PHOTOCYCLIZATION REACTION OF 5-STYRYL-1,3-DIMETHYL-URACIL

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(Received April 1, 1985; in revised form July 8, 1985)

Summary

The photolysis of a dilute acetonitrile solution of 5(*Z*)-styryl-1,3-dimethyluracil in the presence of oxygen gives the dehydrocyclized product in 26.7% yield. Adding benzophenone to the 5(*E*)-styryl-1,3-dimethyluracil solution improved the yield of the photocyclization owing to the efficient $E \rightarrow Z$ photoisomerization due to benzophenone sensitization. Studies on the salt, sensitization and quenching effects on the photocyclization of the compound indicate that the photocyclization occurs from the lowest excited singlet $^1(\pi, \pi^*)$ state of 5(*Z*)-styryl-1,3-dimethyluracil.

1. Introduction

The mechanistic aspects and synthetic applications of the photocyclization of stilbene and its analogues have been extensively studied for a long time [1]. The photolysis of stilbene in the presence of oxidants such as oxygen and iodine leads to the formation of *trans-4a,4b*-dihydrophenanthrene by conrotatory ring closure of *Z*-stilbene in the lowest excited $^1(\pi, \pi^*)$ state, followed by oxidation to phenanthrene [2 - 4].

The dehydrophotocyclization reaction of stilbene analogues has great potential in the synthesis of polyhomocyclic aromatic compounds [5] such as chrysenes [6] and helicenes [7] and has been extended to its heterocyclic analogues [8] with considerable success. Electron densities at the reactive positions, free valence indices and electronic overlap populations have all been used quite successfully to predict the photocyclization mode of diarylethylenes [1, 9].

Owing to the presence of the n, π^* states introduced by the heteroatom, the heteroaromatics exhibit photophysical and photochemical behaviour quite different from that of ordinary stilbenes containing only π, π^* excited states [10]. In general, azaphenanthrenes are relatively in-

accessible by classical methods. Loader and Timmons [11] and Perkampus and Kassebeer [12] reported the synthesis of azaphenanthrenes by the photocyclization of styrylpyridines and styryldiazines respectively. They found that azastilbenes photocyclized less efficiently than stilbene since the electron-withdrawing heteroatom reduces the photoreactivity and its reactive state should be the lowest $^1(\pi, \pi^*)$ state [13].

In our previous papers [14] we discussed the interesting result that the photocyclization of 1,2-bispyrazylethylene occurs through the $^1(n, \pi^*)$ state in contrast to that of ordinary stilbenes which occurs through the $^1(\pi, \pi^*)$ state.

Pyrimidine nucleosides bearing substituents in the 5-position of the heterocyclic ring are biologically significant compounds frequently occurring in nature [15]. With respect to the effect of the replacement of one phenyl ring in stilbene with a pyrimidine base, we studied the mechanism of the photocyclization of 5-styryl-1,3-dimethyluracil (5-SDU), a C-5 modified pyrimidine base, to a fused pyrimidine base under different conditions.

2. Experimental details

2.1. Materials

5(E)- and 5(Z)-SDU were prepared by following the literature method [16] and were recrystallized from n-octanol and ethanol respectively. Benzophenone (Aldrich) was recrystallized three times from cyclohexane. Azulene (Aldrich) was sublimed under vacuum. Sodium acetate (Wako) was recrystallized twice from water–ethanol (1:4, by volume). Commercially available styrene, uracil, mercuric acetate, trimethylphosphate (all Aldrich) and palladium chloride (Inuisho) were used without further purification. Extra pure solvents were used as received or after purification by distillation or by using standard methods [17].

2.2. Instruments

Nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60A spectrometer. IR spectra were obtained using a Perkin–Elmer Model 267 spectrophotometer in KBr pellets. UV–visible spectra were recorded with a Cary 17 spectrophotometer. Mass spectra were determined at 25 eV with a Hewlett–Packard 5985 A gas chromatography–mass spectroscopy (GC–MS) system by the electron impact method. Elemental analyses were carried out with an F & M Scientific Corporation C.H.N. Analyzer Model 180. Fluorescence spectra were recorded using an Aminco–Bowman spectrophotofluorometer with an Aminco $X–Y$ recorder at room temperature. Liquid chromatograms were recorded using a Waters Associate Model 244 High Performance Liquid Chromatograph equipped with a Model 6000A solvent delivery system, a Model 440 absorbance detector (254 nm and 280 nm) and a Model U 6K universal injector.

