

Influence of Cyclodextrin Encapsulation on Norrish–Yang Photoreaction of Valerophenone

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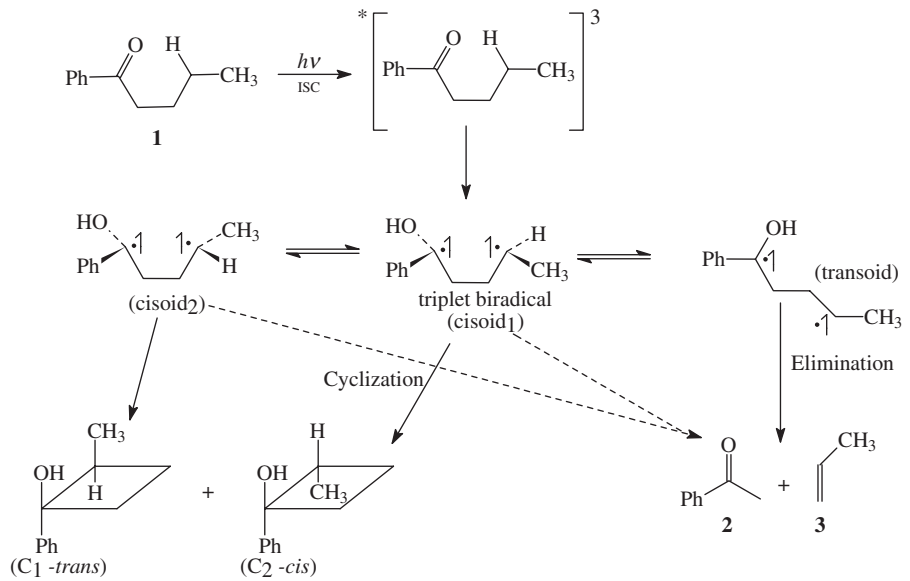
In the solid-state Norrish–Yang photoreaction of valerophenone, studied in presence of various cyclodextrins, not only was elimination suppressed, but a remarkable diastereoselectivity was also observed. The predominant formation of one cyclobutanol (C_1-*trans*) is rationalized as being due to a restricted rotational motion of the 1,4-biradical, and also stabilization of the same by hydroxyl groups present in the rim of the cyclodextrin cavity. Additional supports for the coinclusion of a side chain into the γ-CD cavity from molecular minimization calculations and ^{1}H–^{1}H NOESY spectra are also presented.

Cyclodextrins are cyclic oligosaccharides composed of α-(1,4)-linkages of a number of D-(+)-glucopyranose units.[1] In addition to their potential to form inclusion complexes, the utility of cyclodextrins as reaction vessels for photochemical transformations has been well recognized and exploited.[2,3] Over the past several decades, investigations on the photoreactions of aryl alkyl ketones have provided a wealth of information concerning the structure and solvents on triplet reactivities.[4–6] Alkyl aryl ketones containing γ-hydrogen atoms undergo characteristic 1,5-shifts through the 1,4-biradical intermediate to yield both Norrish-type II elimination (E),[7] as well as Yang and Yang cyclization (C)[8] products. For example, in the photolysis of valerophenone (**1**), γ-hydrogen abstraction from the triplet state forms a triplet biradical, which readily equilibrates between the cisoid and transoid forms (Scheme 1). While the transoid form undergoes fragmentation, the two cisoid forms, in addition, can also cyclize to give isomeric cyclobutanols.

Modifications of the photochemical reactivities through inclusion complex formation with cyclodextrin have been studied by Ramamurthy et al.[2,9] In their study on the photolysis of dibenzyl ketones and benzyl phenylacetates in cyclodextrin, it was observed that the host imposes cage effects on the translational motion of the benzyl radical pairs. An extension of this concept to the 1,4-biradical intermediate, obtained from various ketones in β-cyclodextrin, has also been reported.[10] In the solid state, inclusion into β-CD leads to an increase in the cyclization product (compared to a solution-phase study), this trend becomes more pronounced as the alkyl chain becomes longer. The ratio of the elimination to cyclization products resulting from Norrish type-II hydrogen abstraction is dependent on the length, but not on the bulkiness of the alkyl substituent. These observations are rationalized based on the steric constraints exerted by the CD cavity on the rotational



Scheme 1.

