

Direct Photoisomerization of Benzalpyrrolinone and Oxidipyrromethene Models for Bilirubin

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Direct photoisomerizations of benzalpyrrolinones yield the corresponding *E*-isomers via a singlet state, since no effect of oxygen on the reaction rates was observed. The *Z*-oxidipyrromethene was photoisomerized to the *E*-isomer in a degassed system. In an aerobic system the oxidipyrromethene **3** was photoisomerized at the early stage of the reaction and photooxygenated slowly at latter stage of the reaction. For bilirubin, other (possibly *Z*→*E*) than self-sensitizing $^1\text{O}_2$ reaction should have occurred because of the lack of a solvent effect on the self-sensitized photooxidation reaction rate at the early stage.

1. Introduction

In the related study of phototherapy of neonatal jaundice, we reported the sensitized and unsensitized photoisomerization of benzalpyrrolinones^{1,2}. The triplet of benzalpyrrolinones was involved in the sensitized photoisomerization, since oxygen inhibited the reaction¹. In present we would like to report the reaction path of direct photoisomerization of benzalpyrrolinones and oxidipyrromethenes. The behavior of bilirubin which might be related to phototherapy of neonatal jaundice, was extrapolated to be similar to that of the oxidipyrromethenes.

2. Results and Discussion

Z-Benzalpyrrolinone **Z-1**. An appropriate concentration ($3.7 \times 10^{-5} M$) of methanolic **Z-1** solution was photoisomerized² with or without oxygen by irradiation with monochromatic light (323 nm, λ_{max} of **Z-1**). The pertinent results are reported in Table 1. The triplet quencher, $^3\text{O}_2$, does not interfere with the photoisomerization. The singlet state might be involved in the direct photoisomerization of **Z-1**.

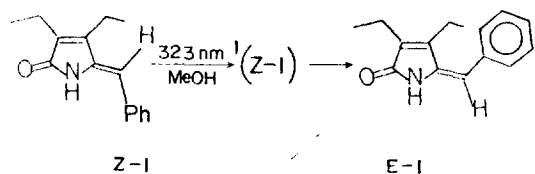
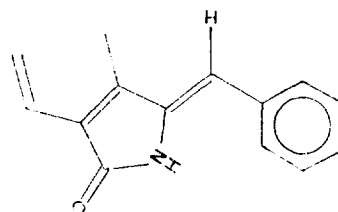


TABLE 1: Percentage Change of *Z*-Benzalpyrrolinone (**Z-1**) vs. Irradiation Time

| Irradiation time (min) | % | |
|------------------------|---------|-----------|
| | Aerobic | Anaerobic |
| 1/2 | 6.2 | 5.2 |
| 1 | 18.3 | 17.5 |
| 3 | 26.5 | 26.1 |
| 5 | 32.3 | 31.7 |
| 10 | 36.3 | 35.5 |
| Dark, 6.5 hrs | 0 | 0 |

Z-5-Benzylidene-4-methyl-3-vinyl-3-pyrrolin-2-one (**Z-2**).

The photoisomerization of **Z-2** was reported^{1,3}. When an appropriate concentration (abso. ≈ 1) of methanolic substrate solution was irradiated with monochromatic light (342 nm), photoisomerization rate was checked³. The pertinent results are reported in Table 2. Ground state oxygen, a triplet quencher, does not interfere with the reaction; presumably, the singlet state of **2** is involved in the direct photoisomerization.



Z-2

5'-Oxo-3,5-dimethyl-4,3',4'-triethyl-(1',5')-dihydro-(2,2')-dipyrromethene (**3**). When a methanolic solution (2 ml) of oxidipyrromethene **3** was irradiated at 417 nm (monochromatic light, Hg lamp) the absorption maximum peak disappeared and new absorption peaks appeared at 320 nm and 265–268 nm.

