

Reaction Control by a Host–Guest Complexation Method

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Abstract. Very successful stereo-, regio-, and enantio-controls of the photoreaction of a guest compound were achieved by irradiation of the host–guest complex in the solid state. In order to discover the reason for the successful control, the X-ray crystal structure of the complex was studied. The complexation method was also effective to freeze the equilibrium in solution and isolate the labile tautomeric isomer as an inclusion complex.

Key words. Irradiation, solid state, enantiocontrol, organic reaction.

1. Introduction

Since guest molecules are arranged close together and in one conformer in a host–guest complex, inter- and intramolecular photoreactions of the guest compound would proceed regio- and stereo-selectively and efficiently by irradiation of the complex in the solid state. When an optically active host compound is used, enantio-control of the reaction is expected. When the complexation is applied to an equilibrium mixture of tautomers, one labile tautomer can be isolated as a host–guest complex. By an irradiation of the complex in the solid state, stereo- and enantio-controls of the reaction of the labile tautomer can be achieved.

2. Regio- and Stereo-controls

Photodimerization of chalcone (**1a**) is not easy either in solution or in the solid state. For example, irradiation of **1a** in solution gives a mixture of **1a**, its *cis*-isomer, and polymer. Irradiation of **1a** in the solid state gives a complex mixture of all possible stereoisomeric photodimers in low yields. X-ray crystal structural studies of two dimorphs of **1a** showed that the distance between the double bond center is greater than the limit of an intermolecular reaction (4.2 Å). However, irradiation for 6 h in the solid state of a 1 : 2 complex of 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**2**) and **1a** which had been prepared by recrystallization of the two components from solvent gave the *syn*-head-to-tail dimer (**3a**) selectively [1, 2]. Similar irradiation of 1 : 2 complexes of **2** and **1b–d** gave **3b–d**, respectively, in the yields shown in Table I. The reason for the well controlled reaction can be interpreted as follows: in the complex with **2**, two molecules of **1** are packed close together in the positions which give *syn*-head-to-tail dimer **3**. In order to clarify the reason, X-ray crystal analysis of a 1 : 2 complex of **2** and **1a** was carried out. The X-ray analysis disclosed that the above assumption is correct and the distance between the double bond centers of **1a** is short enough (3.682 Å) to react easily [3].

Benzylideneacetone (**4**) is also photoinactive in the solid state. However, irradiation of a 1 : 2 complex of **4** with 2,6-diphenylhydroquinone (**5**) in the solid state gave the *syn*-head-to-tail dimer (**6**) in 70% yield. An X-ray crystal structural study of the complex showed that a hydrogen bond between the components makes the packing tight and the distance between the double bonds shorter (3.787 Å) [2, 3].

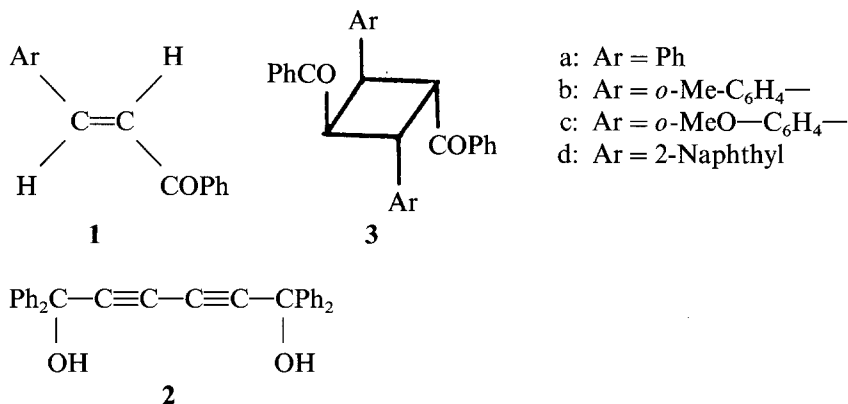
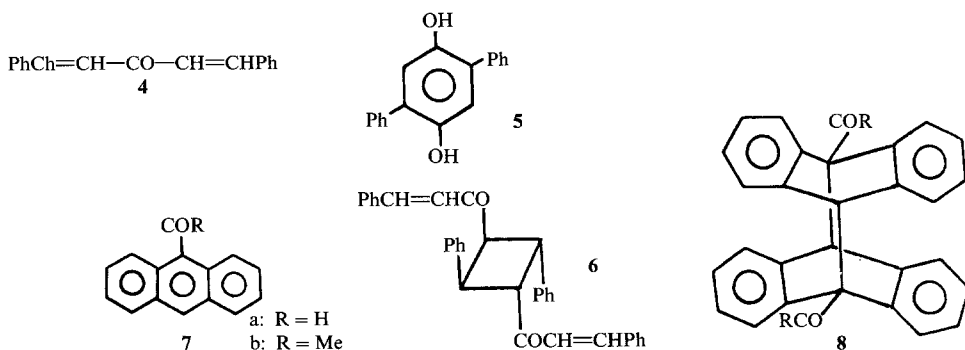