Published on the web October 31, 2005; DOI 10.1246/bcsj.78.2000

motion of the 1,4-biradical. Kinetic studies on the photoreaction of valerophenone have been investigated as a function of the temperature, pH, and wavelength in an aqueous medium.[11] Type-II quantum yields for the photoreaction are close to unity, and the values for the formation of the photoproducts are 0.65 (for cleavage to acetophenone and propene) and an overall yield of 0.32 for cyclization to two cyclobutanols at 20 °C. Using X-ray crystallographic studies, Stezowski et al.,[12] have reasoned the photochemical modification of valerophenone in a β-cyclodextrin cavity by proposing a 2:2 β-CD/guest system. These face-to-face, β-CD dimers contain two included aryl alkyl ketone molecules with the β-CD dimers packing in a channel. The guest molecules are packed with their phenyl rings face-to-face, located in the center of the β-CD dimer. This leaves the alkyl chains of the ketones extending to the primary hydroxy ends of the β-CD dimer. Ketones bearing methyl substituents α to the benzoyl group, as in *cis*-4-*tert*-butyl-1-methylcyclohexyl phenyl ketone, undergo photocyclization[5] to afford cyclobutanols. Scheffer et al., have investigated[13] the Norrish–Yang type-II photochemistry of 16 such ketones having the basic *cis*-4-*tert*-butyl-1-benzoylcyclohexane or 2-benzoyladamantane structure in the solid state and in solution. Asymmetric induction studies are carried out by providing the reactants with carboxylic acid substituents to which "ionic chiral auxiliaries" are attached through salt formation with optically active amines. The irradiation of the salts in solution gives racemic cyclobutanols, but in the crystalline state, moderate to near-quantitative enantiomeric excesses are obtained. Photochemical reactions of valerophenone in various surface media,[14] such as silica gel, alumina, and water-ice, have also been reported. A model in which the short-lived biradical intermediate interacts with the surface, in addition to a polar effect on the excited triplet of ketone, is proposed. These interesting features of valerophenone photochemistry, such as the dependence of the E/C ratio and diastereomeric induction on reaction media prompted us to carry out this photoreaction in various cyclodextrins to gain insight into the effect of the cavity size and also how the steric constraints in CDs can be utilized to control the diastereoselectivity of the obtained substituted cyclobutanols.

Experimental

The preparation of 1:1 cyclodextrin complexes was done as per a reported procedure.[15] The existence of an inclusion complex was evidenced by measuring the dissociation constants using the Benesi–Hildebrand equation.[16] 1D and 2D NMR spectra were recorded in D_2O at 25 °C on a Bruker 300 MHz instrument (using the pulse sequences and standard procedures offered by Bruker). The upfield chemical shifts of β-CD protons (H-3 and H-5) in the presence of valerophenone was indicative of the inclusion of the phenyl ring into the β-CD cavity. The formation of only 1:1 stoichiometric complexes with all three cyclodextrins was inferred from a Job's plot[17] (Fig. 1).

For solution photolysis, 0.082 mL of valerophenone in 5 mL of respective solvents was irradiated (Table 1) in a N_2 atmosphere at the appropriate wavelength (254/365 nm). The photolysis of cyclodextrin complexes of **1** was carried out as follows. Microcrystalline CD complexes of **1** (150 mg) were taken in Quartz/Pyrex tubes (for 254/365 nm irradiations respectively), dissolved in 50 mL of distilled water and degassed with high-purity N_2 gas for 30 min. The tubes were then placed in HEBER multilamp photoreactors fitted with (4 × 8 W) 254 nm lamps and (8 × 8 W) 365 nm lamps for 1 h. During photolysis, the tubes were rotated periodically to ensure uniform irradiation. All of the solid-state photoreactions of CD complexes were carried out by placing the solid complexes in Quartz/Pyrex tubes, degassed with N_2 and then sealed. They were then photolysed for 48 h with periodic rotation of the tubes after every 30 min.

