Photodimerization of 5,7-Dimethoxycoumarin

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Three photocyclodimers of 5,7-dimethoxycoumarin (DMC) were isolated and characterized from the photolysis of DMC in acetonitrile. The configuration of the dimers was found to be *anti* head-to-head, *syn* head-to-head and *syn* head-to-tail, respectively. The number and the ratio of the products are solvent dependent. The *anti* head-to-head dimer is favored in nonpolar solvents and the preference decreases as the solvent polarity increases giving almost 100% *syn* dimers and less than 1% *anti* dimer from methanol solution. The overall yields of dimers also increase with the solvent polarity. From sensitization and quenching experiments, *anti* dimer was found to be formed *via* excited singlet state while *syn* dimers were formed *via* both excited singlet and triplet states.

Introduction

5,7-Dimethoxycoumarin (DMC) has only one photochemical functional group (pyrone double bond), but it shows similar photobiological activities as psoralens unlike other coumarin derivatives.[1,2]

The fluorescence quantum yield of DMC ($\Phi_f = 0.65$ at room temperature in ethanol) is higher than that of psoralen and the ratio of phosphorescence to fluorescence quantum yield ($\Phi_p/\Phi_f = 0.05$) is much lower than those of psoralens indicating that the intersystem crossing quantum yield of DMC is lower than those of psoralens.[3] These differences are due to a significant energy gap between the low lying singlet (π, π^*) and (n, π^*) states in DMC.[4]

DMC forms a C_4-cycloadduct with 2,3-dimethyl-2-butene[5] and several photocycloadducts with thymine and/or thymidine.[6,7] However, near-UV photolysis of DMC and adenosine in a dry film state leads to new types of photoadducts involving sugar moiety of the nucleoside and pyrone ring of DMC. Detailed structural assignments by various NMR techniques indicated DMC photobinding to adenosine through covalent bond formation between carbon C_3 or C_4 of DMC and the ribose ring of the adenosine at 5'-carbon.[8,9]

Photodimerization of DMC has been reported to proceed through [2+2] cycloaddition of 3,4-double bond to form a *syn* head-to-tail dimer on direct irradiation in acetonitrile or benzene *via* singlet excited state with quantum yield of 0.068 in acetonitrile which is much bigger than that of coumarin.[10] In the presence of triplet sensitizers such as benzophenone, an *anti* dimer with the quantum yield greater than 0.08 is obtained.

Since this reaction was studied as a model reaction for psoralens it is necessary to identify all the photoproducts formed to understand the photoreaction of DMC thoroughly. In previous studies, however, only the major dimers were isolated and characterized. We report in this paper on detailed studies on the photodimerization of DMC in organic solvents as well as the triplet sensitization and quenching studies.

Experimental

Chemicals

5,7-Dimethoxycoumarin (DMC) was purchased from the Aldrich Chemical Co., Milwaukee, WI, USA, and recrystallized from absolute ethanol twice. Benzophenone and azulene were (Aldrich Chemical Co.) used after recrystallization.

Chloroform-d, benzene-d_6 and a shift reagent, 2,2-dimethyl-6,6,7,7,8,8-heptafluoro-3,5-octadione europium(III) derivative (Resolve-Al EuFOD), were purchased from the Aldrich Chemical Co. All the other chemicals and solvents used were reagent or HPLC grade.

Irradiation and Analysis

Acetonitrile solution of DMC (1 mM) was deaerated by bubbling with a stream of nitrogen gas for *ca.* 10 min and irradiated in a Pyrex reactor for 48 hours. Irradiations were carried out in a Rayonet Photochemical Reactor RPR-208 equipped with RUL-350 nm fluorescent lamps. After irradiation, the photolysis mixture was evaporated under reduced pressure and the mixture was dissolved in dichloromethane and subject to high performance liquid chromatography on a Waters Associates Model 244 liquid chromatograph equipped with Model 6000 A solvent delivery system, Model 440 UV absorbance detector (254 nm), and Model U6K universal injector. The columns were Whatman Partisil PXS 10/25 for analysis and Waters Associates μ-Porasil (10 nm×25 cm) for preparative separation. The dichloromethane solutions of the products in quartz cuvettes were irradiated at 254 nm from a mineral light for various periods of time monitoring the progress of photosplitting by UV absorption at the absorption maximum of DMC.

