CONSEQUENCES OF HYDROPHOBIC ASSOCIATION IN PHOTOREACTIONS: PHOTODIMERIZATION OF ALKYL CINNAMATES IN WATER

S. DEVANATHAN and V. RAMAMURTHY[†]

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012 (India)

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Summary

Photolysis of alkyl cinnamates in water gave δ-truxinates in near quantitative yields. Dimerization of alkyl cinnamates at low concentration (about 10^{-4} M) in water is attributed to hydrophobic association of these solutes. At such low concentrations, photolysis in benzene and methanol yields only geometric isomers. This study illustrates the potential of water as a solvent for photoreactions and stresses the need for increased appreciation of its utility.

1. Introduction

Hydrophobic interactions are often claimed to play a central role in most biological processes. They are described as indirect contributors to the intermolecular forces arising as a result of the surrounding aqueous or mixed-aqueous solvent [1]. The so called "direct" forces are those which operate in the gas as well as in the solution phase, namely van der Waals' interactions, London forces and coulombic forces. Interestingly, the nonpolar solutes present in the aqueous phase experience, in addition to the "direct" forces, yet another intermolecular force termed as the hydrophobic force, solely due to the surrounding aqueous medium, which tends to cluster them together. This multimolecular aggregation or clustering of hydrophobic solutes in water could prove to be of immense value to the organic chemist. The appreciation of hydrophobic interactions probably began with the discovery of micelle formation and the introduction of the micelle as a reaction medium, an area which has stimulated considerable interest among chemists [2]. More recently, however, the uniqueness of the aqueous phase as a reaction medium has been demonstrated [3]. Although the utility of the aqueous phase as a reaction medium for thermal reactions could be

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[†]Present address: Central Research and Development Department, E. I. Du Pont de Nemours and Co., Wilmington, DE 19898, U.S.A.

appreciated, at the time we began our studies its use for photoreactions was yet to be fully demonstrated. With this aim in mind, we undertook an estimation of the potential of the aqueous phase as a medium for photoreactions [4].

The effectiveness of preassociation in bringing about efficient photodimerization was originally demonstrated for concentrated aqueous solutions of dimethylthymine and tetramethyluracil [5]. Efficient photodimerization which resulted from the singlet excited state of these solutes was incompatible with a mechanism involving a diffusion-controlled reaction between the short-lived singlets and the ground state molecules and hence required the presence of preformed aggregates in aqueous solution. In fact such a hydrophobic aggregation could also be expected in very dilute aqueous solutions of poorly soluble organic solutes and this could prove to be much more dramatic by bringing about photodimerization in a very dilute solution. Investigations of a few such systems (coumarins and stilbenes) in our laboratory have been successful and they brought to light the significance of the hydrophobic effect [4].

Photodimerizations of alkyl cinnamates and cinnamic acids have attracted a great deal of attention over the years, in part because of their use as photoresists and their extensive application in microlithography [6]. Both direct and sensitized irradiations of cinnamic acids and alkyl cinnamates in dilute solution result in cis–trans isomerization and ester cleavage [7, 8]. Photodimerization does not compete efficiently with isomerization in dilute solutions but is observed in the solid state [9], in organized media [10, 11] and in solution when high local concentrations are achieved [12]. Here, we demonstrate that efficient dimerization can be obtained by irradiation of dilute aqueous solutions of alkyl cinnamates 1 - 5. This remarkable observation is attributed to the association of alkyl cinnamates in water resulting from hydrophobic effects. The results described below demonstrate the potential of water as a solvent for photoreactions and stress the need for an increased appreciation of its utility.

2. Results

Alkyl cinnamates 1 - 5 (Scheme 1) were photolysed in organic solvents (benzene and methanol) and in aqueous media. Since we conjectured that the long alkyl chain might in some way control the nature of the association and thereby the stereochemistry of the dimer, several long-chain alkyl cinnamates were investigated. Of these, ethyl cinnamate was investigated in greatest detail. While cinnamates 1 and 2 were readily soluble in water, 3 - 5 were less soluble. Photolysis solutions of 3 - 5 always contained a layer of undissolved cinnamate. The formal concentrations of 1 and 2, prepared by stirring them in water, were about 10^{-3} M while those for 3 - 5 were below 10^{-4} M.