After the completion of photolysis and extraction from the CD cavity using hot $CHCl_3$, the reaction mixture was analyzed using a Shimadzu GC-17A, CYDEX-B Chiral capillary column (30 m) with a FID detector and high-purity nitrogen as the carrier gas. Only with this column were the two diastereomeric cyclobutanols well separated, since our attempt to resolve the diastereomeric cyclobutanols was unsuccessful with a SE-30 capillary column. Under the conditions used for analysis, low-molecular-weight gases such as propene, were not detected. Diastereomeric cyclobutanols were isolated and characterized from their GC-MS and NMR data[18] (for the *cis*-isomer, a doublet is observed at upfield due to the anisotropic diamagnetic shielding of methyl protons by the phenyl ring and for the *trans*-isomer, the corresponding doublet appears downfield due to the anisotropic deshielding by phenyl ring). IR spectra show peaks at 3500 cm^{-1} (ν_{-OHstr}), and the carbonyl stretching frequency around 1700 cm^{-1} is absent. ICD spectra is recorded using a JASCO J-810 spectropolarimeter, furnished with a 150 W xenon lamp. The measurements were performed under a nitrogen flux at 25 ± 1 °C, and the samples were contained in a quartz cuvette of pathlength of 0.1 cm. The acquisition parameters were: wavelength range, 200–500 nm at steps of 1 nm; bandwidth, 2 nm; time constant, 0.5 s; and sensitivity, 2 mdeg/div. The instrument was calibrated by using a 0.06% aqueous solution of ammonium D-10-camphosulphonate, from JASCO.

Results and Discussion

The results of the photoreaction of valerophenone in various solvents and also in presence of different cyclodextrins, either in solution or in the solid state, are presented in Tables 1 and 2. The reaction mixture irradiated at 254 nm (which excites the π, π^* state) was analyzed in a SE-30 capillary column, and a product distribution similar to an earlier report[10] was obtained (Table 1). Irradiation at 365 nm (which excites the n, π^* state directly) did not alter the product distribution upon irradiation in isotropic solvents, but increased the amount of elimination products when **1** was irradiated as its cyclodextrin complexes. Also, the isomeric cyclobutanols were not resolved, and only a single peak was obtained.

When the same reaction mixture (irradiated at 254 nm) was analyzed in a chiral CYDEX-B capillary column (presented in Table 2), C_1 and C_2 were resolved. The ratio C_1/C_2 is also in conformity with that reported[11] previously. In polar solvents, the amount of **2** increased compared to the cyclized products. This is in accordance with reported data,[19] and may be due to greater stabilization and solvation of the newly formed hydroxyl group in the biradical intermediate by polar solvents that suppress cyclization. This biradical consequently undergoes a preferential rotation to form the transoid biradical, resulting in larger amount of acetophenone **2**.

The reaction, when studied inside the hydrophobic environment of cyclodextrins, provide very interesting selectivities. In all of the cyclodextrin catalyzed reactions, the cyclized prod-