2.3. Photocyclization of 5-styryl-1,3-dimethyluracil

5(E)-SDU and benzophenone were dissolved in acetonitrile to give concentrations of 10^{-3} M and 10^{-2} M respectively, and the solution (in a Pyrex vessel) was irradiated in a preparative RPR 208 Rayonet Photochemical Reactor with 350 nm UV light for 10 h with stirring in air. Benzophenone, which is a triplet sensitizer, did not absorb all the light under these conditions (the fraction of photons absorbed by benzophenone was about 16%) and was used in order to increase the concentration of the Z isomer. $([Z]/[E])_{pss}$ (pss, photostationary state) for the benzophenone-sensitized photoisomerization of 5-SDU in chloroform is about 0.94. The photoisomerization of 5(E)-SDU to 5(Z)-SDU increases markedly on sensitization with benzophenone [20]. After irradiation, the solvent was evaporated off with a rotary evaporator. The cyclized product was separated by means of silica-gel column chromatography using ethyl acetate–cyclohexane–chloroform (1:1:2, by volume) as the eluent, and was then recrystallized from chloroform–ethyl ether (isolated yield, 21.48%; yield measured by high performance liquid chromatography, 26.7%; melting point, 172.5 - 175.5 °C); mass spectrum m/e 240 (molecular ion), 225 ($M^{\ddagger} - CH_3$), 212 ($M^{\ddagger} - CO$), 183 ($M^{\ddagger} - C_2H_3ON$), 154 ($M^{\ddagger} - C_3H_4O_2N$), 128 ($M^{\ddagger} - C_4H_4O_2N_2$); UV(CHCl$_3$) λ_{max}: 360, 345, 310 ($\epsilon \approx 10\,000$), 298 and 288 nm; ^{1}H NMR-(CDCl$_3$) δ: 7.6 (m, 6H), 4.0, 3.6 (s, 3H, N—CH$_3$) ppm; IR spectra show aromatic ν_{C-H} bands around 3030 cm^{-1} and the out-of-plane δ_{C-H} bands of E- and Z-olefins at 925 and 725 cm^{-1} disappeared; calculated analysis for $C_{14}H_{12}O_2N_2$: C 69.98%, H 5.03% and N 11.66%; found analysis: C 69.76%, H 5.01% and N 11.44%.

2.4. Quantum yield measurements

10^{-3} M solutions (3 ml) of 5(E)- or 5(Z)-SDU with or without sensitizer, quencher and alkaline salt in Pyrex tubes were irradiated in a merry-go-round apparatus using a 450 W Hanovia medium pressure mercury arc lamp (type 697A36). To isolate the 366 nm mercury emission line, CS 0-52 and 7-37 Corning glass filters were used. A CS 7-54 Corning glass filter and a solution filter of 2.5×10^{-3} M potassium dichromate in 1% sodium carbonate aqueous solution were used to obtain monochromatic light of wavelength 313 nm. Light intensities were measured by means of ferrioxalate actinometry [18] and the quantitative analysis was carried out with a high performance liquid chromatograph. Reactions were carried out to less than 5% conversion to avoid competition of the back and the parallel reactions.

3. Results and discussion

Irradiation of a dilute solution of 5-SDU produces the photocyclodehydrogenation product. The structure of the product was determined by a variety of spectral and elemental analyses.