Irradiation of dilute solutions of 1 - 5 in benzene ($10^{-3} - 10^{-4}$ M) resulted only in geometric isomerization. Even prolonged irradiation did not
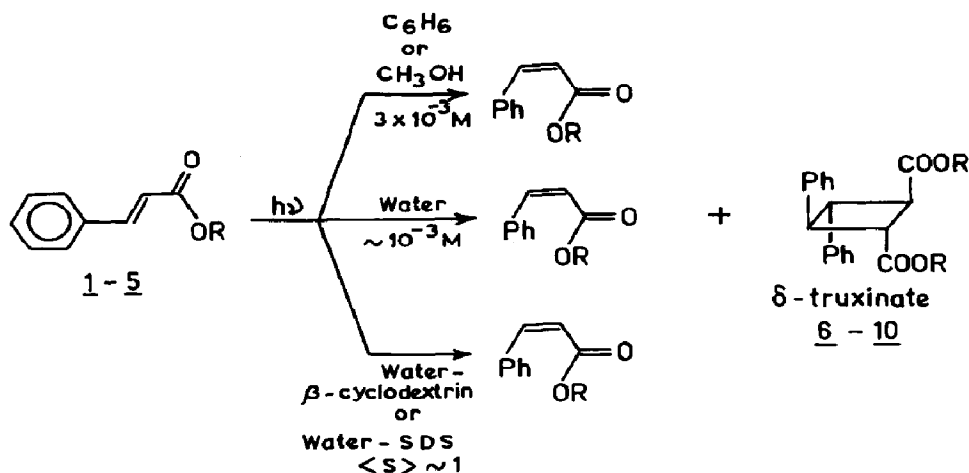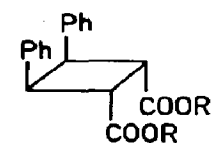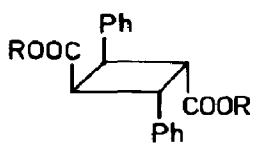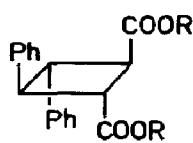
Scheme 1.

give dimers and the irradiated mixture consisted of only cis and trans isomers (Tables 1 and 2). However, photolysis of the neat liquid and concentrated benzene solution (0.5 M) gave dimers in addition to geometric isomers. Ester cleavage products were not detectable under our analysis conditions. Most remarkably, photolysis of saturated aqueous solutions of 1 - 5 (formal concentration, 10^{-3} - 10^{-5} M) readily gave a single dimer in major yield. It is to be noted that under similar concentrations in benzene no dimers were obtained. The dimers were characterized to be a δ-truxinate on the basis of comparison of the spectral data with the literature reports [13, 14]. Although gas chromatographic analysis indicated the presence of another dimer (approximately 5%), it could not be obtained in sufficient amounts for characterization. The mass balance during aqueous photolysis was about 90%, suggesting that if photohydration, a likely reaction, occurs it does not yield any stable products. However, photohydration followed by dehydration to yield the cinnamates themselves could not be ruled out. The 270 MHz proton nuclear magnetic resonance (NMR) spectrum of the crude photolysis mixture did not show any peaks corresponding to the hydrated cinnamates. Generally, the neat liquid irradiation yielded a mixture of dimers and the efficiency of dimerization was lower than that in the aqueous medium.