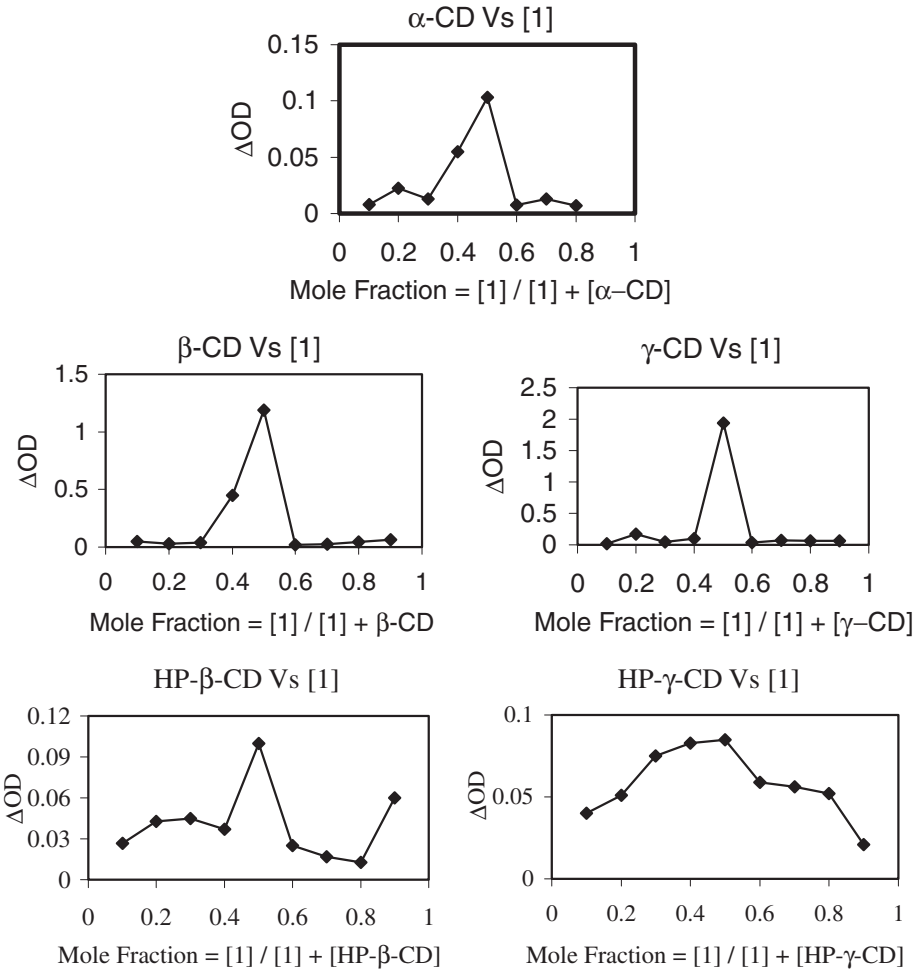


Fig. 1. Job's plots for valerophenone (**1**) in presence of various cyclodextrins.

Table 1. Percentage Conversion and Products Distribution in Photolysis[a] of Valerophenone (**1**) in Different Media (Analyzed by SE-30 Capillary Column)

Medium	Conversion /%	Percentage of Acetophenone **2** /%	Percentage of Cyclobutanols (cap C) /%	E/C ratio
Benzene	79.8 (50.1)[b]	70.7 (72.3)[b]	29.3 (27.6)[b]	2.41 (2.62)[b]
Benzene[c]	—	—	—	3.00
t-Butanol	86.8 (62.8)[b]	79.8 (80.2)[b]	20.2 (19.8)[b]	3.95 (4.05)[b]
t-Butanol[c]	—	—	—	4.20
α-CD/Water	75.8 (59.4)[b]	11.5 (34.6)[b]	88.5 (65.4)[b]	0.13 (0.53)[b]
β-CD/Water	98.4 (95.9)[b]	30.2 (72.0)[b]	69.8 (28.0)[b]	0.43 (2.57)[b]
γ-CD/Water	59.5 (58.2)[b]	26.7 (57.3)[b]	73.7 (42.5)[b]	0.36 (1.35)[b]
β-CD/Solid	58.0 (64.7)[b]	07.7 (54.5)[b]	92.3 (45.4)[b]	0.08 (1.20)[b]

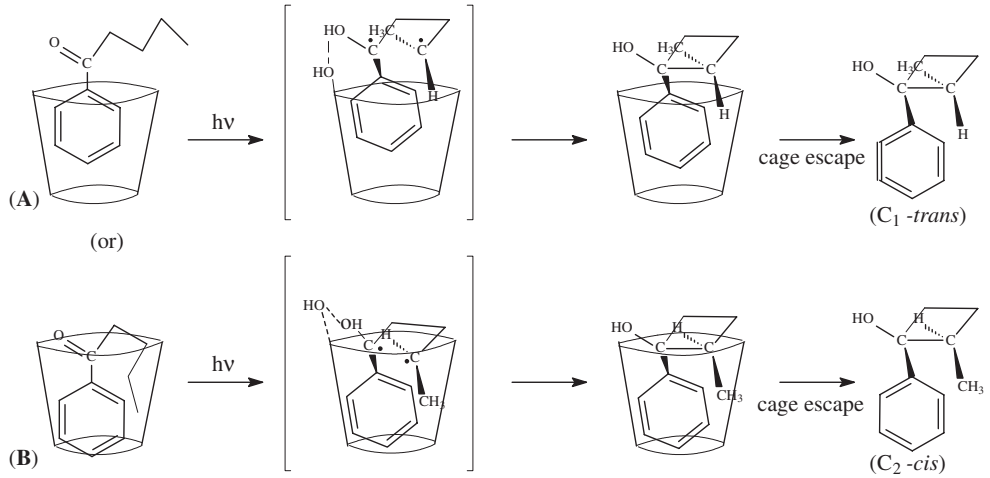
a) Irradiated at 254 nm. Analysed by SE-30 capillary column in a Shimadzu GC-17A chromatograph. b) Numbers in parentheses refer to data from 365 nm irradiation. c) Data from Ref. 10.