As shown in Table 1, 5-SDU has low Φ_f and $\Phi_{E \to Z}$ and a short τ_f compared with stilbene, owing to the presence of the n, π^* excited states just

TABLE 1

Quantum yields and lifetimes for fluorescence, chemical and quantum yields for photo-cyclization and quantum yields for photoisomerization of 5-SDU, stilbene, styryl-pyridines and 1,2-bispyrazylethylene

Compound	Φ_f	τ_f (ns)	Chemical yield[a]	Φ_{cycl}[b]	$\Phi_{E \rightarrow Z}$
Stilbene	0.036	0.09	82%[c]	0.075	0.43
2-Styrylpyridine[d]	0.0008	0.007	66%	0.014	0.25
3-Styrylpyridine[d]	0.075	0.19	35%	0.081	0.56
4-Styrylpyridine[d]	0.0016	0.008	21%	0.015	0.37
1,2-Bispyrazylethylene[e]	0.003	0.28	90%	0.051	0.086
5-SDU	0.023[f]	0.048[f]	27%[g]	0.045[h]	0.049[f]

[a]From ref. 11.
[b]From ref. 19.
[c]From ref. 2.
[d]See refs. 10 and 20.
[e]See refs. 14 and 21.
[f]From ref. 22.
[g]In acetonitrile from the E isomer.
[h]In benzene at 313 nm from the Z isomer (limits of error $\pm 10\%$).

TABLE 2

Effect of benzophenone on the photocyclization reaction of 5-SDU in benzene at 313 nm

[Benzophenone] (M)	$\Phi_{E \rightarrow cycl}$[a]	$\Phi_{Z \rightarrow cycl}$[b]
0	1.54×10^{-3}	4.46×10^{-2}
0.01	2.34×10^{-3}	3.29×10^{-2}
0.02	2.63×10^{-3}	2.53×10^{-2}
0.05	2.19×10^{-3}	1.35×10^{-2}
0.10	1.76×10^{-3}	0.99×10^{-2}

[a]$\Phi_{E \rightarrow cycl}$ is the quantum yield of photocyclization of 5(E)-SDU.
[b]$\Phi_{Z \rightarrow cycl}$ is the quantum yield of photocyclization of 5(Z)-SDU.

as in other azastilbenes, and yields small Φ_{cycl} because of the fast depopulation of the excited singlet state from which cyclization occurs through the efficient radiationless processes. Azastilbenes, particularly the ortho and para isomers, show very low Φ_{cycl} because the degradation of the excitation energy through low-lying n, π^* states is efficient and the electron-withdrawing nitrogen atom reduces the photoreactivity [11].

Table 2 shows that the quantum yield of photocyclization of 5(Z)-SDU at 313 nm (4.46×10^{-2} M) is much greater than that of 5(E)-SDU (1.54×10^{-3} M). The results indicate that the photocyclization reaction occurs from the excited state of the Z isomer formed by the isomerization of the E isomer, as in the case of stilbene.

In some azastilbenes, iodine is not suitable as an oxidant because it complexes strongly with the starting material and enhances intersystem

crossing and/or reacts with the polymer formed in the reaction, effectively screening the solution from the light [11, 14]. In the photocyclization reaction of 5-SDU, oxygen was used to oxidize the dihydro intermediate in order to avoid the possible inhibition by iodine. The photocyclization does not occur in the absence of oxygen, *i.e.* in thoroughly degassed solutions of 5(*E*)- and 5(*Z*)-SDU. This suggests that the dehydrophotocyclization proceeds through a dihydro intermediate (I, Scheme 1); this is analogous to the dehydrophotocyclization of stilbene [2]. The trans configuration is suggested for the two tertiary hydrogens in I, by analogy with the trans stereochemistry of the related dihydrophenanthrenes [2].
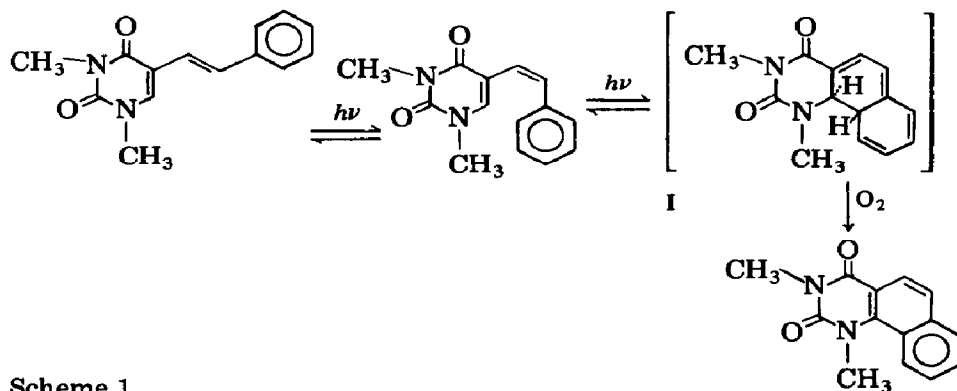
Scheme 1.