Compound I. UV (*n*-Hexane): λ_{max} 285 nm; MS: m/e 412 (M⁺), 206 (monomer, 1/2 M⁺), 178 (1/2 M⁺-CO), 163 (1/2 M⁺-CO-CH₃); ¹H-NMR (CDCl₃, 300 MHz, δ, ppm): 6.01 (2H, d, J=2.3 Hz, H6 or H8), 5.97 (2H, d, J=2.3 Hz, H6 or H8), 3.39−3.55 (4H, m, cyclobutyl protons), 3.40 (6H, s, methoxy protons) 3.24 (6H, s, methoxy protons), IR (KBr): 3303, 3271, 2953, 1763, 1621, 1592, 1467 cm⁻¹.

Compound II. UV (*n*-Hexane): λ_{max} 285 nm; MS: m/e 412 (M⁺), 206 (monomer, 1/2 M⁺), 178 (1/2 M⁺ -CO), 163 (1/2 M⁺-CO-CH₃); ¹H-NMR (CDCl₃, 300 MHz, δ, ppm): 6.01 (2H, d, J=2.3 Hz, H6 or H8), 5.99 (2H, d, J=2.3 Hz, H6 or H8), 4.08 (2H, m, cyclobutyl protons), 3.76 (2H, m, cyclobutyl protons), 3.61 (6H, s, methoxy protons) 3.47 (6H, s, methoxy protons), IR (KBr): 3296, 3267, 2950, 1757, 1613,

1589, 1467 cm^{-1}.

Compound III. UV (*n*-Hexane): λ_{max} 283 nm; MS: m/e 412 (M$^+$), 206 (monomer, 1/2 M$^+$), 178 (1/2 M$^+$-CO), 163 (1/2 M$^+$-CO-CH$_3$); ^{1}H-MMR(CDCl$_3$, 300 MHz, δ, ppm): 6.16 (2H, d, J=2.3 Hz, H6), 5.81 (2H, d, J=2.3 Hz, H8), 4.33 (2H, t, J=8.6 Hz, cyclobutyl protons), 3.99 (2H, t, J=8.6 Hz, cyclobutyl protons), 3.76 (6H, s, methoxy protons), 3.69 (6H, s, methoxy protons) IR (KBr): 3299, 3271, 2943, 1759, 1631 1591, 1467 cm^{-1}.

Spectroscopic Measurements

A Cary 17 and Shimadzu UV-3100S spectrophotometer were used for the measurements of UV absorption spectra. ^{1}H-NMR analyses were carried out in chloroform-d and benzene-d$_6$ on a Bruker AM-300 spectrometer, using tetramethylsilane internal standard and EuFOD shift reagent.

Solvent Effects

Sample solutions (3 ml) in Pyrex ampoules were degassed by three freeze-pump-thaw cycles with cooling in liquid nitrogen and then sealed. These samples were irradiated in a merry-go-round apparatus with Hanovia 450 W medium pressure mercury arc lamp (Type 679A36). To isolate mercury emission line of 366 nm, CS#0-52 and #7-37 Corning glass filters were used. Relative yields of dimers were measured by HPLC on a Whatman partisil PXS 10/25 column using dichloromethane and tetrahydrofuran (100/1, v/v) as eluents with a flow rate 1.2 ml/min and a UV absorption at 254 nm.