ucts were formed in larger amounts, and the amount of elimination product decreased (lower E/C ratio). Another significant observation was, out of the two possible diastereomers, one diastereomer (C_1-*trans*) was formed in larger amount compared to the other (C_2-*cis*). This is more pronounced in solid-state irradiations. Interestingly, in the hydroxypropyl derivatives of all the three CDs (namely HP-α-CD, HP-β-CD, and HP-γ-CD) C_2-*cis* was formed more compared to native CDs, thus resulting in lower C_1/C_2 ratios. It is relevant to note that diastereomeric cyclobutanols, unresolved in a SE-30 capillary column, were well separated in a chiral CYDEX-B capillary column. They are also isolated and characterized by spectra.

Table 2. Percentage Conversion and Products Distribution in Photolysis[a] of Valerophenone (**1**) in Various Solvents and in Presence of Cyclodextrins (Analysed Using CYDEX-B Chiral Capillary Column)

Medium	Conversion /%	Percentage of			E/C ratio[b]	C_1/C_2	X[f]
		2/%	C_1/%	C_2/%			
Benzene[c]	80.1	65.7	27.4	5.00	2.03 (2.64)[g]	5.48 (1.19)[g]	1.9
Hexane[c]	76.2	58.8	33.9	7.30	1.43	4.64	—
Methanol[c]	89.6	77.1	12.7	8.40	3.66	1.51	1.80
Ethanol[c]	86.5	78.1	12.4	6.60	4.11	1.88	2.90
t-Butanol[c]	80.4	79.7	9.61	5.73	5.20 (4.06)[g]	1.68 (0.68)[g]	4.96
α-CD/Water[d]	74.7	12.3	58.6	23.8	0.15 (1.08)[g]	2.46 (1.21)[g]	5.30
β-CD/Water[d]	90.7	10.7	60.9	28.2	0.12 (0.92)[g]	2.16 (1.22)[g]	0.20
γ-CD/Water[d]	79.2	14.7	52.9	27.8	0.18 (1.65)[g]	1.90 (0.55)[g]	4.60
HP-α-CD/Water[d]	61.3	16.0	43.5	33.8	0.21	1.29	6.70
HP-β-CD/Water[d]	83.2	14.5	39.4	39.8	0.18	0.99	6.10
HP-γ-CD/Water[d]	82.4	17.0	32.0	42.3	0.22	0.76	8.70
α-CD/Solid[e]	68.6	9.20	83.2	—	0.12	High	7.60
β-CD/Solid[e]	55.2	2.90	79.6	14.5	0.03	5.49	3.00
γ-CD/Solid[e]	49.5	6.70	71.5	21.8	0.07	3.28	—

a) Irradiated at 254 nm, analysed using CYDEX-B chiral capillary column with Shimadzu GC-17A chromatograph with high-purity nitrogen as the carrier gas and FID detector. b) E/C ratio is obtained from the ratio of $2/(C_1 + C_2)$. c) Irradiated for 4 h. d) Irradiated for 1 h. e) Irradiated for 48 h. f) Unidentified products. g) Numbers in parentheses refer to data from 365 nm irradiation.



Scheme 2.

This remarkable efficiency of cyclodextrin in suppressing elimination pathway, and also promoting the selective formation of one of the diastereomers is attributed to the geometric constraints imposed by the CD cavity on the initially formed 1,4-biradical intermediate. The suppression of the elimination pathway is attributed to the constrained environment encountered by the biradical within the CD cavity, which facilitates its cyclization, while an elimination pathway involving the cleavage of the α,β-carbon–carbon bond necessitates a significant formation of the longer transoid biradical.

An analysis of the reaction mixture irradiated at 365 nm (which excites n, π^* state directly) in the chiral CYDEX-B column exhibited no variation in either the E/C or C_1/C_2 ratio under solution irradiation. However, in aqueous cyclodextrin complexes, an increase in the E/C ratio and a decrease in the C_1/C_2 ratio were observed.

