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Cyclodextrin mediated solvent-free enantioselective photocyclization of *N*-alkyl pyridones†

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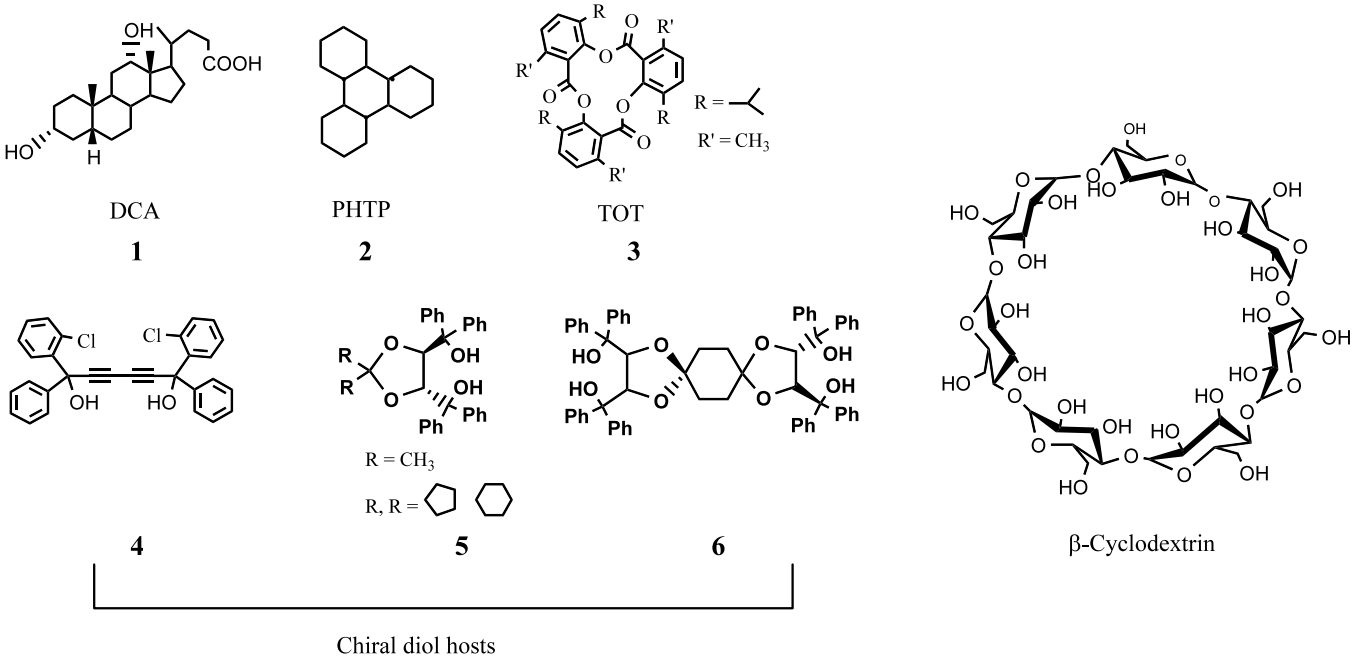
Abstract—Irradiation of *N*-methyl pyridone and *N*-ethyl pyridone included in β-cyclodextrin yields the photocylized product, chiral 2-azabicyclo[2.2.0]-hex-5-en-3-ones, in ~60% enantiomeric excess. The inclusion complex is readily made by mechanically mixing the host β-cyclodextrin and the guest pyridone.

Following the communication by Hammond and Cole in 1965 on the photosensitized isomerization of *cis*-diphenylcyclopropane,[1] several groups have performed enantio- and diastereoselective phototransformations both in solution and in the solid state.[2] In solution, in spite of considerable efforts, the enantiomeric excess (e.e.) obtained under ambient conditions continues to be less than 50%. A recent novel approach involving a chiral template introduced by Bach for the photoconversion of achiral pyridone to the chiral bicyclic product has considerable potential.[3] The best results in solution have been obtained via the chiral auxiliary methodology yielding in select examples diastereomeric excess (d.e.) close to 100%.[4] Asymmetric photochem-



Scheme 1. Organic chiral hosts used during the solid state photoreactions.

Keywords: inclusion complex; cyclodextrin; chiral induction; pyridone.

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† Dedicated to Professor S. V. Kessar on the occasion of his 70th birthday.