TABLE 1

Product distribution upon photolysis of alkyl cinnamates[a]

Medium	Percentage of product[b]		
	Cis	Trans	Dimer
Ethyl cinnamate (1)			
Neat liquid	24	33	43
Benzene (0.003 M)	64	36	—
Methanol (0.003 M)	60	40	—
Water (0.003 M)	7	7	85
n-Butyl cinnamate (2)			
Neat liquid	33	53	14
Benzene (0.003 M)	45	55	—
Benzene (0.5 M)	46	41	13
Water (0.002 M)	20	33	47
n-Hexyl cinnamate (3)			
Neat liquid	28	50	22
Benzene (0.003 M)	44	56	—
Benzene (0.5 M)	38	46	15
Water (10^{-4} M)	10	40	50
n-Octyl cinnamate (4)			
Neat liquid	27	53	20
Benzene (0.003 M)	50	50	—
Benzene (0.5 M)	50	43	6
Water (10^{-4} M)	27	43	30
n-Dodecyl cinnamate (5)			
Neat liquid	29	57	14
Benzene (0.003 M)	56	44	—
Benzene (0.5 M)	50	40	10
Water (10^{-4} M)	29	42	29

[a] All irradiations were carried out under identical conditions for 24 h.
[b] Product analysis based on ^{1}H-NMR and gas chromatography; error limit, ±5%.

Relative yields and efficiencies of dimerization for 1 - 5 in neat liquid, benzene and in aqueous media are summarized in Table 1. The data presented in Table 1 and Fig. 1 correspond to relative yields only and the product ratios were not corrected for the gas chromatograph detector response. However, the mass balance being satisfactory (about 90%), the reported product distributions are useful for drawing significant mechanistic conclusions. The plot of the reaction mixture composition *vs.* the irradiation time shows that isomerization precedes dimerization, at least in the case of ethyl cinnamate (Fig. 1). It can be concluded from Fig. 1 that the geometric isomerization is faster than dimerization and the dimerization occurs from a photostationary state mixture that is established in a few hours.

Direct and indirect support for the aggregation proposal was sought. Experiments were devised with the use of additives that are expected to alter the aggregation behaviour in predictable ways. It is known that lithium

TABLE 2

Product distribution upon photolysis of ethyl cinnamate in water[a]

Conditions[b]	Percentage of product[c]		
	Cis	Trans	Dimer
Water	7	22	70
Water + LiCl (3 M)	5	11	84
Water + guanidinium chloride (3 M)	10	25	55
Water + β-cyclodextrin (1:5)	56	43	—
Water + SDS; ⟨S⟩: 1[d]	58	41	—

[a]All irradiations were done under identical conditions using RPR 254 nm lamps. Solutions were of equal optical density and were irradiated in a "merry-go-round" style for 24 h.
[b]Concentration of ethyl cinnamate in all solutions was 0.003 M.
[c]Product distribution based on gas chromatography analysis; error limit, ±5%.
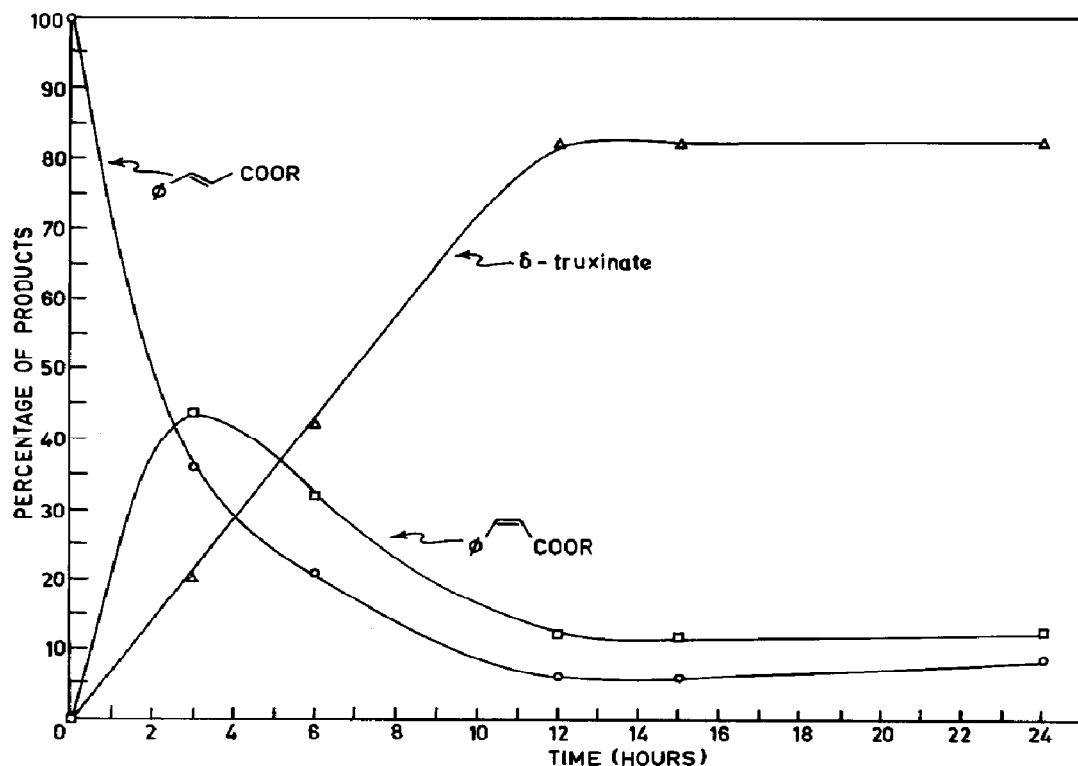[d]⟨S⟩, occupancy number.

