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ASYMMETRIC INDUCTION IN BENZOIN BY PHOTOLYSIS OF BENZALDEHYDE ADSORBED IN CYCLODEXTRIN CAVITIES

V. Pushkara Rao and Nicholas J. Turro*
Chemistry Department, Columbia University
New York, New York 10027.

Abstract Irradiation of solid β-cyclodextrin complexes of benzaldehyde produces optically active benzoin as a major photo-product with an enantiomeric excess of up to 15%.

Introduction

The *utilization of inclusion complexes of cyclodextrins in the modification of chemical reactivity of organic* molecules has been of much interest,[1] but so far their use in photochemistry and in asymmetric synthesis has been limited.[2] We report the utility of a cyclodextrin as a tool in asymmetric induction in the simple synthesis of optically active benzoin from the photochemistry of benzaldehyde by solid complex formation with the chiral template β-cyclodextrin.

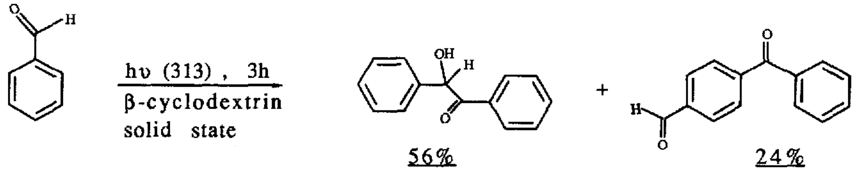
The photolysis of benzaldehyde in benzene solution[3,4] produced benzoin as the major primary photolysis product via a free radical process. Extended photolysis produced, as secondary products, almost equal amounts of deoxybenzoin, benzoin and 1,2-diphenylethane-1,2-diol. On the other hand, irradiation of benzaldehyde in ethanol yielded 1,2-diphenylethane-1,2-diol with only a trace of benzoin. Photo-CIDNP studies in perdeuterobenzene confirm the free radical nature of the photolysis by showing that excited triplet benzaldehyde abstracted hydrogen from the ground state benzaldehyde to form a radical pair, which collapsed to give benzoin.[4]

Results

Benzaldehyde readily forms solid inclusion complexes with α, β and γ-cyclodextrin: To a saturated solution of each of the cyclodextrins in distilled water, equimolar amounts of benzaldehyde were added and magnetically stirred at room temperature for 12 h. The white precipitate which was formed was filtered and washed with diethyl ether and dried at 50° C for 5 h to yield solid complexes. The presence of an inclusion complex in the solid state was inferred by comparing the X-ray powder diffractograms of the solid complexes with those of the pure cyclodextrins. Complexation was also evident from their FT-IR spectra and ^{13}C-CPMAS solid state NMR spectra of β and γ-complexes of benzaldehyde.[10] Additional support for the presence of an inclusion complex in the solid state comes from the observation that a known weight of the complex, when extracted with diethyl ether, yielded one equivalent of guest in the cases of α and β- cyclodextrin complexes and two equivalents of benzaldehyde in the case of the γ-cyclodextrin complex. Thus, a stoichiometric 1:1 complex was formed between β-CD/α-CD and benzaldehyde, and a 1:2 stoichiometric complex was formed between γ-CD and benzaldehyde. These complexes were stable to air and oxygen. Photolyses of the solid cyclodextrin complexes were carried out with a Hanovia 450-W Hg medium-pressure lamp for 3 h at room temperature in a quartz vessel under vacuum. The photolysis vessel was tumbled continuously during the irradiation to ensure homogeneous photolysis of the sample. Conversions were limited to less than 20%. After photolysis, the solid complexes were dissolved in excess water and extracted with diethyl ether and chromatographed with hexane/ ethyl acetate (5:1) to isolate the products in pure form.