TABLE 2: Percentage Change of Vinyl-benzalpyrrolinone **Z-2** vs. Irradiation Period

| Irradiation time (min) | % | |
|------------------------|---------|-----------|
| | Aerobic | Anaerobic |
| 1/2 | 3.7 | 5.1 |
| 1 | 11.1 | 11.7 |
| 3 | 19.5 | 20.4 |
| 5 | 26.6 | 26.6 |
| 10 | 32.0 | 33.1 |
| 15 | 32.8 | 35.0 |
| dark, 12 hr | 0 | 0 |

The percentage change of **3** at 417 nm and the absorbancy at the new peaks (at 320 and 265 nm) are summarized in Table 3. At the beginning of the irradiation, the peak at 417 decreased as the peak at 265–268 nm increased; and the peak 417 was broadened and slightly distorted toward longer wavelengths. Interestingly the peak observed at 265 nm is the same as the new peak obtained by irradiation of **3** in the degassed system (see below). The reaction slowed after a given irradiation period (10–80 min) and then accelerated following longer subsequent irradiation. The new peak at 320 nm is the same as the peak of product from photooxygenation of **3**. In the dark the peak at 265 nm decreased and the peak at 310 nm was constant while the peak at 417 nm increased after photooxidation of **3** under either aerobic or anaerobic conditions.

To determine if there was any solvent effect on the reaction rate (initial reaction rate), an appropriate concentration of **3** ($2.7 \times 10^{-5} M$, 2 ml, in 1 cm path cuvette) in several solvents was irradiated with monochromatic light from tungsten lamp, 15W, or mercury lamp, 200W. The concentration was monitored at 408 nm in chloroform and 417 nm in methanol. The results are tabulated in Table 4. The initial reaction rate was faster in methanol. The reaction is a $Z \rightleftharpoons E$ photoisomerization instead of photooxidation of initial stage. If 1O_2 was involved, the reaction rate should have been faster in deuteriochloroform than in chloroform or methanol since the 1O_2 life time is longer in deuteriochloroform than in chloroform or methanol.⁴

Actually, the conclusion about the photoisomerization was derived from all of the above observation. Presumably, the

TABLE 3: The Percentage Change of Oxodipyrromethene 3 at 417 nm and the Absorbancy Differences at 320 and 265–268 nm vs. Irradiation Period

| Irradiation Time (min) | % or A ($A_{t=t}$, $A_{t=0}$) | | | |
|------------------------|------------------------------------|----------------|----------------|----------------|
| | at 417 | | 320 | 265 |
| 0 | 0 % | 0 ^c | 0 ^d | 0 ^d |
| 10 | 21.5 % | 0.20 | 0.000 | 0.085 |
| 23 | 21.5 % | 0.20 | 0.000 | 0.085 |
| 78 | 21.5 % | 0.20 | 0.000 | 0.085 |
| 143 | 30.8 % | 0.287 | 0.050 | 0.080 |
| 309 | 51.2 % | 0.477 | 0.125 | 0.065 |
| 475 | 68.3 % | 0.637 | 0.205 | 0.050 |

| | | | | |
|-------|--------|-------|-------|-------|
| 18 hr | 59.2 % | 0.552 | 0.175 | 0.000 |
| Dark | | | | |
| 24 hr | 59.2 % | 0.552 | 0.175 | 0.000 |

^aAborbancy at time t , ^baborbancy at time 0, ^cdisappearing, ^dappearing.

TABLE 4: Disappearance Percentage of Oxodipyrromethene 3 under Several Conditions vs. Irradiation Period

| Irradiation time (min) | % | | | Condition |
|------------------------|----------|----------|------|----------------|
| | $CDCl_3$ | $CHCl_3$ | MeOH | |
| 10 | 1 | 1.2 | 2.6 | Tungsten lamp |
| 60 | 2.1 | 7.6 | 11.1 | at 417 |
| 20 | 2.0 | 3.1 | 27.0 | Hg-lamp at 409 |

intermediate for the isomerization should be more polar than the ground state since the reaction rate is faster in a polar solvent (methanol) than in a less polar solvent (chloroform).

Furthermore, when a methanolic solution of **3** (2 mg/50 ml) under N_2 was irradiated with a medium pressure Hg-lamp 100W. In a pyrex tube for 20 min, only two spots could be seen on an analytical TLC after evaporation of solvent. One corresponded to the starting material and the other was the *E*-isomer. When the solution was irradiated for a longer period (1 hr), several spots were observed on analytical TLC.