Fig. 1. Variation in the product distribution with respect to time during photolysis of ethyl cinnamate in water.

chloride increases hydrophobic association while guanidinium chloride serves to deaggregate organic and biological molecules in water [15]. Noticeable consequences of such perturbations were found in the resulting dimer yields from ethyl cinnamate (Table 2). In a similar manner, the encapsulation of

ethyl cinnamate into the hydrophobic pockets of cyclodextrin and sodium dodecylsulphate (SDS) micelles would isolate them from their associates thus totally preventing dimerization. This was indeed observed upon addition of an excess of β-cyclodextrin to the aqueous solutions. Also photolysis of ethyl cinnamate in SDS micelles with an occupancy of less than one resulted only in geometric isomerization. Results of irradiation of ethyl cinnamate conducted in the presence of the above additives (lithium chloride, guanidinium chloride, β-cyclodextrin and SDS micelles) under identical conditions and matched optical densities are summarized in Table 2. Physical evidence for aggregation of organic molecules is generally obtained through osmometric (molecular weight) measurements and optical absorption measurements (deviation from Beer's law). The former being unavailable, UV absorption measurements were made over the range 220 - 320 nm for aqueous ethyl cinnamate solutions with concentrations varying between 10^{-4} and 10^{-5} M. Although there were some difficulties in making accurate measurements, a non-linear Beer's plot was obtained in the region 285 - 310 nm; below 285 nm linear behaviour was observed (Fig. 2).
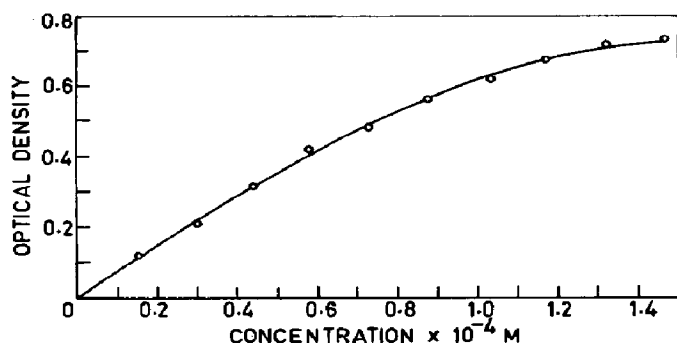

Fig. 2. Beer's law plot for ethyl cinnamate: optical density variation at 280 nm and 290 nm with respect to concentration.