The effect of CD is also remarkable, since it promotes the selective formation of one diastereomer of cyclized product over the other. This effect is more pronounced in the solid state, and also in the smaller α-CD. As the size becomes larger, this effect decreases considerably. This can be explained as follows. The inclusion of valerophenone into the CD cavity can occur in either of modes A and B (Scheme 2). In mode A, the *n*-butyl group of valerophenone is outside the CD cavity, and in mode B it is also included along with the phenyl group. However, the photolysis of complex A gives predominantly the (C_1-*trans*) isomer and that of B gives predominantly the other isomer (C_2-*cis*). It is also relevant to note that the hydroxyl group of the 1,4-biradical is stabilized by the hydroxyl groups present at the rim of the CD cavity.

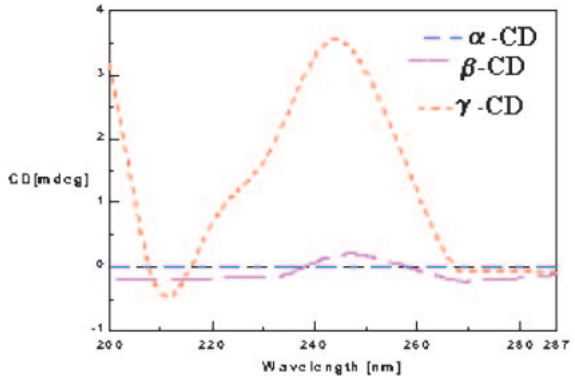


Fig. 2. ICD spectra of valerophenone (0.5×10^{-4} M) in presence of α-, β-, and γ-CDs (4×10^{-3} M).

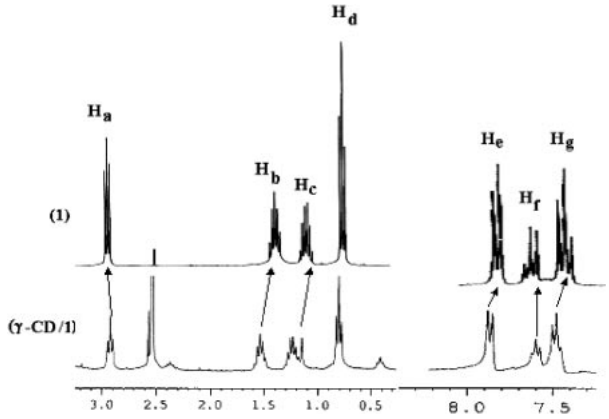


Fig. 3. ^{1}H NMR spectra of **1** and its γ-CD complex in D_2O at 25 °C.

While the smaller cavity of α-CD facilitates the formation of A over B, in the larger cavity in γ-CD, B can also be accommodated to a significant extent. This explains the preferential formation of C_1-*trans* over C_2-*cis* in solid α-CD complexes, and the decreased selectivity with an increase in the size of CD. Support for this conclusion can be obtained from the ICD spectra of valerophenone in presence of α-, β-, and γ-CDs (Fig. 2). While ICD is negligible with α-CD, a very small positive cotton effect peak is observed with β-CD. The intensity of this positive ICD peak is increased significantly with γ-CD. While the positive ICD peak is attributed to axial inclusion of aryl ring into the CD cavity (as the transition dipole moment of the guest is parallel to the axis of the cyclodextrin in accordance with empirical sector rules of Kajtar[20] and Harata et al.[21]), the increase in sign with γ-CD can be accounted by proposing the coinclusion of the side chain into the γ-CD cavity, as in B, which ensures a tighter fit of the aryl ring inside the γ-CD cavity. This clearly proves that in α- and β-CD, the side chain stays out, while in γ-CD it is also included inside the cavity. The small reduction in selectivity in the photolysis of aqueous CD-complexes may be rationalized by the existence of a dynamic equilibrium between the complexed and uncomplexed substrate.