Irradiation of solid β-cyclodextrin complexes of benzaldehyde resulted in an intermolecular reaction to give benzoin and 4-benzoylbenzaldehyde (7:3, 80%; Scheme 1). The latter product, which is not formed in the photolysis of benzaldehyde in organic solvents, was characterized by spectral characteristics and by comparison with its authentic sample.[5] The formation of this rearranged product in the solid state irradiation of benzaldehyde contrasts its photo-reactivity in isotropic media and in aqueous solutions containing β-cyclodextrin (*vide infra*). Another interesting feature of this solid state irradiation is that the benzoin formed in β-cyclodextrin cavity is optically active and the enantiomeric excess calculated from the optical rotation, is 15±1%.[6] Similar irradiation of the α-cyclodextrin complexes did not result in any detectable reaction even after prolonged irradiation (10 h). Irradiation of the γ-cyclodextrin complexes (3 h) in the solid state undergo reaction resulting both benzoin and 4-benzoyl benzaldehyde in 78% yield (55:45). However, enantiomeric excess observed for the benzoin formed in γ-cyclodextrin cavity is negligible (<1%).

Scheme 1



R-(-)-Benzoin
$[\alpha]^{25}$ -18.8 ± 0.4 (c = 1.5, acetone)
% E.e. = 15 ± 1%

Aqueous cyclodextrin complexes were prepared by sonicating a mixture of cyclodextrin (5 mmol) and benzaldehyde (0.5 mmol) in water (100 ml). In aqueous medium, the photolysis of either α- or β-cyclodextrin complexes of benzaldehyde under argon atmosphere, resulted in photoreduction to give meso and d,l-1,2-diphenylethane-1,2-diols as major products (60-70%, meso/d,l = 0.9); benzoin and 4-benzoylbenzaldehyde (~3%, <<1% respectively) are formed in only trace amounts in these aqueous irradiations and therefore, optical rotation of benzoin could not be measured. In the absense of substantial amount of benzoin formation in the solution photolysis of benzaldehyde, it may be interesting to look at the optical activity of benzoin formed in a cyclodextrin aqueous solution experiment using cyanide as a catalyst.[7] However, such an experiment is out of scope of the present investigation.

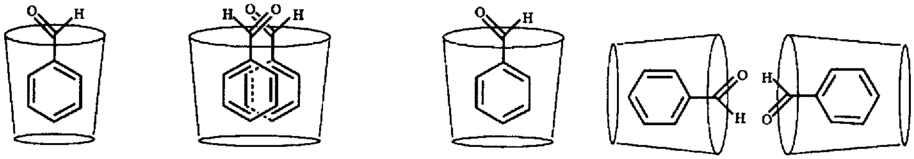
Discussion

The observed photochemical behavior of benzaldehyde-cyclodextrin complexes in the solid state is unique and different from that of these complexes in aqueous solution and from benzaldehyde in organic solvents. Based on the product studies in the solid state (Scheme 1), it is very clear that two benzaldehydes are in close proximity in the microcrystalline complexes of β and γ-cyclodextrins, since they can undergo intermolecular reaction to give benzoin and 4-benzoylbenzaldehyde. The observation of 4-benzoylbenzaldehyde suggests that γ- and β-cyclodextrins provided a unique "super cage" environment to the radical pair, derived from the hydrogen abstraction of triplet benzaldehyde from the ground state benzaldehyde, which allows enough motion for the pair to undergo para-rearrangement (Scheme 3). The primary product of rearrangement of this radical pair upon p-coupling is expected to give the enol of 4-benzoylbenzylalcohol, but the isolated product was in its oxidized form. At this stage it is not clear whether or not this oxidation to give 4-benzoylbenzaldehyde occurred in the solid state or during the extraction of the reaction mixture from the aqueous solution.

Since cyclodextrins are known to show enantioselectivity in complex formation of racemic compounds,[1] it is possible that asymmetric induction observed in the photolysis of β-cyclodextrin complexes was due to optical resolution of racemic benzoin formed in the reaction. To rule out this possibility, racemic benzoin was dissolved in cyclodextrin and stirred for 12 h. The solid complex thus formed was dissolved in excess water and the benzoin was extracted with diethyl ether, which showed a negligible amount of optical rotation (<1%).