Table I. Reaction time, products, and yields of photocycloaddition reaction of **1a-d** in the complex with **2**, in the solid state.

Chalcone	Reaction time (h)	Product	
		No.	Yield (%)
1a	6	3a	90
1b	6	3b	85
1c	1.5	3c	88
1d	1	3d	82

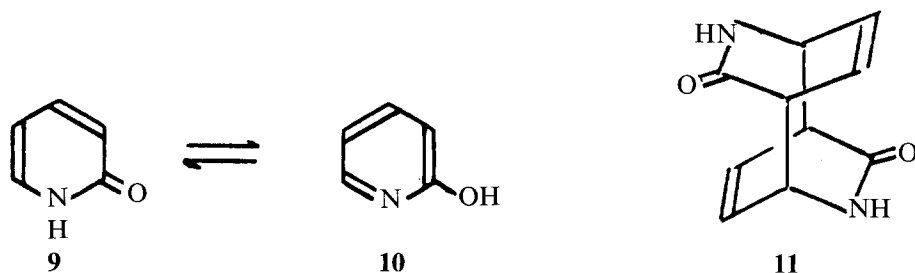


Although irradiation of 9-formylanthracene (**7a**) in solution for 24 h gives the *anti*-photocycloaddition product (**8a**) in a low yield [4], irradiation of a 1:2 complex of **2** and **7a** in the solid state for 8 h gave **8a** in 86% yield [2]. An X-ray crystal structural study of the complex showed that two molecules of **7a** are arranged between two host molecules by forming a hydrogen bond in the direction which gives the *anti*-dimer (**8a**) by the photodimerization and that the distance between the two reaction centers of **7a** is short enough to react readily (4.042 Å) [3]. Similar irradiation of a 1:2 complex of **2** and 9-acetylanthracene (**7b**) in the solid state for 1.5 h gave **8b** in 87% yield.

3. Control and Acceleration of Photoreaction by a Combination of Freezing of Equilibrium by Complexation and Irradiation of the Complex in the Solid State

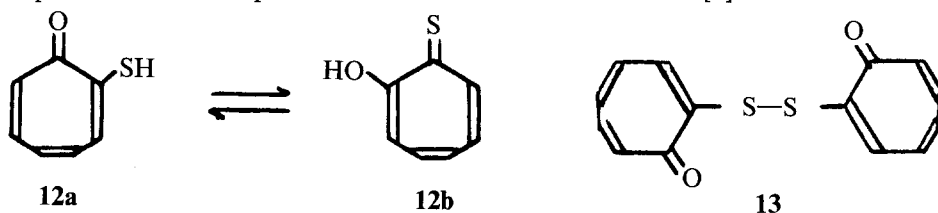
Since 2-pyridone (**9**) exists as an equilibrium mixture with 2-hydroxypyridine (**10**), it is difficult to isolate **9** in a pure state. However, the complexation method is applicable for an isolation of the *keto*-form (**9**) in a pure state. For example, **9** was isolated by complexation with **2** and **5** as 1:2 complexes with **2** and with **5**, respectively. The structure of the former complex was studied by an X-ray crystal analysis [5]. Inclusion of the *keto*-form is reasonable, because **2** and **5** form stronger hydrogen bonds with the carbonyl oxygen of the *keto*-form than with the hydroxyl oxygen of the *enol*-form.

