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Cyclodextrin mediated enantio and diastereoselective geometric photoisomerization of diphenylcyclopropane and its derivatives†

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Abstract—*cis*-Diphenylcyclopropanes upon direct excitation and triplet sensitization undergo geometric isomerization to the corresponding *trans* isomers. In solution the *trans* isomers are formed as a 1:1 enantiomeric or diasteromeric mixture. Upon inclusion within β-cyclodextrin the same molecules give the *trans* isomers enriched in one optical isomer. Enantiomeric excess and diasteromeric excess induced by the optically active host β-cyclodextrin although small is mechanistically significant. © 2002 Elsevier Science Ltd. All rights reserved.

Recently several groups including ours have actively pursued asymmetric induction of products during photochemical reactions.[1] Zeolites, host–guest complexes and crystals have been used as suitable media to carry out asymmetric photochemical reactions.[2] Cyclodextrin (CD) is a host capable of carrying out such reactions.[3] They are inexpensive ($0.12/g for α, β and γ CD; Wacker biochem) and readily available. An important property of the CD is its chirality. The selective inclusion of optical isomers by CD has been the underlying factor in its use as a stationary phase in the GC and HPLC chiral separations.[4] Recently, we showed that using cyclodextrins moderate enantiomeric excesses could be obtained during photocyclization of tropolone ethers.[5] In spite of random attempts, their utility as reaction media to effect chiral induction during photochemical reaction remains less explored.[6] To further probe the utility of cyclodextrin as a chiral medium we have investigated the photoisomerization of *meso cis*-diphenylcyclopropane and its derivatives to the optically active *trans* form. Results of this study are presented in this report.

1,2-Diphenylcyclopropane has played a central role in the quest for new methods of asymmetric induction in organic photochemistry.[7] Following the original report by Hammond and Cole (ee 6.7%), the chiral induction on the *cis* to *trans* isomerization process has been investigated by at least five independent research groups and the best ee obtained thus far is only 10%.[7] We have chosen *cis*-diphenylcyclopropane **1** and *cis*-diphenylcyclopropane-1-carboxylic acid derivatives (ester **3** and two amides **5** and **7**, Scheme 1) as substrates to examine the potential of CD as a medium to perform chiral induction during photochemical reactions. Results presented in this report show a modest improvement in optical selectivity over previous attempts during the geometric isomerization of *cis*-1,2-diphenylcyclopropane systems. Compounds **1** and **3** were studied for enantioselectivity and compounds **5** and **7** for diastereoselectivity within cyclodextrins. Photochemistry of compounds **3**, **5** and **7** did not require any sensitizer whereas the isomerization of compound **1** was effected with the help of a triplet sensitizer (4-methoxyacetophenone). We believe that the isomerization of **1** occurs from the triplet state while that of **3**, **5** and **7** from excited singlet state. In the case of **1** direct excitation resulted in considerable side reactions.

Addition of ether solution of *cis*-diphenylcyclopropanes **1**, **3**, **5** and **7** to a saturated aqueous solution of cyclodextrin and stirring overnight precipitated a white solid which was filtered and washed several times with diethyl ether to remove the uncomplexed guest. The precipitate was then dried under reduced pressure (10^{-3} torr) at 50°C for 12 hours. The molar ratio of the diphenylcyclopropanes and the CD was calculated by estimating the amount of guest extracted from a known amount of the complex. Compounds **1** and **3** formed 1:1 complexes while compounds **5** and **7** form 1:3 complexes with the host β CD. Based on the measure-

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† Dedicated to Professor K. Venkatesan on the occasion of his 70th birthday.

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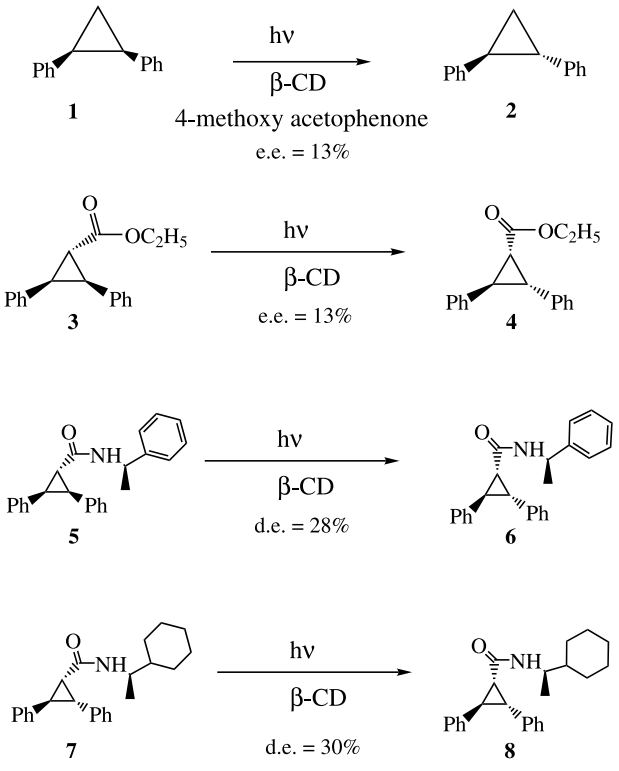
ments we cannot rule out the formation of higher levels of complexation such as 2:2 or 3:3, etc.

