. Irradiation of a mixture of powdered **1a** and excess **13** gave the photodimer **14** in almost quantitative yield. This result can be interpreted as follows: solid-state complexation of **1a** and **13** gives their 1 : 2 complex and its irradiation turned into **14** and **1a**, and the latter includes excess **13** by further mixing which upon irradiation converts into **14** and **1a**, and finally all of **13** converts into **14**. In this reaction, **1a** is used as a catalyst in organic reaction, or as an enzyme in a biological reaction (*15*).

Surprisingly, the solid-state complexation occurs sometime even enantioselectively (*24*). A mixture of powdered **6** and *rac*-β-ionone epoxide **25** was kept at room temperature for 1 day and then washed with hexane to give a complex of **6** and (+)-**25** as crystals and hexane solution. From the complex, (+)-**25** of 88% ee was obtained in 24% yield by distillation *in vacuo*. From the hexane solution, (−)-**25** of 36% ee was obtained in 50% yield (*24*). Similar some other examples have also been reported (*24*).

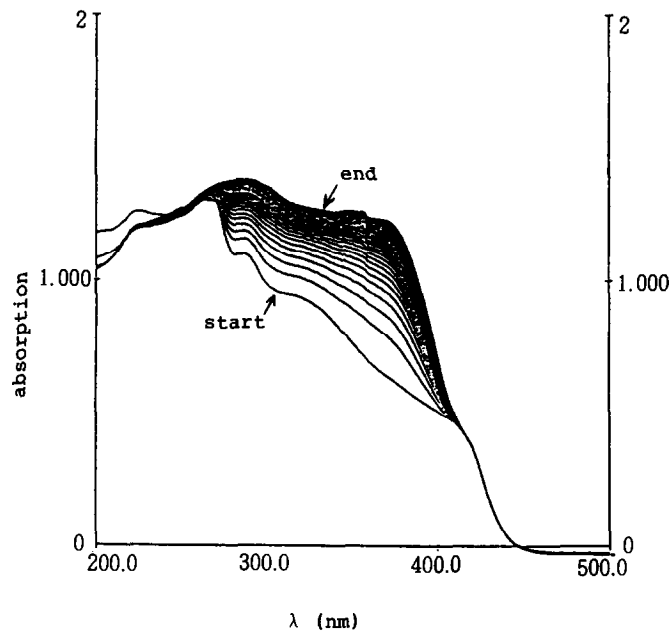
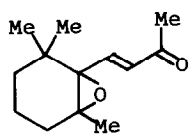


FIG. 3. Ultraviolet spectrum of a mixture of powdered **1a** and **13** in the solid state (measured every 10 min for 6 h).

The above data show that molecules move freely in the solid state when conditions are appropriate. We then became aware of that organic reaction might occur in the solid state, and we found that reaction occurs in the solid state sometimes faster and sometimes more selectively than in solution.



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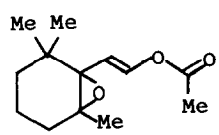

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Baeyer–Villiger oxidation of ketones with *m*-chloroperbenzoic acid in the solid state was found to proceed faster than in solution (*25*). By combining of the reaction and the enantioselective inclusion complexation described above, an interesting kinetic resolution of **25** in the solid state was achieved. By mixing powdered **6**, *rac*-**25**, and *m*-chloroperbenzoic acid, (+)-**25** forms complex with **6**, and the uncomplexed (−)-**25** is oxidized into (−)-**26**. By this method, (+)-**25** of 66% ee and (−)-**26** of 72% ee were obtained (*24*).

Reduction of ketones with sodium borohydride or borane ethylenediamine complex also occurred in the solid state, although the reaction proceeds slower than in solution (*26*). Nevertheless, the solid-state reduction occurred enantioselectively when inclusion complex of ketone with optically active host such as **6** (*27*), **11**