In order to understand the above observations on the product distribution for the β- and γ-cyclodextrin complexes of benzaldehyde, knowledge of the structure of the complex is essential. Such (X-ray) information is only available for the α-cyclodextrin complex. Nonetheless, an intuitive approach supported by qualitative data and literature on related systems is of some value in interpreting the results. Possible structures, based on the experimental stoichiometries of the cyclodextrin inclusion complexes of benzaldehydes, are shown in Scheme **2**.

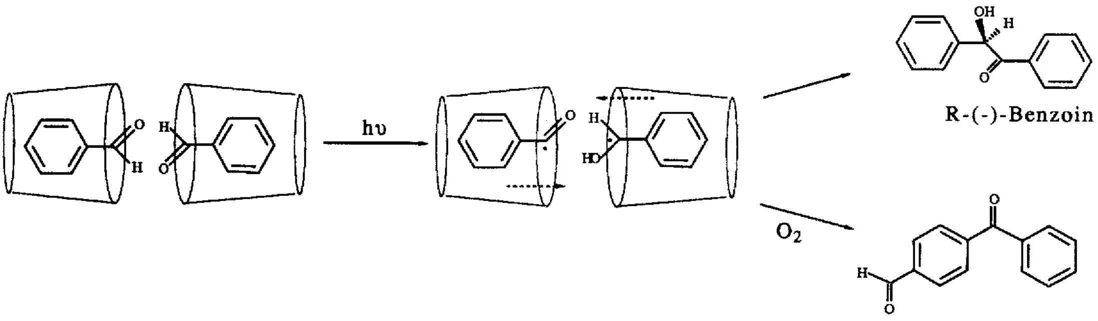
Scheme 2 Possible structures of benzaldehyde-cyclodextrin complexes



(1:1) α-cyclodextrin complex; (1:2) γ-cyclodextrin complex; (1:1) (2:2) β-cyclodextrin complexes

The X-ray crystal structure of the α-cyclodextrin complex of benzaldehyde has been reported[8] and shows that α-cyclodextrin molecules are stacked along the α-axis in head to tail fashion to form a channel type structure and the guest molecules are aligned inside the column. The stoichiometry of the α-cyclodextrin complex is 1:1. This structure explains the lack of any detectable intermolecular photoreaction between benzaldehyes in the solid α-cyclodextrin complexes. In the case of the β-cyclodextrin complex, the fact that benzaldehyde undergoes bimolecular reaction suggests that two benzaldehydes are in close proximity in the solid complex. However, the possibility of two benzaldehydes existing in a single cyclodextrin cavity can be ruled out based on stoichiometric ratio 1:1 between host (β-CD) and guest. The observed reactivity may be explained from a two guest-two host (2:2) complex generated by the association of two 1:1 inclusion complexes (Scheme **3**). Such 2:2 complexes with β-cyclodextrins have earlier been invoked in order to explain the stereoselective photodimerization of anthracene derivatives.[9]

Scheme 3 Schematics of benzaldehyde photochemistry in β-cyclodextrin.



Since γ-cyclodextrin has a larger cavity (cavity diameter 9.0 Å) than β-cyclodextrin, the presence of two benzaldehydes in one γ-CD cavity is possible (Scheme **2**). This assumption is further supported by the observed 2:1 stoichiometric ratio between γ-CD and benzaldehyde, obtained from GC analysis. The occurrence of asymmetric induction in benzoin formation only in β-CD but not in γ-CD is indirect evidence that benzaldehyde has a looser orientation in the γ-cavity than in the β-CD cavity. To obtain more insight into the structure of these complexes, solid state nmr studies which include T1-relaxation and contact-time measurements are in progress. In conclusion, this study demonstrates the ability of cyclodextrins to modify the photochemical behavior of benzaldehyde and to induce asymmetry in the formation of benzoin. Although the enantioselectivity obtained in the present study is modest for practical asymmetric synthesis, considering the limited success in achieving asymmetry by photochemistry,[11] the present results open new possibilities for the role of inclusion complexes of cyclodextrins in inducing asymmetry both in photochemical and thermal reactions.

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