To check if oxygen had any effect on the photoisomerization of **3**, a 2.8 ml solution of the dipyrromethene **3** (0.162 mg → 25 ml methanol) was irradiated at 417 nm (monochromatic light, tungsten lamp) with or without air (degassed 3 times at 3.0×10^{-6} Torr.) and monitored at 417 nm by vis. spectroscopy. The pertinent results are reported in Table 5.

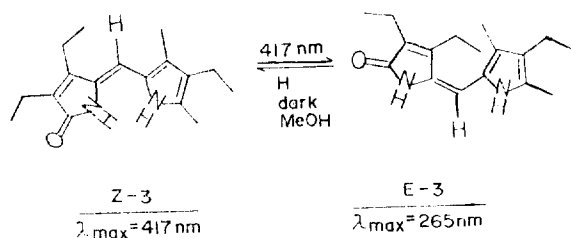
In anaerobic condition only one peak at 265–268 nm grew in the irradiation of **3**, whereas in aerobic condition two peaks at 265–268 nm and 220 nm grew. This results confirmed the above conclusion that the absorption band at 265–268 nm corresponded to *E*-**3**.

Photoisomerization of **3** in the presence of oxygen has no significant effect on rate, an observation which weighs against participation of triplet state of **3**. The small difference (inhibition) is uncertain because of interference from dark reverse reaction. When the photoisomerized reaction mixture was placed in the dark (15 hrs), the dark reverse reaction ($E \rightarrow Z$) was observed in the presence and absence of air. The dark reverse reaction ($E \rightarrow Z$) occurred to a greater extent in methanol and was faster under aerobic conditions than under anaerobic conditions, even though the reverse reaction was slow compared to the photoisomerization. When air was introduced after the isomerization of the degassed system, the dark reverse reaction rate was intermediate between the above extreme case. When a drop of trifluoroacetic acid was added after photoisomerization of substrate **3** in the degassed system, and $E \rightarrow Z$ dark reverse reaction occurred immediately and completely. This is probably an acid catalyzed reaction. The singlet state of the substrate **3** is presumably involved in the photoisomerization in accord with the expected effect of oxygen on the reaction rate.

TABLE 5: Percentage Change of 3 for Several Conditions vs. Irradiation Period

| Irradiation time (min) | % | | |
|------------------------|-------------------------|-------------------------|-------------------------|
| | Aerobic | Anaerobic | Anaerobic+air* |
| 7 | 12.3 | 13.5 | |
| 20 | 21.3 | 24.5 | |
| 40 | 24.6 | 27.8 | |
| 60 | 24.6 | 27.8 | |
| Dark, 15 hr | 90% <i>E</i> - <i>Z</i> | 43% <i>E</i> - <i>Z</i> | 73% <i>E</i> - <i>Z</i> |

*Using the same procedure as the degassed system, but air was introduced after 60 min irradiation.



5'-Oxo-3',4'-diethyl-5-methyl-1',5'-dihydro-(2,2')-dipyrrromethene (4). When oxodipyrrromethene **4** ($2.9 \times 10^{-5} M$) was irradiated with monochromatic light (Hg-lamp, 200W) in several solvents (386 nm in chloroform and deuteriochloroform, 399 nm in methanol), the absorption peak at 386 nm in chloroform and deuteriochloroform (399 nm in methanol) decreased and a new absorbance peak at 265 nm increased in the early stage of the photochemistry (the peak at 265 nm is same as that of **3** photoisomerization). The pertinent results are summarized in Table 6.

When the "photooxidized" reaction mixture was placed in the dark, the dark reverse reaction occurred. It may be noted that the initial reaction rate is fastest in methanol. If 1O_2 were involved (or the photooxygenation reaction was implicated), the reaction rate should have been faster in deuteriochloroform than in chloroform, since the 1O_2 life time is longer in deuteriochloroform than in chloroform.⁴ A photoisomerization reaction is deduced from these observations.