Quenching and Triplet Sensitization

A series of solutions (3 ml) of 2 mM DMC in dichloromethane and varying azulene concentration (0-3 mM) were put into Pyrex ampoules, degassed and sealed, and irradiated by the same method used in the measurement of solvent effects. Azulene absorbed less than 2% of the light. The relative yields of three dimers in each sample were determined to compare with that of the reference sample containing no azulene. Solutions (3 ml) containing DMC (0.025 M) and benzophenone (0.15 M) were put into Pyrex ampoules, degassed, sealed and irradiated at 366 nm. Solvents used were dichloromethane and acetonitrile as a nonpolar and a polar solvent, respectively. The same method was used for the measurement of relative yields as the quenching studies.

Results and Discussion

Figure 1 shows a typical HPLC elution chromatogram of an irradiated DMC solution in acetonitrile. There are three photoadducts and are labelled I, II, and III, respectively. The UV absorption spectra of the photoproducts show a large blue shift of λ_{max} (Figure 2), from 325 nm in DMC to near 285 nm. This is in conform with the change of conjugated enone chromophore to a simple substituted benzene chromophore due to the saturation of the pyrone double bond suggesting that the reaction occurs at C$_3$-C$_4$ double bond. Infrared spectra of the three photoproducts are very similar. They show a shift of the carbonyl stretching band from 1710 cm^{-1} in DMC to 1760 cm^{-1}, and disappearance of the medium intensity band at 1595 cm^{-1}. These can be attributed to the saturation of the double bond in pyrone moiety of DMC. They show also some symmetric and asymmetric stretching bands of saturated C-H in place of the alkenyl C-H stretching band at 3050 cm^{-1} in DMC supporting the reacton to occur
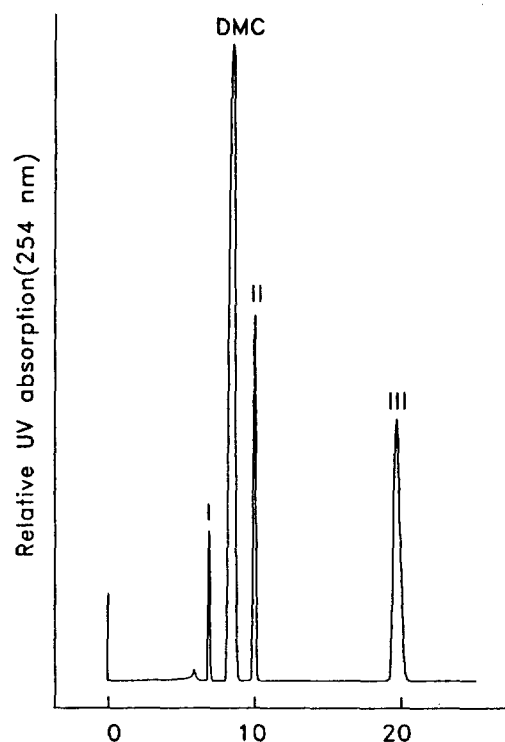

Figure 1. HPLC elution profile of the photolysis mixture of DMC, Column: Partisil PXS 10/25, Eluent: MC/THF=100/1 (v/v).
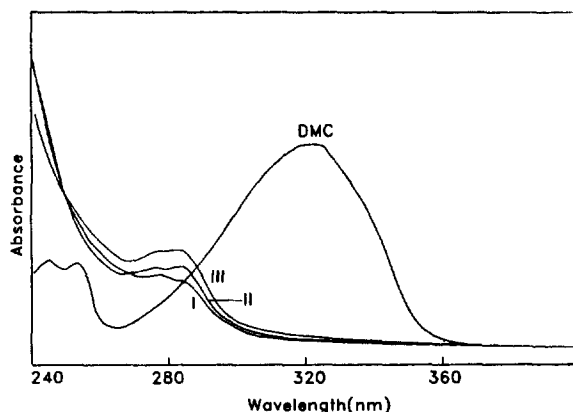

Figure 2. UV absorption spectra of DMC and its dimers.

at 3,4-double bond of DMC.