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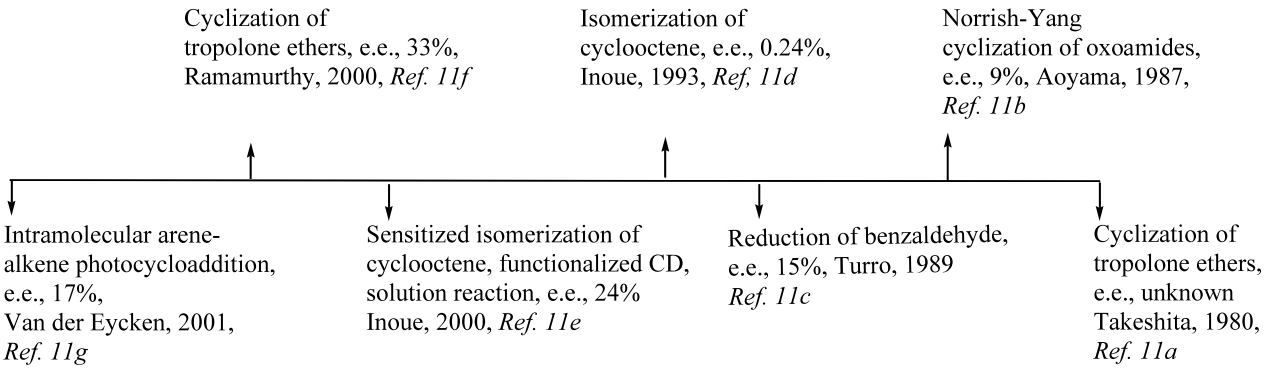
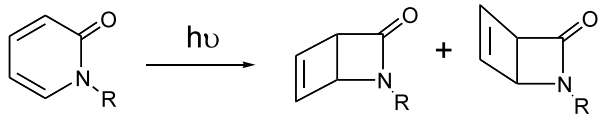


Scheme 2. Previous studies on asymmetric induction during photoreactions of achiral guests included in cyclodextrins.

istry in the crystalline state has its origin in the report by Green and Schmidt in 1973 on the photodimerization of achiral 1,4-diaryl dienes.[5,6] This is based on 'chance' crystallization of achiral molecules in a chiral space group. Because of its limited probability there are only very few examples of asymmetric induction during photolysis of achiral molecules in the crystalline state. A remarkable methodology known as 'ionic chiral auxiliary approach' introduced by Scheffer in 1990 facilitated achiral molecules to crystallize in a chiral space group.[7] Based on this strategy Scheffer has provided a number of examples that yield photoproducts in very high e.e. (or d.e.) in crystalline state. Recognizing the problem of crystallizing achiral molecules in a chiral space group, several researchers have explored chiral hosts as the reaction medium. The earliest such report is that of Natta on the photopolymerization of 1,3-dienes included in the channels of perhydrotriphenylene,[8] and the most successful ones are those of Toda using chiral diol hosts **4**–**6**.[9] Among the chiral hosts thus far explored (Scheme 1), cyclodextrin alone is most readily available at a nominal cost and is capable of including a large variety of organic molecules.

In spite of progress in the field of 'asymmetric photochemistry', unlike thermal chemistry a general strategy is still lacking. Our approach has been to employ readily available and inexpensive hosts to bring about asymmetric induction in photochemical reactions. One such medium we have been exploring is the inorganic host zeolite.[10] Equally inexpensive and readily available organic host is cyclodextrin. Although several groups have recognized the potential of cyclodextrins as chiral hosts both in solution and in solid state, the e.e. obtained during photoreactions have not been high (Scheme 2).[11] Given this background, we were pleased to note that e.e. as high as 74% was obtained in the bicyclic product when β-cyclodextrin–*N*-methyl pyridone complex was irradiated in the crystalline state. Interestingly, the complex could be made by simply mixing the host cyclodextrin and the guest pyridone. Results of these studies are presented in this letter.

Photochemistry of *N*-methyl pyridone and *N*-ethyl pyridone as cyclodextrin complexes were examined. As illustrated in Scheme 3 upon irradiation, the achiral *N*-alkyl pyridone is transformed to chiral 2-azabicyclo[2.2.0]-hex-5-en-3-one.[12] In aqueous solution, UV irradiation of *N*-alkyl pyridones yielded, as expected, the 2-alkyl-2-azabicyclo[2.2.0]-hex-5-en-3-ones as a racemic mixture. Even addition of β-cyclodextrin in excess to the aqueous solution resulted only in negligible e.e. (<5%) in the product (Fig. 1). Since the β-



R = CH_3, C_2H_5

Scheme 3.