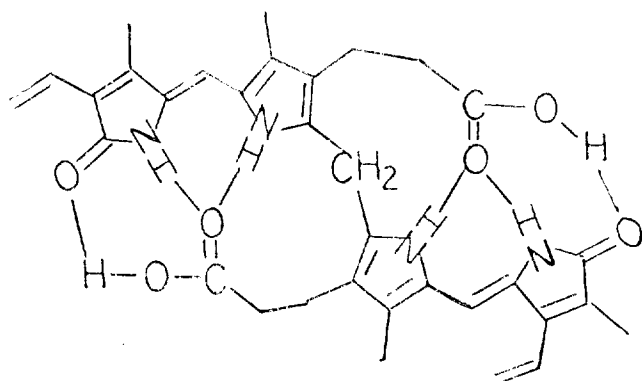
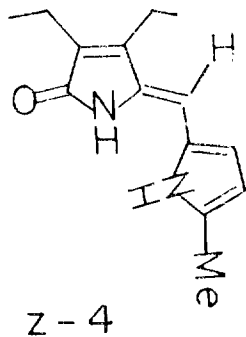


TABLE 6: Disappearance Percentage of the Oxodipyrrromethene 4 in Three Solvents vs. Irradiation Time

| Irradiation time | % | | |
|------------------|-------------------|-------------------|------|
| | CDCl ₃ | CHCl ₃ | MeOH |
| 2 | 4.1 | 2.4 | 12.8 |
| 16 | 5.2 | 4.1 | 12.8 |

Furthermore, only one spot other than starting material was observed by analytical TLC, when the oxodipyrrromethene (**4**) was irradiated in methanol with broad spectrum light for short time period (20 min). When the solution was irradiated for a longer period (1 hr), on analytical TLC showed several spots. The initial reaction is a photoisomerization. Since the reaction rate is faster in methanol than in showed several spots. The initial reaction is a photoisomerization. Since the reaction rate is faster in methanol than in chloroform, an intermediate in the photoisomerization was presumably a polar specie. The behavior of bilirubin was extrapolated to be similar to that of the oxodipyrrromethenes (e.g. **3**, **4**). To test this idea the following experiment was performed.

Bilirubin IX- α . Bilirubin in three different solvents (CHCl₃, MeOH, CDCl₃, $1.65 \times 10^{-5} M$ for each solvent) was irradiated at 452 nm (monochromatic light), and the initial reaction was monitored. The results are summarized in Table 7. Bonnett and Stewart⁵ observed that when bilirubin was irradiated in 0.05 M NH₃ in CD₃OD, a five fold increase in photooxidation over that found for methanol control. Thus, they concluded that photooxidation of bilirubin is self-sensitizing 1O_2 reaction, since 1O_2 life time is longer in CD₃OD than in methanol.

However, it is noted that reaction rate at early stage is fastest in methanol (see Table 7). Reactions other than the self-sensitized degradation of bilirubin should have occurred in the system because the self-sensitizing 1O_2 reaction should be fast in deuteriochloroform (cf. 1O_2 life time: CH₃OH, 7 μ sec; CHCl₃, 60 μ sec; CDCl₃, 300 μ sec).⁴ Photoisomerization of bilirubin (probably Z \rightarrow E), like other structurally related benzalpyrrolinones and oxodipyrrromethenes, is presumably a part of the photodegradation reaction. The observation that Z \rightleftharpoons E photoisomerization of benzalpyrrolinones, oxodipyrrromethenes and bilirubin IX- α can occur may explain the recognized excretion of unconjugated bilirubin in the bile of jaundiced infants or Gunn rats undergoing light treatment.⁶

3. Experimental

3.1 General. The benzalpyrrolinones and oxodipyrrromethenes were prepared by the reported methods^{2,3,7} in this laboratory. The bilirubin used for kinetic studies was purchased from Matheson. Solvents were reagents grade. Visible and uv spectra were recorded on a Cary-14 spectrophotometer. For degassed experiment, a pyrex to quartz fused 10 mm quartz cell was subjected to at least

TABLE 7: Percentage Disappearance of Bilirubin in Three Solvents vs. Irradiation Time

| Irradiation time (min) | % | | | Condition |
|------------------------|-------------------|-------------------|------|---------------|
| | CDCl ₃ | CHCl ₃ | MeOH | |
| 3 | 0 | 0.5 | 1.1 | Tungsten lamp |
| 30 | 1.9 | 2.2 | 5.2 | |
| 4 | 2.4 | 1.7 | 3.9 | Hg-lamp |
| 20 | 8.3 | 5.3 | 7.1 | |

three cycles of freeze-pump-thaw treatment at a pressure of 4.0×10^{-6} Torr.