3. Discussion

The following points are interesting to note: (a) alkyl cinnamates readily dimerize in aqueous solutions to yield a single dimer, namely δ-truxinate, as the major product; (b) the dimerization is quite efficient in water whereas at such low concentrations of alkyl cinnamates in organic solvents only geometric isomerization is observed; (c) the association of alkyl cinnamates in water is suggested by the variation in the dimerization efficiency in the presence of additives which are known to alter the water structure and by the non-linear behaviour of the electronic absorption properties with respect to concentration.

The photochemical behaviour of cinnamic acids and alkyl cinnamates has been extensively investigated. The reactions of *trans*-cinnamic acids in the crystalline states are well-known examples of [2 + 2] photodimerization and the classic studies by Schmidt have demonstrated that such reactions

are strictly controlled by the packing arrangement of the molecule in the crystal [9]. α- and β-truxillic acids (dimers of cinnamic acids) are quantitatively obtained from the α and β forms of the cinnamic acids. Very recently it has been shown that alignment of alkyl cinnamates in n-butyl stearate liquid crystals results predominantly in α-truxillates [10]. However, irradiation of cinnamates as neat liquids and in microemulsions gave a mixture of isomers with δ-truxinate predominating in the mixture [11, 12]. Therefore, the selectivity obtained in aqueous media (δ-truxinate in above 90% yield) is remarkable and could be of synthetic value especially in the absence of other methods which could yield β-truxinate selectively. Such a selective dimerization could be due either to prealignment of cinnamates in the molecular associations or to preference in the excited states (S_1 or T_1) that undergo reaction.

Significant selectivity in the product distribution (exo, endo) has been reported during the Diels—Alder reaction in water [3]. But no such selectivity was observed during the photodimerization of stilbenes [4]. Formation of the head—head dimer (δ-truxinates) in the present study may indeed result from the head—head alignment of alkyl cinnamates in the associated structures (Scheme 2). Although the absence of head—tail dimers is consistent with this model, the non-formation of β-truxinates is surprising. The preference for the formation of δ-truxinates over β-truxinates can be rationalized on the basis of the reactive state involved in the reaction. Careful investigation of alkyl p-nitrocinnamates has revealed that dimerization from S_1 yields β-truxinates and from T_1 a mixture of β- and δ-truxinates with the latter predominating [16]. An extension of this study would lead one to conclude that in an aqueous medium dimerization essentially occurs from T_1 to yield preferentially the δ-truxinates. However, we have no firm evidence to show that the intersystem crossing of alkyl cinnamates from S_1 to T_1 is indeed enhanced in water, though the polarity of the medium could play a significant role in this process.

Probable Structure of Associated Alkylcinnamates

Expected dimers
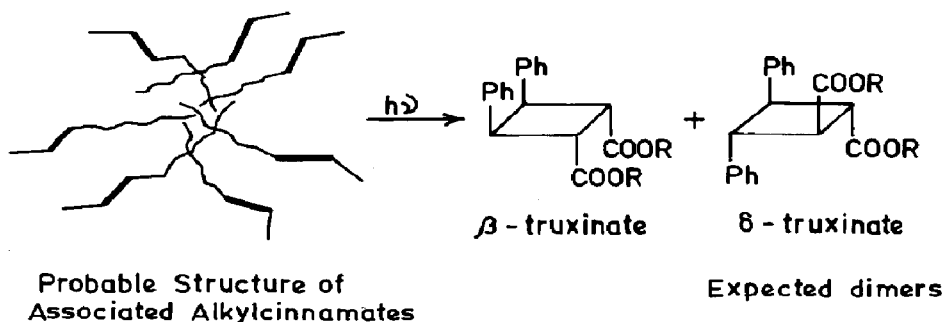
Scheme 2.

In addition to the stereoselective dimer formation, a dramatic enhancement in the rate of dimerization was observed (Table 1). We attribute this to self-aggregation of alkyl cinnamates in water. This hypothesis is prompted by the following observations.