In order to gain additional evidence for the coinclusion of a side chain of valerophenone **1** inside the γ-cyclodextrin cavity, the γ-CD/valerophenone complex was characterized under photolysis conditions using ^{1}H-, ^{13}C-, ^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, and ^{1}H–^{1}H NOESY NMR spectroscopic techniques, since the chemical-shift values of the guest protons show appreciable changes, if the guest molecule is included in the CD cavity. The ^{1}H NMR spectra of **1** and its γ-CD complex are shown in Fig. 3. As can be seen from Fig. 3, the δ values of the H_e and H_g protons are shifted to upfield ca. 0.03 ppm and 0.02 ppm, respectively, whereas the H_f protons are shifted downfield to 0.005 ppm compared with the corresponding values for free substrate **1**. The δ values of H_c, H_b, and H_a undergo small upfield shifts (0.017, 0.013, and 0.01, respectively). Also, when the guest molecule is included into the CD cavity, NOE correlations between the protons of the guest molecule with the protons of the CD cavity can be observed. As shown in the Fig. 4a, the NOESY spectrum of **1** displays NOE correlations between the H-5 protons of γ-CD and the H_b proton of **1** (peak A), as well as correlations between the H-3 protons of γ-CD and the H_c protons of **1** (peak B), which indicate that the alkyl chain of the valerophenone is well included into the CD cavity. Also, NOE correlations between the H-5 protons of γ-CD with the *ortho*-protons of the phenyl group (peak C) and H-6 proton of CD with the *para*-proton of phenyl group (peak D) are observed. Considering the structural features of the CD cavity, the H-5 protons near the narrow side and the H-3 protons near the wider side, one can deduce a possible inclusion complexation geometry of complex **1**, as illustrated in Fig. 4b.

In this context, it is relevant to note that in order to minimize the magnitude of this dynamic equilibrium, which would increase the amount of substrate in a bulk solvent, 1:1 complexes are prepared first, washed with diethyl ether to remove any surface-adsorbed substrate, and then dissolved in water. Hence, it is more likely that the reaction from the substrate in its complexed mode is the major pathway, and this is anticipated due to the two following reasons: a) the solubility of valerophenone in water is negligible, and hence it would rather prefer the hydrophobic cavity of CD and b) a lower yield of the cleavage product, namely acetophenone (which is the major product in solution photolysis), is observed in photolysis of CD-included valerophenone. While it is very difficult to quantify the proportion of substrate in its complexed form, or in its free state, since it depends on the type of CD, the molar concentration of the substrate (for the equivalent 150 mg of the CD-complex, the amount of **1** decreases in the order 21, 18.7, and 16 mg from α-, β-, and γ-CD, respectively), the temperature and the binding constants in water, it is reasonable to assume that the proportion of acetophenone in each CD-complexed photolysis is a measure of the amount of uncomplexed valerophenone. Cyclobutanols are observed predominantly from the CD-complexed substrate.

In order to understand the effect of cyclodextrin in facilitating the cyclization pathway, energy minimization studies for valerophenone and the two cyclobutanols were carried out in cyclodextrins using the Insight II discover program in the IRIX system. Calculations were performed in vacuum and structures were minimized using the AMBER[22] force field, and an RMS derivative a 0.0001 was achieved in each case.

The observed data (Table 3) show that the complex formed with the guest **1** is more stable in all three CDs ($\alpha < \beta \approx \gamma$).