3.2 Direct Photoisomerization

Z-Benzalpyrrolinone (*Z*-1) (0.084 mg, 3.7×10^{-4} mmoles) was dissolved in 10 ml methanol. The solution (2.8 ml) in uv cell (1 cm path) were irradiated at the absorption maximum wavelength (323 nm) using 10 nm bandpass monochromatic light from a Bausch and Lomb monochromator (Model 33-86-07) equipped with a Hg-lamp(200W). The results were reported in Table 1.

Z-5-Benzylidene-4-methyl-3-vinyl-3-pyrrolin-2-one (*Z*-2). The procedure was the same as *Z*-1 except the excitation wavelength differed (342 nm).

5'-Oxo-3',4'-triethyl-3,5-dimethyl-1',5'-dihydro-(2,2')-dipyrromethene (3). The oxodipyrromethene 3 (7.1 mg, 2.6×10^{-2} mmoles) was dissolved in methanol in a 10 ml volumetric flask. When the solution was irradiated at 417 nm (λ_{\max} of 3=417) by monochromatic light, (Hg-lamp) the disappearance peak at 417 nm and appearance peaks at 320 nm and 265 nm were monitored (see Table 3). After 8 hrs irradiation the reaction mixture was allowed to reverse in the dark and monitored. To determine the solvent effect on reaction rate (initial rate) the above concentration of the solution 3 was irradiated in several different solvents. The results are reported in Table 4.

To check the effect of oxygen on the photoisomerization, the oxodipyrromethene 3 in methanol was examined under aerobic and anaerobic condition (see Table 5).

5'-Oxo-3',4'-diethyl-5-methyl-1',5'-dihydro-(2,2')-dipyrromethene (4). Procedure is the same as above (see also Table 6).

Bilirubin IX- α . See Table 7 and the procedure in Section of Results.

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The Significant Structure Theory of Liquids Applied to Homogeneous Nucleation Theory

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The surface tensions, the chemical potentials and the densities of various liquids such as argon, nitrogen, helium, ammonia, and water are calculated using the significant structure theory of liquids. And using these calculated values, the critical supersaturation ratios and the radii of the above materials are determined according to the classical Becker-Döring and the revised Lothe-Pound theories. The results are compared with the experimental values and well agreed with the available experimental data.

Introduction

Most of the homogeneous nucleation theories of the vapor-liquid condensation make use of the capillarity approximation in which the free energy of formation of a droplet is described in terms of the experimental surface tension and the density of the bulk liquid.

Among them, the classical Becker-Döring¹ and the revised Lothe-Pound theories are known as the most useful ones.

Using the capillarity approximation, the Helmholtz free energy of *n*-cluster droplet in Becker-Döring theory is given by

$$F_{B-D}(n) = F_{cap}(n) = \mu_{exp}n + \sigma_{exp}4\pi \left(\frac{3}{4\pi\rho}\right)^{2/3} n^{2/3} \quad (1)$$

where μ_{exp} , σ_{exp} , and ρ are the chemical potential, flat-plane surface tension, and density of the macroscopic liquid state, respectively.

And in Lothe-Pound theory, that is given by

$$F_{L-P}(n) = F_{cap}(n) + F_{trans}(n) + F_{rot}(n) - f_{rep} \quad (2)$$

The translational free energy is given in terms of the partition function as

$$F_{trans}(n) = -kT \ln \left[\left(\frac{2\pi nmkT}{h^2} \right)^{3/2} \frac{V}{C_1} \right] - kT \quad (3)$$