The selective inclusion of the *keto*-form (**9**) can be used to effect an efficient dimerization of **9**. Moreover, since molecules of **9** are packed regularly in a host-guest complex, regio- and stereo-selective intermolecular reaction of **9** is expected. Irradiation of a 1:2 complex of **2** and **9** in the solid state for 6 h gave the *trans-anti*-dimer (**11**) in 76% yield [2]. This efficient reaction is in contrast to that in solution which gives **10** in 40% yield after irradiation for 72 h [6]. An X-ray crystal structural study of a 1:2 complex of **2** and **9** showed that two molecules of **9** are arranged between two molecules of **2** in the positions which give the *trans-anti*-dimer (**11**) by dimerization and the distance between the reaction centers is very short (3.837 Å) [5].



Freezing of the equilibrium by the complexation method is applicable to some other compounds. 2-Mercapto substituted tropone (**12**) has been reported to exist as an equilibrium mixture of 2-mercapto-tropone (**12a**) and 2-hydroxytropothione

(12b), and the latter is predominant both in solution [7] and in the solid state [8]. The equilibrium is frozen and the former was isolated by complexation with 2. When a solution of 2 and 12 in petroleum ether was kept at room temperature, a 1:1 complex of 2 and 12a was obtained in 90% yield as orange prisms of mp 101–103°C. The structure of 12a in the complex with 2 was elucidated by an X-ray crystal structural study, and the study disclosed that 12a has a delocalized structure (Figure 1). This is a very interesting result because the delocalized structure has never been reported for either tropolone or 12. As an exception, ferric troponate has been reported to have a delocalized structure [9].



A packing diagram of the complex shows that two molecules of 12a are packed in the *anti*-positions to each other and the distance between the two seven-membered rings is short enough (3.49 Å) to cause a π - π interaction. The stacking of 12a in the complex is comparable to that of graphite (3.5 Å). Although 12 is thermally labile and gives dimer 13 easily, 12a in the complex is stable. The stability is probably due to the packing of 12a in the *anti*-direction.

1,2,4-Triazole (14) also exists as an equilibrium mixture of the two tautomers, 1,2,4-triazacyclopenta-3,5-diene (14a) and 1,2,4-triazacyclopenta-2,5-diene (14b), and it is difficult to isolate one tautomer in a pure state. The former was isolated in a pure state as a 1:1 complex with 1,1-bis(2,4-dimethylphenyl)but-2-yn-1-ol (15). The complex was obtained from a solution of 14 and 15 in MeOH as colorless prisms of mp 101–102 °C, in 88% yield [10]. An X-ray analysis of the complex showed that 14a is included and the closest contact is a hydrogen bond between the hydroxyl group of 15 and the nitrogen at N4. The distance of the hydrogen bond was found to be 2.697 Å [10].

Cycloocta-2,4,6-trien-1-one exists as an equilibrium mixture of a stable form (16a and 16b) and an unstable form (17) in a 95:5 ratio at 20°C [11]. Conversion