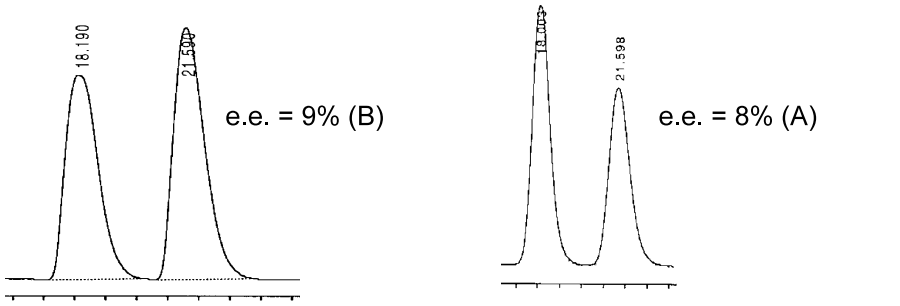
The complexes were characterized by their UV, X-ray powder diffraction and solid state NMR. The UV absorption spectrum of the CD complex and the solution spectrum are identical. The X-ray powder pattern of the precipitated white solid complex differed from that of pure CD suggesting the precipitate to be a true complex and not a mechanical mixture of CD and the guest. The room temperature ^{13}C CP MAS NMR spectra of β CD and compounds **1**, **3**, **5** and **7** complexed with β CD were different. In general the ^{13}C signals due to cyclodextrin carbons in the complexes were broad. It is generally accepted that loss in resolution of the cyclodextrin carbon signals is an indication of the inclusion of guests within its cavity.[8] 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.

Irradiation of complexes was carried out both as solids and aqueous solutions. A typical experimental procedure consisted of the following: The complexes were irradiated as solids and as aqueous solutions (for compounds **1** and **2**). For solid irradiation, a weighed amount of the dried complex (100 mg) was finely crushed and placed between two quartz plates. In the case of compound **1** sensitizer was required (20 mg). This was mixed with the complex by crushing both in a mortar pestle. This finely ground mixture was placed between two quartz plates. The sample was then subjected to UV irradiation (Rayonet reactor using light ranging from 250 nm for compound **3**, 300 nm for compounds **4** and **5**, 350nm for compound **1**) for the required amount of time (ranging from 3 to 8 hours). Following irradiation, the complex was dissolved in water (500 ml) and extracted at least three times with dichloromethane except for compounds **4** and **5**. The dichloromethane extracts were then dried using magnesium sulfate followed by evaporation of the solvent to get the products. Compounds **4** and **5** were extracted directly by adding acetonitirle to the irradiated complex and allowing it to stir overnight as exposure to moisture led to difficulty in analysis. The solvent was then filtered and the filtrate evaporated to get the products. The products of compounds **1** and **2** were analyzed by HPLC (Chiracel OJ wavelength used = 254 nm, solvent mixture used = hexane:isopropyl alcohol 97:3, flow rate = 0.7 ml/min), compound **3** by chiral GC (Supelco β-dex 320/1701 custom made, conditions for the analysis = 140°C isotherm for 40 minutes). Achiral GC column (Supelco SPB-5, conditions for the analysis = 215°C isotherm for 45 minutes) was used for the analysis of product diastereomers of compound **4** and **5**. For solution irradiation (done for compound **1**) a weighed amount (~60 mg) of dried complex was dissolved in distilled water (100 ml) along with the sensitizer (10 mg), purged with nitrogen gas and then subjected to irradiation for 3 hours. Extraction and analysis procedures were the same as with solid irradiation. Conversions typically remained within 20%. Neither triplet sensitized nor direct irradiations could be taken to total conversion. The former stopped after ~50% conversion probably due to inability of the sensitizer to reach all included molecules and the latter resulted in side products. Results of photolysis of **1**, **3**, **5** and **7** in the solid state are summarized in Scheme 1. Solution irradiations typically gave less than 2% ee or de. The ee and de reported in this letter are an average of four independent runs and the values differed within ±5%. The enantiomeric and diastereomeric excess was independent of the duration of extraction in the time period 12–48 hours. In no case did we determine the absolute configuration of the isomer being enhanced.