(i) The lifetime of T_1 and the rate of interaction between the ground and excited triplet methyl cinnamates (leading to dimer) in toluene have been estimated to be 10.3 ns and $8.8 \times 10^6 \, M^{-1} \, s^{-1}$ respectively [8]. If these numbers hold good in water, dimerization of alkyl cinnamates (about 10^{-3} M) from T_1 would not be able to compete with geometric isomerization. No corresponding reliable numbers are available for the S_1 state of alkyl cinnamates. Therefore, in water, if dimerization occurs from T_1 at all, it has to occur from a preassociated species wherein the effective concentration is expected to be very much higher than 10^{-3} M.

(ii) Examination of Table 2 reveals that lithium chloride, a salt known to increase the hydrophobic association, increases the dimer yield, and guanidinium chloride, a salt established to decrease the hydrophobic association, decreases the dimer yield with respect to pure water. These results indicate the importance of hydrophobic association in the dimerization of alkyl cinnamates in water.

(iii) When β-cyclodextrin and SDS micelles, species capable of complexing individual molecules of alkyl cinnamates, are used, the dimerization is completely inhibited. Both β-cyclodextrin and SDS micelles serve as hydrophobic pockets in aqeuous solution, deaggregating the alkyl cinnamates and thus preventing their dimerization. It was necessary to maintain a low occupancy number in the micellar media to avoid having more than one cinnamate per micelle. At higher occupancies dimerization dominates because of the encounter between an excited state and a ground state cinnamate present within a micelle. Similarly, high concentrations of β-cyclodextrin were required to deaggregate the cinnamates present in the aqueous medium. Since the inclusion phenomenon is an equilibrium process, a higher cyclodextrin concentration was required to shift the equilibrium towards the complexed species. In the absence of complete complexation dimerization will still occur.

(iv) The results of UV absorption spectra measurements support the aggregation proposal: a plot of optical density *vs.* concentration showed nonlinear behaviour for ethyl cinnamate (Fig. 2).

Thus the results presented here for alkyl cinnamates illustrate the significant role of hydrophobic interactions in altering the course of photoreactions in aqueous solution. Investigations on stilbenes, coumarins and alkyl cinnamates have clearly established that photoreductions of organic molecules in water could yield novel results. Recent studies by several groups [3] including ours [4] have established dramatically the uniqueness of water as a solvent for organic reactions.

4. Experimental details

Alkyl cinnamates 1 - 5 were prepared by reported procedures [17] and were purified by passing through a silica-gel column (hexane–chloroform mixture as eluent). β-Cyclodextrin, lithium chloride, guanidinium chloride

and sodium dodecylsulphate, all from Sigma, were used as received. Benzene, methanol (AR samples) and doubly distilled water were utilized for photolysis and spectral measurements. UV absorption spectra were recorded using a Shimadzu UV-180 spectrophotometer and product analyses were carried out on a Chemito gas chromatograph (Model 3800) using an SE-30 (5%, $\frac{1}{4}$ in × 5 ft) column; proton NMR spectra were recorded on a Bruker WH-270 spectrometer.

4.1. Photolysis of 1 - 5 in water

The alkyl cinnamates 1 - 5 were sparingly soluble in water. However, solutions of cinnamates having formal concentrations of around 10^{-4} M could be prepared by magnetically stirring about 20 mg of 1 - 5 in 100 ml of water for 24 h. These aqueous solutions were irradiated in quartz tubes using a Rayonet reactor fitted with RPR-254 nm lamps after bubbling with oxygen-free nitrogen for 30 min. After irradiation, the aqueous solution was extracted with ether and was analysed by gas chromatography. Preparative irradiations were also carried out in a similar way. The products were purified by repeated thin-layer chromatography (silica gel and hexane–chloroform mixture) and were characterized by their spectral properties. Spectral data of the dimers obtained by irradiation of 1 - 5 in water are summarized below.