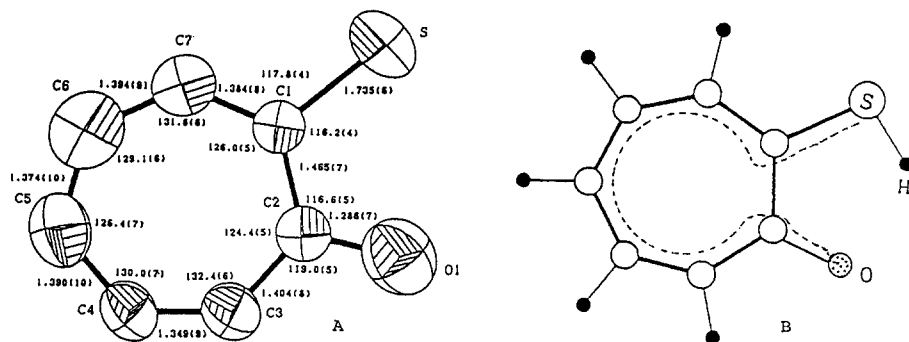
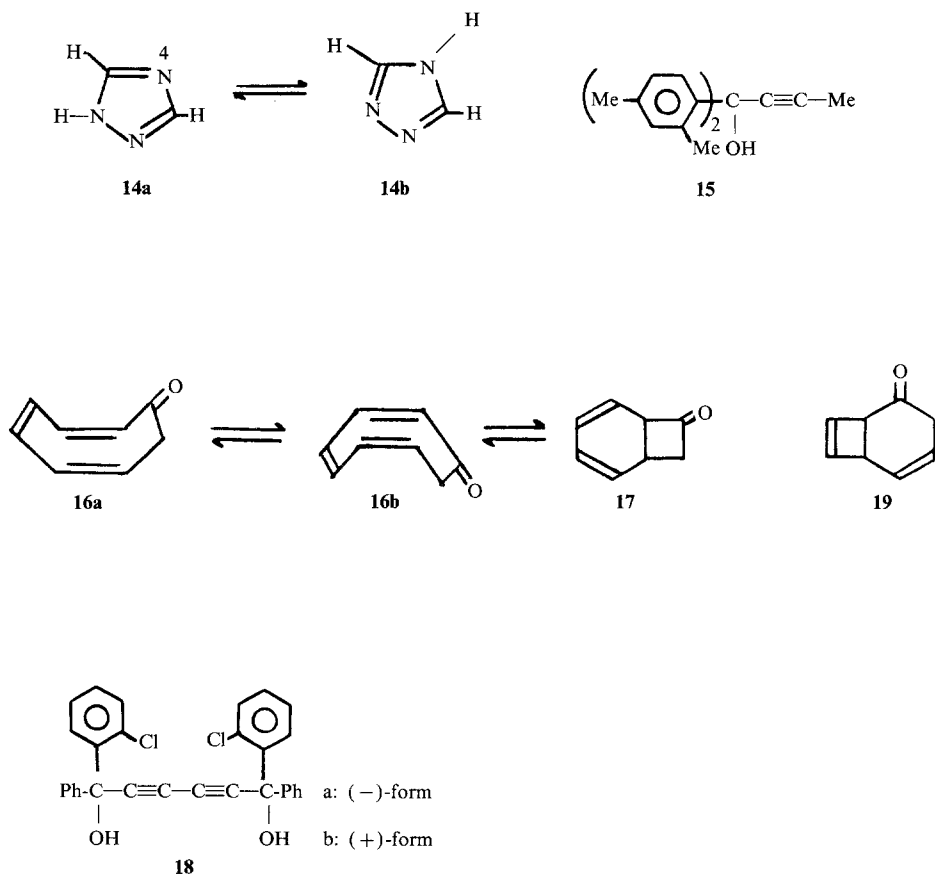


Fig. 1. Bond lengths and angles with numbering of the atoms (A) and a delocalized structure (B) of 12a in the complex with 2.

between the two optical conformers **16a** and **16b** is rapid around room temperature with the activation energy of 11.9 kcal/mol [11]. By complexing with optically active 1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**18**), the flipping equilibrium of **16** was frozen in one conformer as a 1 : 2 complex. The IR spectrum of the complex did not show any carbonyl absorption which is assignable to **17**. In order to know whether one enantiomer is included selectively or not, photoconversion of **16** in the complex to bicyclo[4.2.0]octa-4,7-dien-2-one (**19**) was carried out. When a 1 : 2 complex of **18a** and **16** was irradiated in the solid state for 168 h, 50% conversion occurred and (–)-**19** was obtained in 28% yield ($[\alpha]_D -69.0^\circ$ (*c* 0.12, CHCl_3)) [12]. Although the optical purity of **19** was not determined, it is clear that one of the two enantiomers **16a** and **16b** is included selectively or at least predominantly.