3.1. Benzophenone effect

The effect of benzophenone on the photocyclization reaction of 5-SDU in benzene is given in Table 2.

There is a lot of evidence that the photocyclization to the dihydrophenanthrene intermediate occurs via the excited singlet state of stilbene. For example, the cyclizations are not inhibited by the presence of relatively large concentrations of dissolved oxygen [23] and no dihydrophenanthrene is detected when stilbene triplets are produced by energy transfer from a wide variety of triplet state photosensitizers [24]. Furthermore, stilbene analogues containing atoms or groups which increase the intersystem crossing efficiently do not photocyclize readily [20].

From our previous studies [22], the triplet energy of 5(*E*)-SDU was estimated to lie between 41.8 and 47 kcal mol^{-1}. Therefore, benzophenone (E_T = 69 kcal mol^{-1}) can transfer its triplet energy to 5(*E*)-SDU with a diffusion-controlled rate.

As the concentration of benzophenone increases, the quantum yield $\Phi_{Z \to \text{cycl}}$ of photocyclization of 5(*Z*)-SDU decreases markedly, indicating that the photocyclization reaction occurs from the excited singlet state as in the case of stilbene. No $Z \to E$ photoisomerization is observed in the presence of oxygen while the photocyclization product is not detected when the solution is thoroughly degassed. The quantum yield $\Phi_{E \to \text{cycl}}$ of photocyclization of 5(*E*)-SDU increases up to a certain concentration of benzo-

phenone and then decreases (Table 2). With the low concentration of benzophenone, *i.e.* when benzophenone absorbs only a small portion of the exciting light, the quantum yield of photocyclization increases as the population of 5(Z)-SDU from which the cyclization occurs increases owing to the efficient photoisomerization [22] from 5(E)-SDU in the triplet manifold ($\Phi_{E \rightarrow Z}$ is 0.049 and 0.39 for direct photoisomerization and benzophenone-sensitized photoisomerization respectively in the degassed chloroform solvent). When the concentration of benzophenone becomes very high, *i.e.* when the exciting light is mostly absorbed by benzophenone, the increased triplet population of 5(Z)-SDU that results from the triplet sensitization of benzophenone leads to the decrease in the quantum yield of the photocyclization which occurs from the lowest excited singlet state.

3.2. Azulene effect

Azulene quenching studies are a useful tool for investigating the multiplicity of the reactive states.

Using the steady state assumption for the excited species, the following Stern–Volmer equation can be written:

$$\frac{\Phi^0_{cycl}}{\Phi_{cycl}} = 1 + k_q \tau [Az]$$

where Φ^0_{cycl} is the quantum yield of photocyclization in the absence of azulene, Φ_{cycl} is the quantum yield of photocyclization in the presence of azulene, k_q is the diffusion-controlled quenching constant, τ is the lifetime of the quenched species and [Az] is the concentration of azulene.

In the photocyclization reaction of stilbene, the decay of the 450 nm absorption of dihydrophenanthrene in the dark with azulene is initially more rapid than in experiments without azulene but azulene does not efficiently prevent the formation of dihydrophenanthrene [24]. This result again indicates that the photocyclization reaction is probably a reaction at the first excited singlet level of the stilbene molecules.