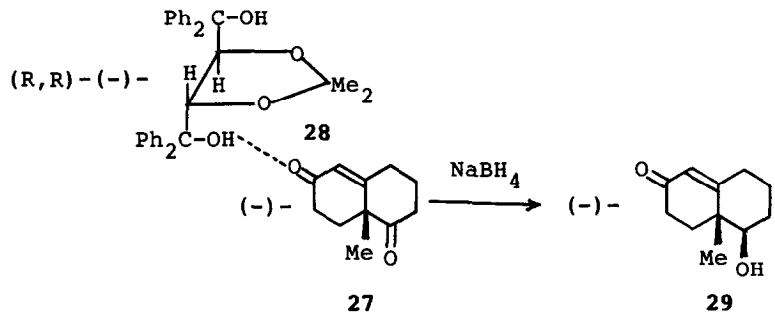
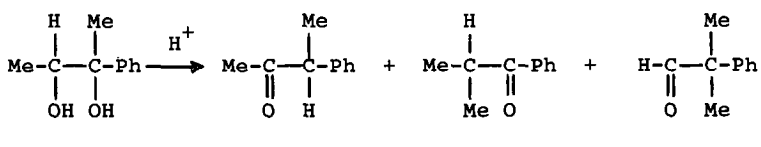


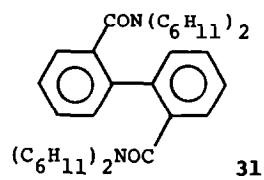
FIG. 4. Reaction control of the reduction of **27** with the host **28**.

(*27*), and β-cyclodextrin is reacted with reducing reagent (*28*). Selective reduction of the nonconjugated carbonyl group of **27** in solution is not easy. Complexation of *rac*-**27** with **28** gave a 1 : 1 complex of (−)-**27** and **28**. Treatment of the complex with sodium borohydride in the solid state gave (−)-**29** selectively (*26*). X-ray crystal structure analysis of the complex showed that (−)-**27** is included by forming hydrogen bond between the hydroxyl group of **28** and the conjugated carbonyl group of the (−)-**27** as shown in Fig. 4. Since the conjugated carbonyl group is shielded by forming the hydrogen bond, sodium borohydride might attack the unshielded nonconjugated carbonyl group to give (−)-**29**.

The pinacol rearrangement in the solid state was also found to proceed faster and more selectively than that in solution (*29*). A highly selective rearrangement was observed in the reaction of pinacol in its host–guest complex in the solid state. For example, treatment of the powdered 1 : 1 complex of **30** and the host **31** with HCl gas or *p*-toluenesulfonic acid (*p*-TsOH) at room temperature for 3 h gave **32** in 44% yield as the sole isolable product (*29*). This is in contrast to the reaction of **30** with dil H_2SO_4 under reflux (115°C) which gives **32**, **33**, and **34** in 48, 29, and 5% yields, respectively. In crystalline lattice of the complex, sterically less hindered hydrogen might rearrange selectively.



30 **32** **33** **34**



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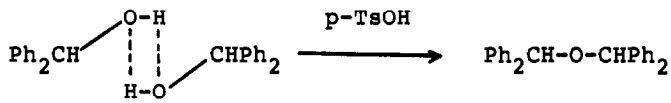
Some benzylic acid rearrangements also proceed more efficiently than in solu-

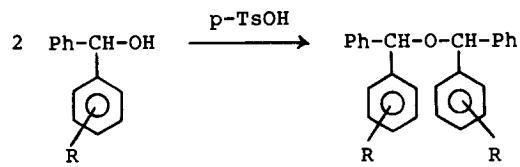


35a **36a**

FIG. 5. Solid-state S_N1 reaction of **35a**.

tion. The rearrangement by CsOH, RbOH, and $Ba(OH)_2$ proceeded faster in the solid state than in solution. However, LiOH and $Sr(OH)_2$ were inert to the rearrangement in the solid state, although these are effective in solution (*29*).

Hydrolysis of ester can also be carried out efficiently without using solvent. Treatment of solid or liquid ester with NaOH at room temperature followed by acidification gave the acid. In this case, the reaction proceeded much more smoothly than in solution because the alcohol produced is easily removed by evaporation from the surface of the reaction mixture. Grignard reaction also occurs in the solid state (*30*). Efficient dehydration, Meyer–Schuster rearrangement, and chlorination of alcohols in the solid state were also studied (*31*). The most interesting reaction of alcohol is its solid-state S_N1 reaction. Treatment of crystalline secondary alcohols (**35**) with *p*-TsOH gave ethers (**36**) in good yields via S_N1 reaction.