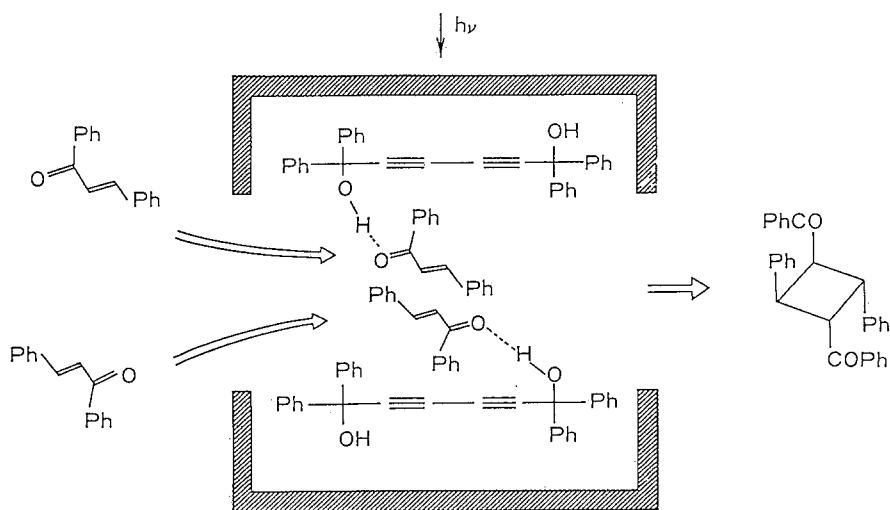
Photoreaction of **16** in pentane has been reported to give racemic **19** in 30% yield after irradiation for 21 days [11]. Therefore, it is obvious that the photoreaction of **16** in the complex proceeds not only enantioselectively but also much more efficiently.



4. Control and Acceleration of Photoreaction by a Combination of Host-Guest Complex Formation by Solid-Solid Reaction and Irradiation in the Solid State

We found that the host-guest complex is formed by a solid-solid reaction of host and guest compounds [13]. The solid-solid reaction can be done either by grinding both components using an agate mortar and pestle or agitating using a test-tube shaker, and in some cases just by keeping a mixture of host and guest compounds at room temperature [13]. For example, when a mixture of finely powdered **2** and an equimolar amount of finely powdered benzophenone is agitated using a test-tube shaker for 0.2 h at room temperature, a 1:1 complex of both components was obtained in quantitative yield. The IR spectrum of the product was identical to that of an authentic sample prepared by complexation in solution. The complexation method for the solid-solid reaction is applicable to a variety of host and guest compounds. Interestingly, freezing of equilibrium of **9** and **10** occurs even by complexation with **2** in the solid state.

When the complex formation by solid-solid reaction is combined with the photoreaction in the solid state, a stereoselective photoreaction can be carried out continuously. In other words, the host compound can be used catalytically. Upon irradiation of 1:1 and 1:2 mixtures of **2** and chalcone (**1a**) in the solid state with occasional mixing by an agate mortar and pestle for 10 and 40 h, respectively, **3a** was obtained selectively in 80 and 82% yields, respectively. These results show the formation of a 1:2 complex of **2** and **1** before the photodimerization reaction, since **1a** itself does not give **3a** upon irradiation in the solid state. Furthermore, irradiation of a 1:4 mixture of **2** and **1a** under the same conditions for 72 h gave **3a** in 87% yield. This result shows that host compound **2** was used almost twice like a catalyst. This is illustrated in Scheme I. By mixing **2** and **1a**, their 1:2 complex is formed, and the irradiation to the complex gives **2** and **3a**. Further mixing forms new complexes which upon irradiation gives **3a**. Finally, all **1a** is converted to **3a**.