The EI mass spectra of photoproducts show a molecular ion peak at m/z 412 for all the photoadducts supporting the products to be dimers of DMC. The fragmentation patterns for the three photoproducts are very similar and show a mojor peak at m/z 206 (base peak) corresponding to DMC.

The dichloromethane solution of the photoproduct was irradiated at 254 nm in a quartz cuvette and the photosplitting was monitored by means of UV absorption measurements (Figure 3). The spectra show gradual increase of the absorption band at 325 nm, typical of unsaturated lactone ring, on extending the irradiation time. After 10 minutes of irradiation the spectrum is practically superimposable on that of the parent compound, DMC. In addition, these photosplittings give only DMC. The mass spectra as well as the photo-
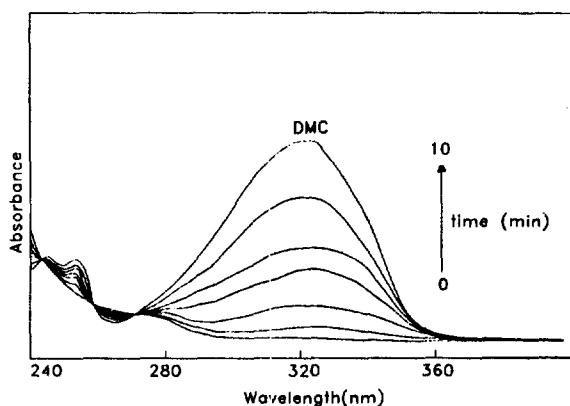
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Figure 3. Photosplitting of DMC dimer(II) on irradiation at 254 nm.

Table 1. Coupling Constants for Cyclobutyl Protons (Hz)

-	$J_{1,2}$	$J_{1,3}=J_{2,4}$	$J_{1,4}=J_{2,3}$	$J_{3,4}$
anti-HH	5.5	6.6	−1.3	4.1
syn-HH	9.5	8.6	1.2	7.3
syn-HT	8.3	0	8.3	8.3

Figure 4. NMR spectra of photoproduct I in $CDCl_3/C_6D_6$.

Figure 5. NMR spectra of photoproduct II in $CDCl_3/C_6D_6$.

splitting of I, II, and III yielding DMC suggest that these photoproducts are C_4-cyclodimers of DMC.

The stereochemical structure of the dimers can be assigned on the basis of NMR analysis. The resonance peaks of 3- and 4-protons undergo upfield shift supporting the cycloaddition to occur on the pyrone double bond. New absorption signals were observed in a spectral region typical for cyclobutyl protons in coumarin dimers. The pattern of the cyclobutyl proton signals in I and II is typical of AA'BB' system, which requires either a plane or a twofold axis of symmetry in the molecule. Vicinal coupling constants in cyclobutane system vary in a wide range so that some overlap between them occurs and have been found to be sensitive to substituents and strain effects.[11] On the contrary, both experimental[12,13] and theoretical[12] evidences have been provided showing that the *cis* diagonal couplings (^4J) are positive, while negative in cyclobutane systems. The $^3J_{2,3}$ coupling constants in the dimers were obtained from the analysis of cyclobutane AA'BB' subspectra[14] (Table 1).