35 **36**

a: R=H **e**: R=o-Me

b: R=o-Cl **f**: R=m-Me

c: R=p-Br **g**: R=p-Me

d: R=p-NO_2

Efficiency of the solid-state substitution was much higher than that in benzene or MeOH (*31*). This result is very interesting because the S_N1 reaction has been interpreted to occur efficiently in polar solvent which stabilizes the carbonium ion intermediate by solvation. X-ray crystal structure analysis of **35a** showed that two **35a** molecules form a pair through hydrogen bond formation as shown in Fig. 5. Therefore, substitution reaction between the two **35a** might occur efficiently. The efficient conversion of the pair of two **35a** to **36a** suggests that the substitution occurs at the front side of alcohol. If this speculation is correct, the S_N1 reaction should proceed by retension of the configuration of alcohol. Treatment of a 1 : 1 complex of **11** and MeOH with *p*-TsOH in the solid state gave the substitution product **37** of the same configuration as that of **11** (Fig. 6). In the solid-state substitution, MeOH might attack the carbonium ion from **11** from the same side

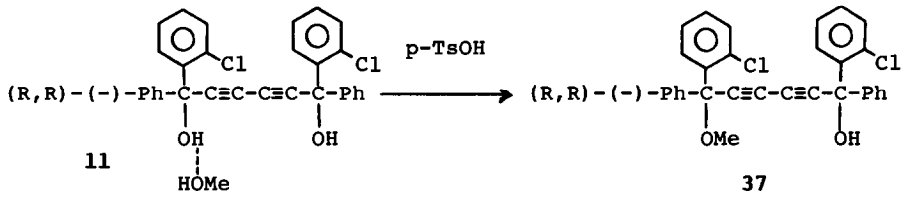
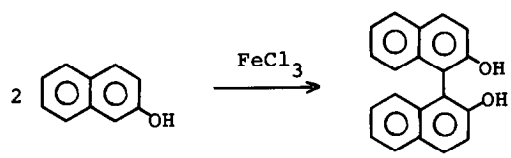


FIG. 6. S_N1 reaction which proceeds via a retention of the configuration.

of the hydroxyl group removed, since the MeOH is fixed at the same side as is the hydroxyl group.

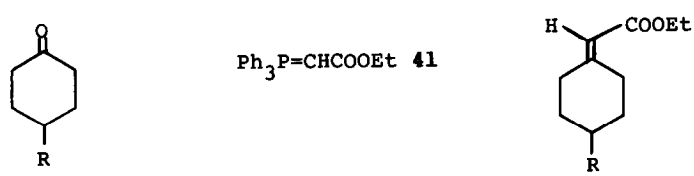
The coupling reaction of carbon compounds which proceeds via a dimerization of radical species formed by one-electron oxidation with metal ion also occurs efficiently in the solid state. For example, coupling of phenol derivatives with $FeCl_3$ to biphenol can be carried out more efficiently in the solid state than in solution. Treatment of 2-hydroxynaphthalene (**38**) with $FeCl_3$ powder at 50°C for 2 h gave the dimer **39** in 95% yield (*32*).



38 **39**

Coupling reaction of acetylenic compounds with cupric salt such as a $CuCl_2$–pyridine complex also proceeds efficiently in the solid state (*33*). It is interesting that the coupling of α,ω-diacetylenic compound in the solid state gives linear polymer, although the same reaction in solution gives cyclic dimer (*33*).

Enantioselective Wittig–Horner reaction occurred in the solid state. Treatment of a 1 : 1 complex of **28** and **40a** with the reagent **41** at 70°C in the solid state for 4 h gave **42a** of 42.8% ee in 50.8% yield (*34*). By the same way, **42b** of 65% ee was obtained in 47% yield from **40b**.



40 **42**

a: R=Me

b: R=t-Bu

CONCLUSION

Some examples of molecular recognition in the solid state and of the application of the recognition to separation of isomers and enantiomers and to reaction control have been reviewed. In the future, we would like to expand the study of molecular recognition to many other compounds, from simple organic compounds to biologically active materials. Development of the application of the molecular recognition to the control of many other reactions is also an important subject in the future.

Nevertheless, the author hopes in this short review it is understood that the importance of recognition among molecules is the same both in biological and usual organic reactions.

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