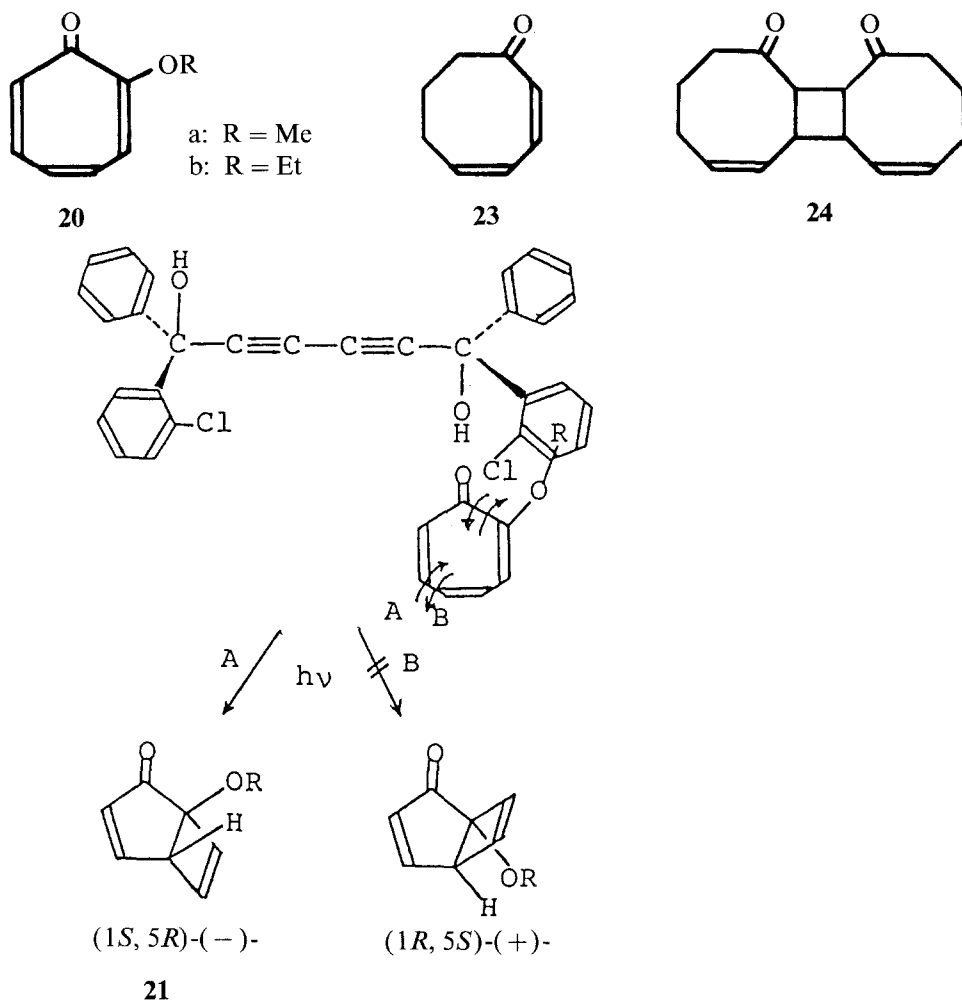


Scheme I

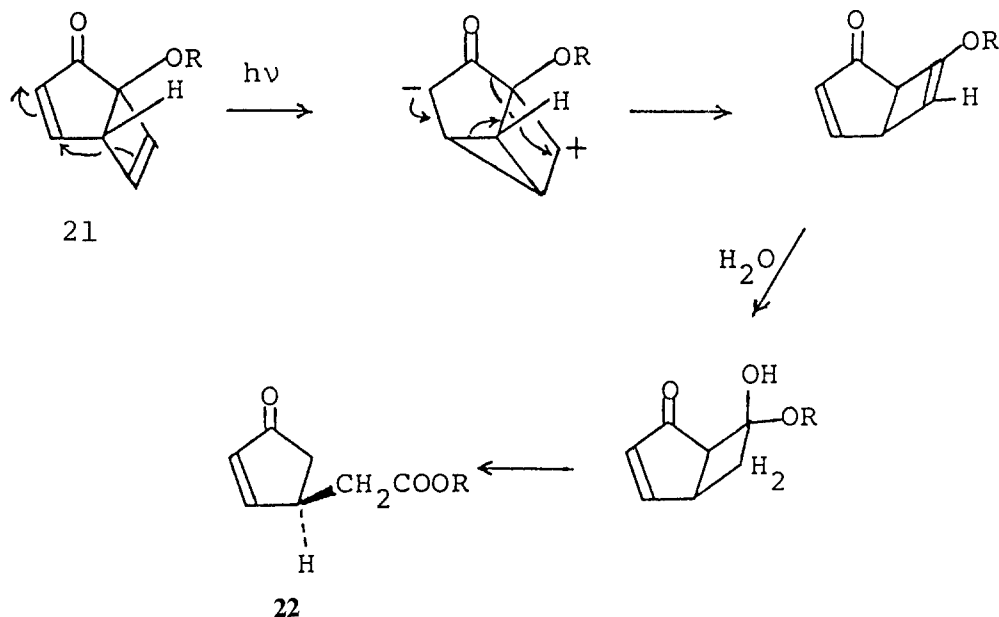
5. Enantiocontrol

Irradiation of a 1 : 1 complex of **18a** and 2-methoxytropone (**20a**) in the solid state for 72 h gave (1*S*, 5*R*)-(–)-1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (**21a**) of 100% ee in 11% yield together with (*S*)-(+)-methyl-4-oxocyclopent-2-ene-1-acetate (**22a**) of 91% ee (26% yield) [14, 15]. Similar irradiation of a 1 : 1 complex of **18a** and 2-ethoxytropone (**20b**) gave **21b** of 100% ee (12%) and **22b** of 72% ee (14% yield).

The enantioselective photoreaction of **20** in the complex with **18a** occurs only in the A direction according to a steric hindrance of the *o*-chlorophenyl group of **18a** (Scheme II). This interpretation was shown to be reasonable by an X-ray crystal structural study of the complex [16]. Formation of **22** is due to the side-reaction in the presence of water (Scheme III) [17]. According to a photochemical enolization, **22** is partly racemized [17].

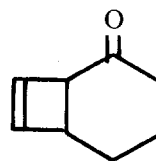
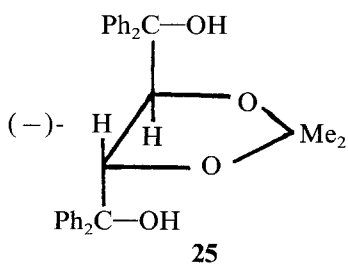


Scheme II



Scheme III

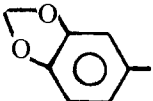
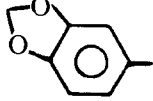