The *anti* configuration of the dimer I was proven by [1] H-NMR spectra. In $CDCl_3/C_6D_6$ (1 : 1, v/v), aromatic protons H_6 and H_8 absorbed at 5.97 and 6.01 ppm, respectively. Cyclobutyl protons were observed at 3.39-33.5 ppm which are considerably higher than any of the other cyclobutyl protons. This shielding effect is attributed to the diamagnetic anisotropy of a C=O group in front of the cyclobutyl protons strongly supporting the *anti* configuration. The cyclobutyl protons in dimer II exhibited a pair of symmetric multiplets which are identical with the *syn* head-to-head dimer of other coumarin derivatives. Aromatic protons in $CDCl_3$ with 2 drops of C_6D_6 absorbed at 5.98 and 6.01 ppm and the absence of a selectively shielded aromatic proton H_8 suggests a head-to-head structure. The H_8 in dimer III is very much upfield shifted and H_6 is slightly upfield shifted in $CDCl_3$. This strong shielding effect on H_8 is caused by diamagnetic aniso-
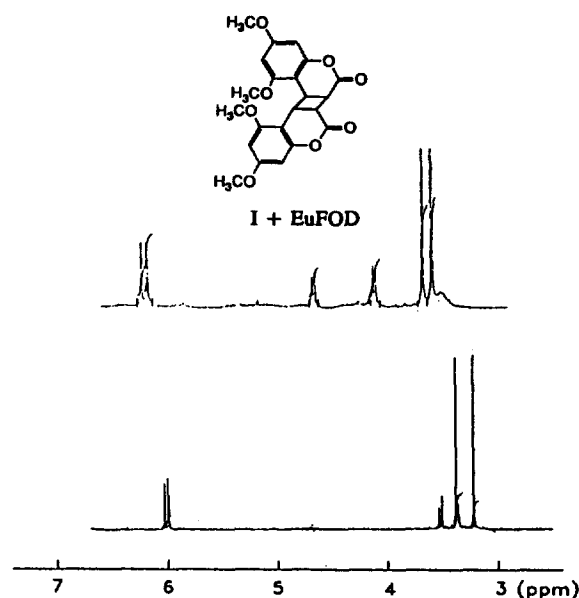
tropy of a phenyl ring situated in front of the proton which is possible only in the *syn* head-to-tail configuration. This large upfield shift of H_8 is characteristic of *syn* head-to-tail dimer. The cyclobutyl protons showed a pair of symmetric triplets which is possible only in the *syn* head-to-tail dimer.
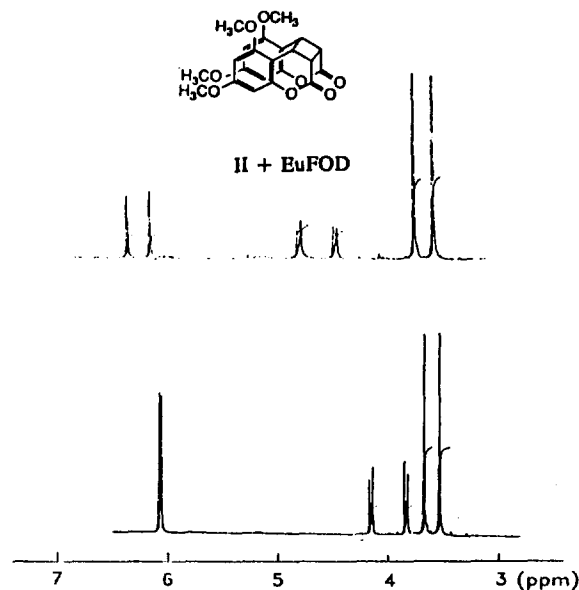
Strong evidences supporting these interpretations were obtained from examining the ^{1}H-NMR spectra of the three dimers in the presence of EuFOD shift reagent.[15] In I and II, the two methoxy protons undergo little or small downfield shift. On the contrary, one of the two methoxy protons in III undergo a large downfield shift upon adding EuFOD indicating that these methoxy protons are nearest to the complexed C=O, which is possible only in the head-to-tail configuration. Almost no shift was observed for aromatic protons in I, while a significant shift of H_6 and H_8 protons was observed in II and III. The extent of two aromatic proton shifts
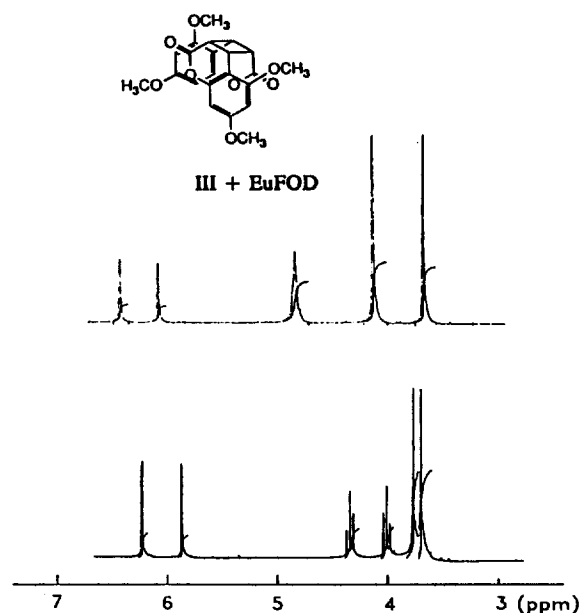
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III + EuFOD