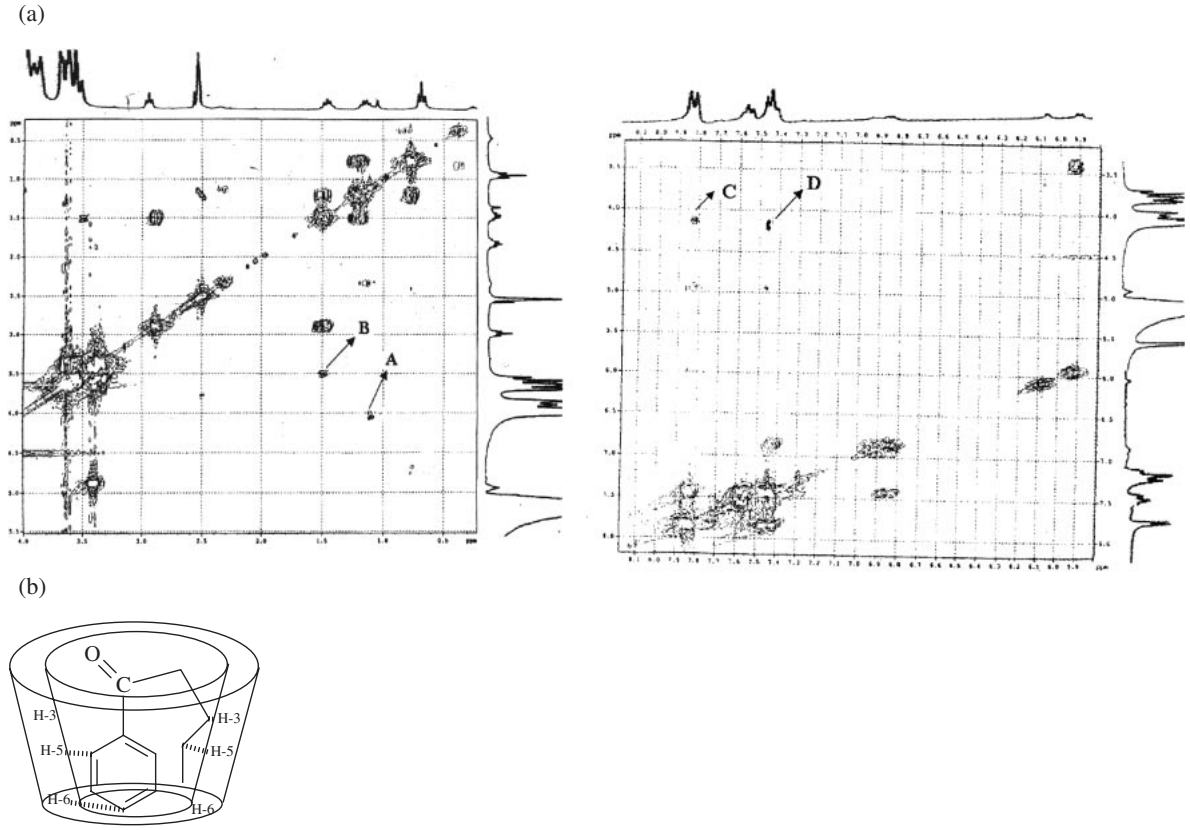


Fig. 4. (a) ^{1}H–^{1}H NOESY spectra of γ-CD/valerophenone (**1**) in D_2O at 25 °C. (b) Possible orientation of **1** in γ-CD cavity.

Table 3. Theoretical Energies of Cyclodextrin Complexes Obtained from Energy Minimization Using AMBER Force Field Calculations

Guest	Cyclodextrin	$\Delta E^{a)}$/kcal mol^{-1}
1	α-CD	−60.01
1	β-CD	−70.66
1	γ-CD	−71.11
C_1	α-CD	−53.28
C_1	β-CD	−65.65
C_1	γ-CD	−68.48
C_2	α-CD	−50.87
C_2	β-CD	−62.31
C_2	γ-CD	−64.45

a) Energy change upon CD complex formation compared to uncomplexed substrate and CD.

The greater stability with β- and γ-CDs may be due to the co-inclusion of an *n*-butyl group along with a phenyl group, which induces a tighter fit. Also, C_1 is more stable than C_2 in all of the CDs. Hence, it is likely that the equilibrium between the cisoid$_1$ and cisoid$_2$ triplet biradicals (Scheme 1) would have been tilted towards the more stable cisoid$_2$ intermediate upon complexation inside the cyclodextrin cavity. The distance between the carbonyl oxygen and γ-hydrogen was also measured in the CD complex of **1**. In all of the CD's it was found to be less than 2.5 Å, indicating that γ-H abstraction followed by cyclization inside the cyclodextrin cavity is energetically favorable upon complexation.

Conclusion

Very interesting product selectivity was observed in the Norrish–Yang photoreaction of CD-complexed valerophenone. The E/C (Elimination/Cyclization) ratio decreased in all cyclodextrins, which may be attributed to the geometric constraints experienced by the produced biradical. A remarkable diastereoselectivity (reported for the first time) was also observed in that, among the two diastereomeric cyclobutanols, one isomer (C_1-*trans*) was formed in a larger amount than the other (C_2-*cis*). The observed results are explained on the basis of the steric constraints encountered by the 1,4-biradical intermediate inside the cyclodextrin cavity by way of restricted rotational motion, and also the stabilization of the same by the hydroxyl groups present in the rim of the cyclodextrin cavity. Additional supports from molecular minimization calculations, ^{1}H NMR and ^{1}H–^{1}H NOESY spectra to explain the greater stabilizing of β-/γ-CD complexes of valerophenone (which is attributed to the coincluion of butyl side chain into the CD cavity along with the phenyl group which ensures a tight fit) are also presented.

Financial assistance from Council of Scientific and Industrial Research (CSIR), New Delhi is gratefully acknowledged.

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