Irradiation of cycloocta-2,4-dien-1-one (**23**) in pentane gives a racemic photodimer, *anti*-tricyclo[8.6.0.0^{2,9}]hexadeca-7,11-diene-3,16-dione (**24**) in 10% yield along with polymeric materials [18]. Efficient and enantioselective photodimerization of **23** was achieved by irradiation of a 2:1 complex of **18a** and **23**. Irradiation of the complex in the solid state for 48 h gave (–)-**24** of 78% ee in 55% yield [12]. Since one unit of the complex contains one molecule of **23** and two molecules of **18a**, at least two of these units should take part in the photodimerization of **23**. Interestingly, irradiation for 6 h of a 1:1 complex of **23** and optically active host (**25**) [19] in the solid state gave (–)-bicyclo[4.2.0]oct-7-en-2-one (**26**) ($[\alpha]_D - 60.6^\circ (c 0.18, \text{CHCl}_3)$) in quantitative yield.

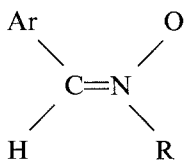
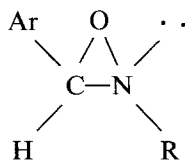


Although optically active oxaziridines are useful reagents for enantioselective oxidation of olefins, those of more than 30% ee have not been obtained by any enantioselective synthetic method. Very efficient enantioselective photocyclization of nitrones (**27**) in the complex with **18** into oxaziridines (**28**) of high optical purity was found (Table II) [20]. Enantioselectivity in the formation of **28b**, **28d**, and **28e**

is high. In the case of **27e**, optically pure **27e** is included in the complex with **18**, and irradiation of the complex gives **28e** in which all three chiral centers are 100% ee [20].