Figure 6. NMR spectra of photoproduct III in $CDCl_3/C_6D_6$.

Table 2. Relative Yields of Dimers in the Direct and Sensitized Reaction

	Benzene		CH₃CN	
	Direct	Sensitized	Direct	Sensitized
anti-HH	0.43	1.34	0.20	1.09
syn-HH	0.09	0.09	0.90	0.30
syn-HT	0.59	—	1.00*	0.12

*Compared to *syn*-HT in acetonitrile.

were different upon adding EuFOD suggesting that one of the two aromatic protons is nearer to the complexed C=O, which is possible only in *syn* head-to-tail configuration.

anti-HH(I)   *syn*-HH(II)   *syn*-HT(III)
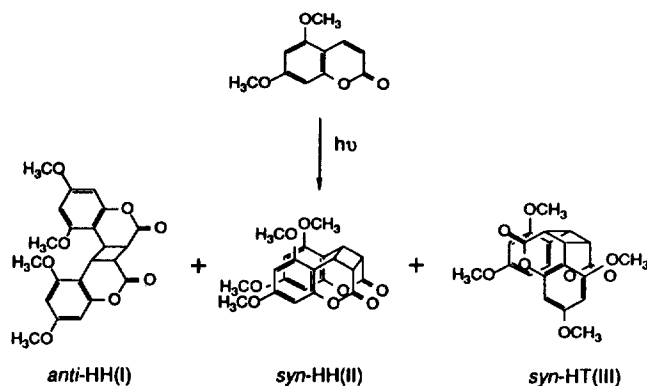
Sensitization provides remarkable selectivity in photodimerization reactions.[16] In triplet sensitized reactions, the sensitizer absorbs a major fraction of the exciting light although DMC also absorbs a small fraction of the light. However, the singlet excited state of DMC formed by this direct excitation should be efficiently quenched by benzophenone before it can collide with other DMC to form a C_4-cyclodimer.[17] The results of photodimerization of DMC in the presence
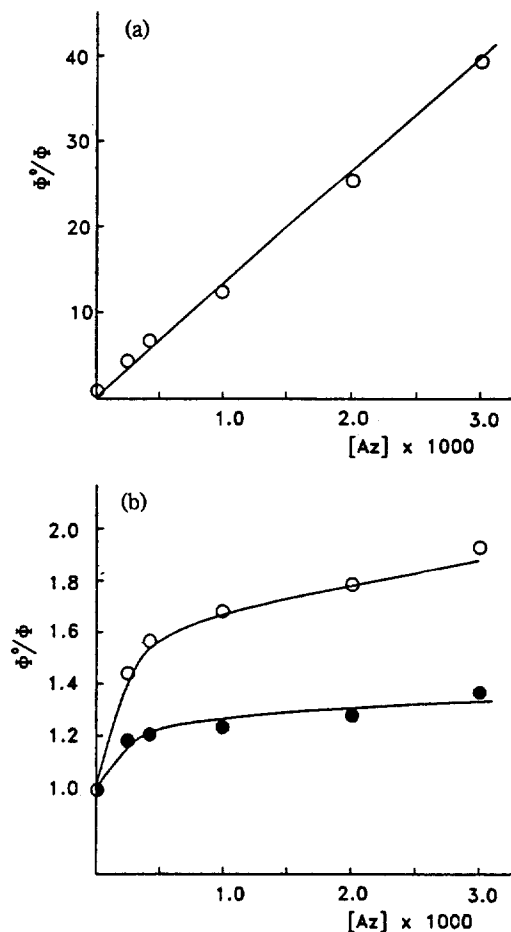
Figure 7. Stern-Volmer plots for the formation of three dimers. (a): *anti* head-to-head, (b): *syn* head-to-head (○) and *syn* head-to-tail (●).