6: IR(neat): 3080, 3060, 1720, 1610 and 1170 cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ = 1.27(t, J = 7.1 Hz, 6H); 3.4(d, J = 9 Hz, 2H); 3.7(d, J = 9.5 Hz, 2H); 4.19 (q, J = 7.1 Hz, 4H); 7.18 - 7.32(m, 10H).

7: IR(neat): 3080, 3060, 1720, 1610 and 1170 cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ = 0.91(t, J = 7.3 Hz, 6H); 1.2 - 1.66(m, 8H); 3.43(d, J = 9.4 Hz, 2H); 3.76 (d, J = 9.4 Hz, 2H); 4.19(q, J = 7.3 Hz, 4H), 7.18 - 7.32(m, 10H).

8: IR(neat): 3080, 3060, 1720, 1610 and 1170 cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ = 0.91(t, J = 7.3 Hz, 6H); 1 - 2(m, 16H); 3.4(d, J = 9.4 Hz, 2H), 3.7(d, J = 9.4 Hz, 2H); 4.19(t, J = 7.3 Hz, 4H); 7.18 - 7.32(m, 10H).

9: IR(neat): 3060, 3020, 1700, 1630 and 1170 cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ = 0.91(t, J = 7.3 Hz, 6H); 1 - 2(m, 24H); 3.44(d, J = 9.5 Hz, 2H); 3.75(d, J = 9.5 Hz, 2H); 4.1(t, J = 7.3 Hz, 4H); 7.2 - 7.34(m, 10H).

10: IR(neat): 3080, 3060, 1720, 1610 and 1170 cm^{-1}. ^{1}H-NMR(CDCl$_3$): δ = 0.9(t, J = 7.3 Hz, 6H); 1 - 2(m, 40H); 3.4(d, J = 9.5 Hz, 2H); 3.7(d, J = 9.5 Hz, 2H); 4.19(t, J = 7.3 Hz, 4H); 7.18 - 7.32(m, 10H).

4.2. Photolysis of ethyl cinnamate in SDS micelles and β-cyclodextrin

Ethyl cinnamate (10 mg) was stirred with SDS (1 g) in 100 ml of water for about 12 h. The clear transparent solution thus obtained was irradiated as described above. Products were extracted using chloroform after diluting the solution below the critical micellar concentration of SDS.

Addition of ethyl cinnamate (50 mg) to a saturated aqueous solution of β-cyclodextrin (645 mg) resulted in precipitation of the complex. The precipitate was collected after filtration and washed with cold water and ether. This precipitate was redissolved in an excess of water, 5 equivalents of

cyclodextrin were added and the solution was irradiated as above. The products were extracted using warm chloroform.

4.3. Photolysis in the presence of additives

In order to assess the importance of association of ethyl cinnamate in the aqueous phase the following experiments were carried out. Five quartz tubes containing identical concentrations of ethyl cinnamate (1×10^{-3} M) in water with additives as mentioned below and matched optical densities were irradiated simultaneously in a "merry-go-round" style using RPR 254 nm lamps. These five quartz tubes contained the following solutions: (i) ethyl cinnamate, (ii) ethyl cinnamate and 3 M lithium chloride, (iii) ethyl cinnamate and 3 M guanidinium chloride, (iv) ethyl cinnamate and 1 g of β-cyclodextrin and (v) ethyl cinnamate and 1 g of SDS. The products were extracted and analysed by gas chromatography. Yields of the dimers are presented in Table 2.

For the sake of comparison, benzene and methanol solutions of alkyl cinnamates and neat alkyl cinnamates were irradiated using RPR 254 nm lamps and analysed by gas chromatography. The results are summarized in Table 1.