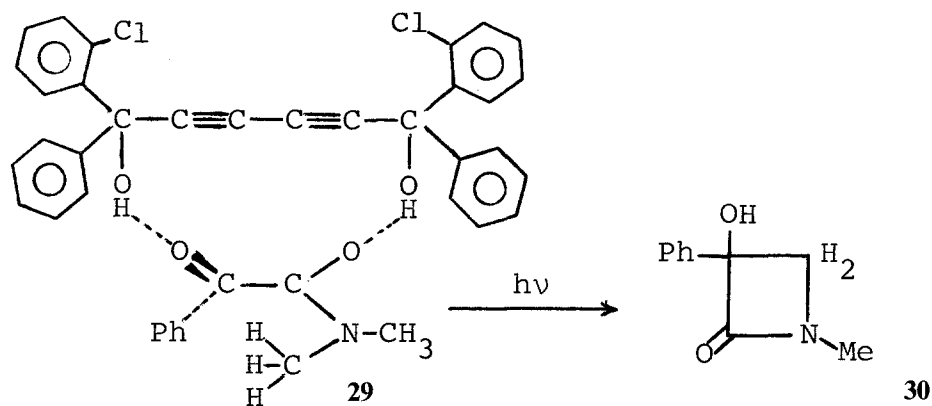
Table II. Melting points of complexes of **27** and **18**, irradiation time, yields, and optical purities of the product (**28**)

Complex			Irradiation time (h)	Product (28)		
Ar	R	mp (°C)		Yield (%)	Optical Purity (% ee)	
a	<i>p</i> -Cl—C ₆ H ₄ —	<i>t</i> -Bu	112–115	32	74	30
b	<i>o</i> -Cl—C ₆ H ₄ —	<i>t</i> -Bu	108–110	12	51	100
c		<i>i</i> -Pr	95–103	16	63	28
d		<i>t</i> -Bu	104–111	21	52	94
e	Ph	<i>i</i> -PrMeCH	126–128	24	40	100

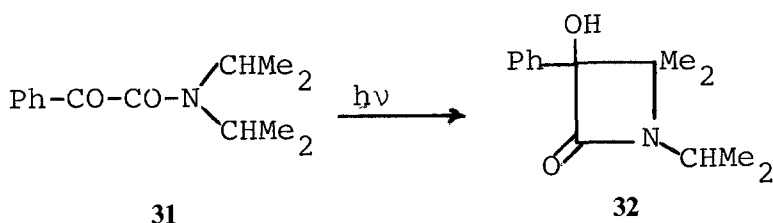
**27****28**

Enantioselective photocyclization of oxoamides to β -lactams has been achieved by irradiation of the complex of oxoamide and an optically active host compound [15, 16]. For example, irradiation of a 1:1 complex of *N,N'*-dimethylbenzoylformamide (**29**) and **18a** in the solid state for 8 h gave (–)-**30** of 100% ee in almost quantitative yield. An X-ray crystal structural study of the complex showed that a molecule of **29** is held in a fixed conformation determined by two hydrogen bonds and by neighboring host molecules which prevent free rotation about the CO—CO single bond in the complex (Scheme IV). Free rotation about this bond would enable the production of the two possible enantiomers. The fixed conformation of the guest molecule by the chiral host molecule causes the least molecular motion during the photocyclization and the high enantioselectivity [16].

The most exciting enantioselective photocyclization of an oxoamide was found in the case of *N,N*-diisopropylbenzoylformamide (**31**). **31** forms chiral crystals which upon irradiation in the solid state gives 93% ee β -lactam (**32**) in 75% yield [21]. This does not need any chiral source.



Scheme IV



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