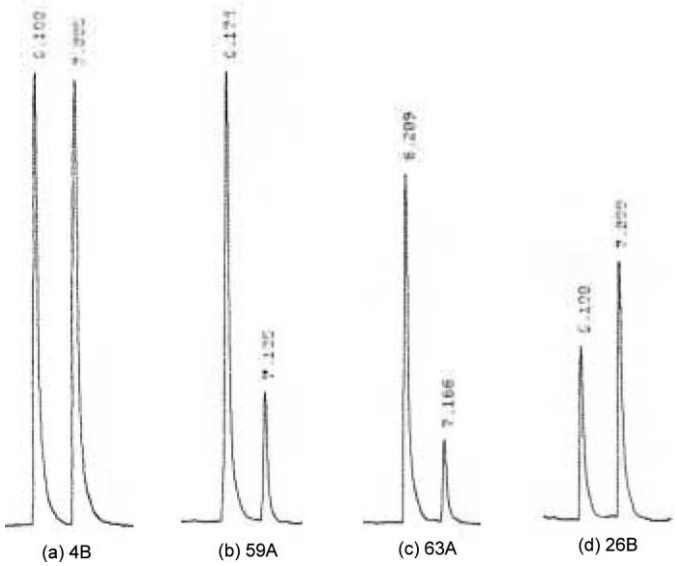


Figure 1. GC traces corresponding to the products of (a) irradiation of β-cyclodextrin and *N*-methyl-2-pyridone in water; (b) irradiation of mechanical mixture of β-cyclodextrin and *N*-methyl-2-pyridone; (c) irradiation of β-cyclodextrin and *N*-methyl-2-pyridone air dried complex prepared from 5% methanol–hexanes; (d) irradiation of β-cyclodextrin and *N*-methyl-2-pyridone vacuum dried complex prepared from 5% methanol–hexanes. The enantiomers were separated on β-dex 350 chiral GC column and the first peak to elute was arbitrarily assigned as A.

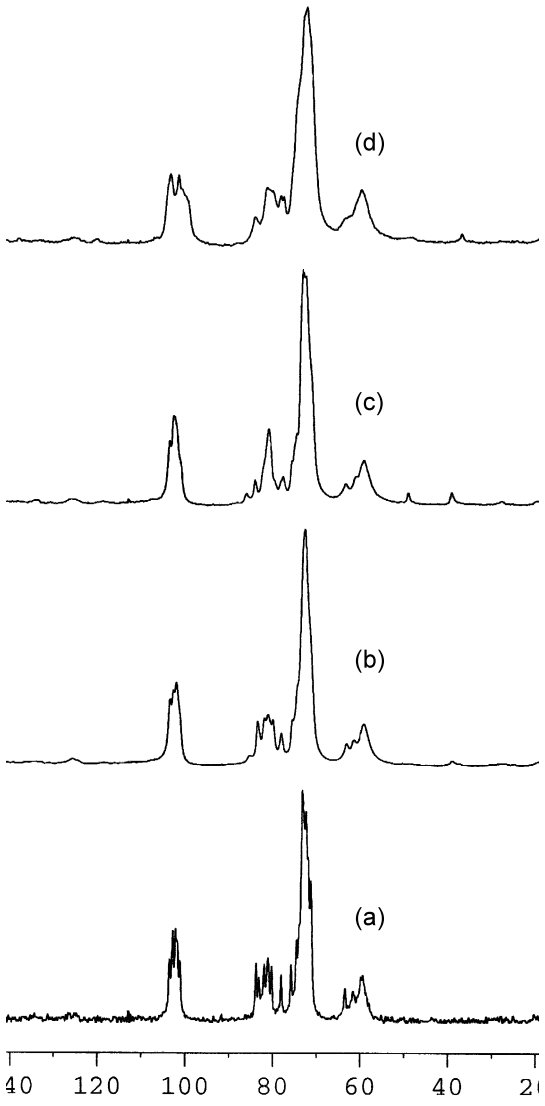


Figure 2. Solid state NMR traces for (a) uncomplexed β-cyclodextrin; (b) β-cyclodextrin and *N*-methyl-2-pyridone—mechanical mixture; (c) β-cyclodextrin and *N*-methyl-2-pyridone—5% methanol–hexanes—air dried; (d) β-cyclodextrin and *N*-methyl-2-pyridone—5% methanol–hexanes—vacuum dried.

cyclodextrin–*N*-methyl pyridone complex was freely soluble in water, solid complex could not be precipitated by the commonly adopted method of addition of the guest to the saturated aqueous solution of β-cyclodextrin.[13] On the other hand, solid complex of *N*-methyl pyridone and *N*-ethyl pyridone with β-cyclodextrin could be prepared by mechanically mixing the host and the guest. Photochemical behavior of solid complexes thus prepared were examined.