Azulene quenching for photocyclization of 5(Z)-SDU in benzene at 313 nm is shown in Table 3. In the Stern–Volmer plots for azulene quench-

TABLE 3

Azulene quenching in the photocyclization of 5(Z)-SDU in benzene at 313 nm

[Azulene]	$\Phi_{Z \rightarrow cycl}$	$\Phi^0_{cycl}/\Phi_{cycl}$[a]
0	4.55×10^{-2}	1
1.0×10^{-3}	3.55×10^{-2}	1.28
2.0×10^{-3}	2.90×10^{-2}	1.57
3.0×10^{-3}	2.47×10^{-2}	1.84
5.0×10^{-3}	1.90×10^{-2}	2.39

[a]Φ^0_{cycl} is the quantum yield of photocyclization in the absence of azulene.

ing of the $E \rightarrow Z$ photoisomerization of 5(E)-SDU in chloroform [22] the slope $k_q\tau$ for the direct photoisomerization, which is believed to occur via the lowest excited singlet state, is 270 M^{-1} and the slope for the benzophenone-sensitized photoisomerization through the triplet manifold is 1120 M^{-1}. In the azulene quenching study for photocyclization of 5(Z)-SDU in benzene, $k_q\tau$ is 278 M^{-1}, i.e. similar to that of the direct photoisomerization of 5(E)-SDU in chloroform. Therefore, the azulene quenching studies are consistent with a singlet mechanism for the photocyclization.

3.3. Salt effect

Heteroaromatics, containing n, π^* excited states introduced by the heteroatom, generally show weak fluorescence due to competitive radiationless processes such as intersystem crossing and internal conversion.

An alkali-metal salt changes the relative position of the excited energy levels by raising the energy level of the $^1(n, \pi^*)$ state.

In the case of retinal [25], fluorescence is enhanced by the added alkali-metal salt because the lowest excited state is converted from the $^1(n, \pi^*)$ state to the fluorescing $^1(\pi, \pi^*)$ state because of the increase in the energy of the $^1(n, \pi^*)$ state resulting from complexation of the lone pair electron with the alkali-metal cation. Without the salt, fluorescence from the π, π^* state competes with internal conversion to the lowest excited n, π^* state, resulting in weak fluorescence.

The quantum yields of photocyclization of 5(Z)-SDU and the intensity of fluorescence of 5(E)-SDU are little affected by changing the concentration of the salt. This result differs from that for 1,2-bispyrazylethylene which gives an enhanced intensity of fluorescence [21] and a decreased quantum yield of photocyclization [14] in the presence of sodium acetate. Since the energy of the $^1(n, \pi^*)$ state of 1,2-bispyrazylethylene lies very close to the energy level of the $^1(\pi, \pi^*)$ state and the salt raises the energy of the lowest $^1(n, \pi^*)$ state, the intensity of fluorescence of 1,2-bispyrazylethylene increases and the quantum yield of photocyclization decreases.

Table 1 shows the very low Φ_f and the very short τ_f of 5-SDU. Therefore, it is suggested that the $^1(n, \pi^*)$ state of 5-SDU should contribute significantly to the lowest excited singlet state. However, the salt effects suggest that the energy of the $^1(n, \pi^*)$ level is not very close to the energy of the $^1(\pi, \pi^*)$ level. In spite of the raising of the energy of the $^1(n, \pi^*)$ level on salt addition, the $^1(\pi, \pi^*)$ state from which the fluorescence and photocyclization are believed to occur should be little affected, because of the considerable energy gap between the $^1(\pi, \pi^*)$ and $^1(n, \pi^*)$ states.

4. Conclusions

A dehydrocyclized product is obtained on irradiating 5-SDU in the presence of oxygen. The degassed solution yields no photocyclization product. $\Phi_{Z \rightarrow cycl}$ is much higher than $\Phi_{E \rightarrow cycl}$ and decreases on adding

benzophenone. An alkaline salt does not affect the quantum yield of photo-cyclization. The effect of azulene on the photocyclization gives a small slope in the Stern–Volmer plot, similar to that of the direct photoisomerization which is believed to proceed through the singlet manifold. These results indicate that dehydrophotocyclization occurs from the excited singlet $^1(\pi, \pi^*)$ state of 5(Z)-SDU by way of a dihydrophenanthrene derivative, but not directly from 5(E)-SDU.

Acknowledgments

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