of benzophenone as a triplet sensitizer are shown in Table 2. Benzene and acetonitrile were used as a nonpolar and a polar solvent, respectively. The sensitized reaction in benzene yielded only *anti* head-to-head dimer, while in acetonitrile *syn* dimers as well as *anti* dimer as major products were observed. The yield of the *anti* dimer increased and those of *syn* dimers decreased in both solvents upon sensitization indicating that the *anti* dimer is formed *via* a triplet excited state.

In order to verify the multiplicity and the lifetime of the excited states responsible for the photodimerization, quenching of the photoreaction of DMC was carried out with azulene. The triplet energy of azulene (30.9 kcal) is lower than that of DMC (60.6 kcal).[3]

If photodimerization occurs *via* only one excited state, the singlet or triplet states, the Stern-Volmer plot should be linear.

$$\Phi_0/\Phi = 1 + k_q \tau [Q]$$

where k_q is the quenching rate constant, τ is the lifetime of quenched species, Φ_0 and Φ are the photodimerization quantum yields in the absence and presence of quencher, respectively. A good linear Stern-Volmer plot and a large Stern-Volmer constant ($k_q\tau = 12000$) for *anti* head-to-head dimer formation (Figure 7) strongly suggest the formation of

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Table 3. Relative Yields of Dimers in Various Solvents

	anti-HH	syn-HH	syn-HT
Benzene	0.43	0.09	0.59
CH$_2$Cl$_2$	0.34	0.25	0.49
CH$_3$CN	0.20	0.90	1.00*
EtOH	0.19	0.62	1.77
MeOH	—	0.51	2.28

*Compared to syn-HT in CH$_3$CN.

anti head-to-head dimer to proceed via a triplet excited state only, which is in full agreement with the results of the triplet sensitized reaction. On the other hand, the syn head-to-head and syn head-to-tail dimers show downward curved Stern-Volmer plots suggesting the dimerization reaction to proceed via both singlet and triplet excited states. The same type of quenching curves for the photodimerization of furocoumarin derivatives have already been reported.[18]

The solvent effects on the photodimerization of organic compounds were extensively studied.[19] Irradiation of DMC in various solvents were carried out and the results are summarized in Table 3. The relative yields of dimer formations were compared to syn HT dimer obtained in acetonitrile. Irrespective of the configuration of DMC dimers, the extinction coefficients are assumed to be the same. It is evident that overall yield of dimer increases with increasing solvent polarity. Hammond et al.[17] has reported thes phenomena to occur because of the self-quenching and the rate of dimerization relative to self-quenching was faster in polar solvents than in nonpolar solvents. It is clear from these data that the preference of the anti dimer I in nonpolar solvents is decreased in highly polar solvents. The trend is completely reversed in a protic solvent, methanol, where the formation of the syn dimers II and III is now favored. Selectivity and enhanced reactivity for the formation of syn dimers are attributed to the polar environment in which DMC undergoes dimerization.

Conclusion

DMC undergoes photodimerization under 350 nm irradiation. Three different dimeric isomers were isolated and characterized. The configuration of the dimers is found to be anti head-to-head, syn head-to-head and syn head-to-tail, respectively. The number and ratio of dimers formed are solvent dependent. The anti head-to-head dimer is favored in nonpolar solvents, while syn dimers are major products in polar solvents such as methanol which yields almost 100% syn dimers with less than 1% anti dimer. The anti head-to-head dimer was formed via triplet excited state, while the syn dimers were formed via both triplet and singlet excited states.

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