A typical experimental procedure involved the following: β-cyclodextrin (0.17 g; 1.49×10^{-4} mol) and 1-methyl-2-pyridone (14.6 μl; 1.49×10^{-4} mol) were ground together using a mortar and pestle. The resulting complex was spread and sandwiched between two Pyrex plates and irradiated for 6 h using a medium pressure mercury lamp. After irradiation, the reactants and the products were extracted from the complex by stirring in 15 mL of methanol and analyzed by GC fitted with a chiral β-dex 350 column. The GC traces corresponding to the products are shown in Fig. 1. The conversion was kept below 15%. It should be noted that total conversion to the product could not be achieved owing to the photoreversibility of the reaction. Even controlling the wavelength of excitation source did not improve the conversion. A similar problem was faced by Toda and co-workers when host–guest complexes of pyridone and diol host **4** were irradiated.[15a,b] We are attempting to improve the chemical yield. The product of cyclodextrin irradiation was identified to be 2-methyl-2-azabicyclo[2.2.0]-hex-5-en-3-one by comparing with authentic samples prepared by solution irradiation.[12] Further, the HPLC (Chiralcel OD) retention times of the enantiomeric 2-methyl-2-azabicyclo[2.2.0]-hex-5-en-3-one products obtained during cyclodextrin irradiation matched that of the same products reported recently.[15c] At this stage we focus on the unusual ability of CD to bring about respectable enantioselectivity. The following results are noteworthy: (a) while the e.e. during solution irradiation is only 4%, the irradiation of the complex in the solid state gave the bicyclic product in 59% e.e. (average of six runs). As far as we are aware, the e.e. reported here is the highest with cyclodextrin as the chiral host. (b) The host–guest complex is prepared by simply mixing the two without the help of solvents. Such an easy process although not common is not unknown.[14] (c) Asymmetric induction during photocyclization of *N*-methyl pyridone has been examined earlier with several chiral hosts. For example, in solid state, the hosts **4**–**6** gave the bicyclic product in nearly 100% e.e.[15] We believe that cyclodextrin has a greater potential as a chiral host by virtue of its ability to include a large number of organic molecules both in solution and in solid state.[16]

The X-ray powder photographs as well as solid state NMR spectra showed that the complex prepared above is not a simple mixture of the host and the guest. The CP-MAS spectra shown in Fig. 2 indicate that the ^{13}C spectral patterns of pure cyclodextrin and the complex are different. It is generally accepted that loss in resolution of the cyclodextrin carbon signals is an indication of the inclusion of guests within its cavity.[17] The line broadening is attributed to the chemical shift modification as well as conformational changes of the glucose units brought by the cavity included guests. The X-ray powder photographs of the pure cyclodextrin and the complex were slightly different, indicating that the complex is crystalline and also not a simple mixture of the host and the guest.

Although the solid complex could not be made using water as the solvent, it was easily made when a hexane–methanol (95:5) solvent mixture was used. In this solvent mixture cyclodextrin was not soluble. The complex was prepared as follows: β-cyclodextrin (0.17 g; 1.49×10^{-4} mol) and 1-methyl-2-pyridone (14.6 μl; 1.49×10^{-4} mol) were added to 10 mL of 5% methanol–hexanes in

a test tube and stirred for 12 h. Methanol–hexanes were decanted and fresh hexanes added, stirred well and decanted to leave a white solid. The solid sticking to the walls of the test tube was allowed to air dry for 12–18 h, collected and irradiated for 6 h. During the ten trials the e.e. of the product varied between 60 and 74% (Fig. 1). The X-ray powder photographs as well as solid state NMR spectra of the complexes prepared using solvent mixture and by mechanical grinding were the same, indicating that the structure of the inclusion complex obtained by the two methods is identical. According to thermogravimetric analysis (TGA) the complex prepared by both methods contained 9% water. Significantly when the complex was dried on a vacuum line (2×10^{-3} torr for 3 h) and irradiated, the e.e. not only decreased (26%) but also the isomer being enhanced switched from A to B (Fig. 1). According to TGA the vacuum dried sample contained less water (2%). This suggested that water plays a crucial role during the asymmetric induction process. Importance of co-inclusion of a hydrogen bonding solvent within the cavity of β-cyclodextrin was established by the following experiment. Addition of small amount of water or methanol (25 μL to 150 mg of the complex) to the vacuum dried sample reversed the isomer being enhanced and increased the e.e. from 26 to 55%. Nonhydrogen bonding solvent such as hexane had no effect.

The behavior of *N*-ethyl pyridone was similar to *N*-methyl pyridone in all respects. The solid complex could be made by grinding as well as using hexane–methanol solvent mixture. Irradiation of the complex made by grinding gave the product in 46% e.e., while the complex made using solvent mixture and air-dried gave the product in 50% e.e. Similar to *N*-methyl pyridone, vacuum drying resulted in the loss of e.e. Unlike β-cyclodextrin, α- and γ-cyclodextrins although formed inclusion complexes, gave the products as a racemic mixture. Irradiation of the aqueous solution as well as solid complexes gave the product in <5% e.e.

Results presented here show that abundantly available β-cyclodextrin still has untapped potentials associated with it. The cost and environmentally benign nature of the chiral host, solvent free process by which the host–guest complex could be made, and the 'greenness' of the reagent (light) used to register the chirality of the product justify further in depth investigation.

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