Scheme 1.

β-Cyclodextrin has a slight preference to include one enantiomer of *trans* DPC (**2**) over the other. This was established by monitoring the ee of the *trans* DPC before complexation to CD (ee = 0%) and after extraction from β-cyclodextrin (ee = 9%; Scheme 2). Interestingly this preference is time dependent. Time dependent complexation study was carried out by loading a racemic mixture of *trans* DPC into β cyclodextrin. The guest was allowed to complex for 3, 6, 12 and 24 hours followed by extraction and analysis. It was found that there was selectivity for one enantiomer over the other at shorter complexation times viz. 3 and 6 hours (9%) and this selectivity decreased to zero when the complex was allowed to equilibrate in aqueous solution for 24 hours. Encouraged by the complexation behavior of **2**, similar time dependent complexation study was carried out with *cis*,*trans* isomers **4**, **6** and **8**. β-CD showed a preference for one enantiomer of *cis*,*trans*-2,3-diphenyl cyclopropyl-1-ethyl ester **4** (6 h: 9%; 24 h: 2%). However, time dependent selective loading with compounds

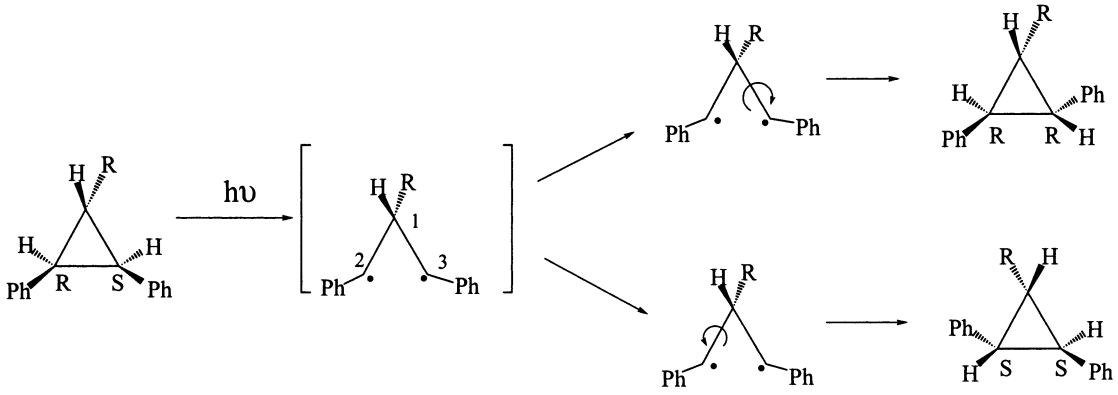


HPLC trace of enantiomers of *trans*-DPC that complexed with β CD

HPLC trace of enantiomers of *trans*-DPC that remained in soluti

Complexation time = 6hours

Scheme 2.



Scheme 3.

6 and **8** did not exhibit much selectivity. All four compounds studied as complexes of β-CD have shown that the chiral cavity of CDs does play a role during the geometric isomerization of diphenylcyclopropane derivatives. Upon excitation the carbon–carbon bond substituted with *cis*-diphenyl groups undergo cleavage either in the excited singlet or triplet state. As illustrated in Scheme 3 rotation of either C_1–C_2 or C_1–C_3 can occur to yield the *trans* isomer. Under normal conditions the rotation of either bond will occur with equal efficiency to yield a recemic mixture. Clearly, when the *meso* diphenylcyclopropanes are present within the cavities of cyclodextrin the rotation efficiencies are unequal to some degree. The chiral cavity offers different extents of steric hindrance for the two modes of rotation. An interesting and important point to note is that in the case of **1** as well as **3** the optical isomer that is favored during photoisomerization is the same one that is preferentially included when the corresponding *trans* isomers (**2** and **4**) were equilibrated with β-CD in aqueous solution. This observation suggests that CD is influencing the photoisomerization of **1** and **3** even at very early stages and is able to bias the isomerization towards the isomer that it prefers to include. Thus a relationship between kinetics of the photoisomerization and thermodynamics of inclusion exists. If this is general one might be able to predict the isomer that would be obtained in excess based on solution equilibrium studies. Further work is needed to understand this phenomenon.

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