References

1 A. Ben-Naim, *Hydrophobic Interactions*, Plenum Press, New York, 1985.
2 V. Ramamurthy, *Tetrahedron*, *42* (1986) 5753.
3 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, *102* (1980) 7816.
   R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, *24* (1983) 1901.
   R. Breslow and U. Maitra, *Tetrahedron Lett.*, *25* (1984) 1239.
   P. A. Grieco, P. Garner and Z. M. Ho, *Tetrahedron Lett.*, *24* (1983) 1897.
   P. A. Grieco, P. Garner, K. Yoshida and J. C. Huffman, *Tetrahedron Lett.*, *24* (1983) 3807.
   P. A. Grieco, K. Yoshida and P. Garner, *J. Org. Chem.*, *48* (1983) 3137.
4 K. Muthuramu and V. Ramamurthy, *J. Org. Chem.*, *47* (1982) 3976.
   M. S. Syamala and V. Ramamurthy, *J. Org. Chem.*, *51* (1986) 3712.
   S. Devanathan, M. S. Syamala and V. Ramamurthy, *Proc. Indian Acad. Sci.*, in the press.
5 G. J. Fisher and H. E. Jones, *Photochem. Photobiol.*, *11* (1970) 429.
   R. Kleopfer and H. Morrison, *J. Am. Chem. Soc.*, *94* (1972) 255.
   J. G. Otten, C. S. Yeh, S. Byrn and H. Morrison, *J. Am. Chem. Soc.*, *99* (1977) 6353.
6 D. P. Specht, P. A. Martic and S. Farid, *Tetrahedron*, *38* (1982) 1203.
   J. L. R. Williams, S. Y. Farid, J. C. Doty, R. C. Daly, D. P. Specht, R. Searle, D. G. Borden, H. J. Chang and P. A. Martic, *Pure Appl. Chem.*, *49* (1977) 523.
   M. Hasegawa, *Chem. Rev.*, *83* (1983) 507.
   J. L. R. Williams, *Fortschr. Chem.*, *13* (1969) 337.
7 B. H. Clampelt and J. W. Callis, *J. Phys. Chem.*, *66* (1962) 201.
   C. Sandris, *Tetrahedron*, *24* (1968) 3569.
   M. B. Hocking, *Can. J. Chem.*, *47* (1969) 4567.
   T. Ishigami, K. Nakazato, M. Uehara and T. Endo, *Tetrahedron Lett.*, (1979) 863.
   Y. Shindo, K. Horie and I. Mita, *J. Photochem.*, *26* (1984) 185.
   V. Ramesh and R. G. Weiss, *Mol. Cryst. Liq. Cryst.*, *135* (1986) 13.
8 W. G. Herkstroeter and S. Farid, *J. Photochem.*, *35* (1986) 71.

9 G. M. J. Schmidt, *Pure Appl. Chem.*, *27* (1971) 647.

10 V. Ramesh and R. G. Weiss, *J. Org. Chem.*, *51* (1986) 2535.

11 H. Amarouche, C. Bouroyne, M. Riviere and A. Lattes, *C.R. Acad. Sci. II*, *298* (1984) 121.

12 H. G. Curme, C. C. Natorle and D. J. Kelley, *J. Phys. Chem.*, *71* (1967) 767.
P. L. Egerton, E. M. Hyde, J. Trigg, A. Payne, P. Beynon, M. V. Mijovic and A. Reiser, *J. Am. Chem. Soc.*, *102* (1981) 3859.
Y. Shindo, K. Horie and I. Mita, *Chem. Lett.*, (1983) 639.

13 D. A. Ben-Efraim and B. S. Green, *Tetrahedron*, *30* (1974) 2357.

14 K. Muthuramu, N. Ramnath and V. Ramamurthy, *J. Org. Chem.*, *48* (1983) 1872.
N. Ramnath and V. Ramamurthy, *J. Org. Chem.*, *49* (1984) 2827.

15 P. H. Von Hippel and T. Schleich, *Acc. Chem. Res.*, *2* (1969) 257.

16 T. Ishigami, T. Murata and T. Endo, *Bull. Chem. Soc. Jpn.*, *49* (1976) 3578.

17 A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longman, London, 1975, 4th edn., p. 842.