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DYE-SENSITIZED PHOTOOXYGENATION OF OXOPYRROMETHENES RELATED TO BILIRUBIN

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In connection with our interest in the photochemistry and photooxidation of bilirubin IXα [BR] (1)[1], which is currently a subject of wide-ranging interest in jaundice phototherapy[2], we have also studied the photooxygenation of structurally related mono- and dipyrroles[3]. Thus, the dye-sensitized photooxygenation of an oxopyrromethene model (2) for one-half of BR allowed us to predict correctly that BR might successfully undergo the McDonagh[4] Path 2 singlet oxygen [$^1O_2$] reaction at positions *a* and *c* to give, presumably, an unstable dioxetane which decomposes to the isolated methylvinylmaleimide (5)[5]. More recently, Bonnett and Stewart[6] isolated the other component predicted from the dioxetane decomposition[4], a dipyrrole dialdehyde (8) from bis attack by $^1O_2$. The original analogy for this type of $^1O_2$ reaction was drawn from Foote's work with enamines[7] although the pertinent reactive site for $^1O_2$ in both 1 and 2 is an ene-amide with a potentially less "electron-rich" (thus less reactive) C=C.

When a 1.64 mmolar solution of 2 in methanol containing 3.3 mg % Rose Bengal and 0.27 ml % conc. NH_4OH was irradiated[8] in a Pyrex immersion well photolysis apparatus with circulating O_2[9], one mole equivalent of O_2 was consumed within 4 hrs, and the long wavelength visible absorption maximum near 417 nm (ε 36,000) was flattened. Evaporation of the methanol followed by column chromatography (silica gel, 70-325 mesh ASTM, M. Woelm, Eschwege) using ethyl acetate and acetone-methanol gave 75 % of the material in the ethyl acetate fraction. This fraction was separated into two principal photoproducts by preparative thin layer chromatography (tlc) (silica gel F, M. Woelm, 1mm thick, ethyl acetate) which were identified as diethylmaleimide (6)[10] [34%][11] and 3,5-dimethyl-4-ethyl-5-methoxy-3-pyrrolin-2-one (9)[12] [35%][11]. A smaller amount of kryptopyrrole aldehyde (12) [10%] was also isolated. The formation of 6 and 9 may be conveniently consistently[4] rationalized in terms of a ground state decomposition of unstable dioxetane 11 formed by attack of $^1O_2$ on 2. Hence, the first-formed products of decomposition of 11 would be 6 and kryptopyrrole aldehyde (12), and the latter has been shown to give 9 under the reaction conditions[12].

In light of the preceding data, we were very surprised to discover that 14[13], 15[14] and the benzal pyrrolinone (16, X=H) were completely stable under the reaction conditions or even longer (48 hr) reaction times. In fact, 14, 15 and 16 (X=H) are recovered unchanged. With 16 (X=H) we could observe only a Z ⇄ E photoequilibrium and isolated both isomers. Attempts to

"activate" the ene-amide C=C by positioning electron donors (OMe and NMe_2) in the para position caused no change in the reactivity toward $^1O_2$, as indeed neither did *p*-Me or *p*-Cl. With each of these substances (16), only a Z ⇄ E photoequilibrium[15] was established. The lack of reactivity of 14 toward $^1O_2$ suggests that substances like it are most likely not implicated as precursors to imides in the photooxygenation of alkylpyrroles[16].

The special reactivity of the ene-amide C=C of 1 and 2 toward $^1O_2$ was further demonstrated by comparison with two similar oxopyrromethenes (3) and (4). Although both 3 and 4 react with $^1O_2$ under the reaction conditions for 2, 3 gave neither 6 nor 10 nor 13, and 4 gave only low isolated yields of 7 (6%) and 9 (10%) with no 12. The principal Rose Bengal-Sensitized photooxygenation products of 3 and 4 are dipyrrole compounds with oxygenation in ring C. Their structures are currently being definitively proved. Apparently, what might be viewed as the normal non-reactivity of ene-amide C=C's with $^1O_2$ has been significantly altered in 1 and 2 by *the presence of ring B and C or A and D pyrrole β-substituents. However, the reasons for their* special reactivity toward $^1O_2$ are not clear. One possibility is that a C=C photoisomer of 2, not the stable ground state isomer, reacts with $^1O_2$. There are four planar representations for 2-4 *which include the various syn and anti* Z and E configurations shown. X-ray crystallography on 2 has shown that the *syn*-Z form is the only one present in the crystal[17], and space-filled molecular models clearly show that the other three isomers are more sterically hindered, especially the *syn*-E isomer[18]. Although 2-4 can in principle undergo an unsensitized photoisomerization, *e.g. syn* Z ⇄ *anti-E*, we have been able to detect (by nmr) a photoisomerization only with 3 and 4 and *not* 2[19], and the photoequilibrium lies largely (>90%) on the side of the *syn*-Z isomer[20]. Most important, the same photoproducts, 6, 9 and 12, arise from 2 whether a self-sensitized or Rose Bengal-sensitized photooxidation is carried out[21].

Another explanation for the differing reactivities of 2-4, 14, 15 and 16 with $^1O_2$ attributes the facility for dioxetane formation to the ease of one electron oxidation. The most highly alkyl-substituted oxopyrromethene (2) should have the lowest half wave potential and hence the greatest reactivity toward $^1O_2$ in an electron or charge-transfer mechanism[7], perhaps involving the pyrrole ring (C) in structures like 17, leading to dioxetane 11. We believe that alkyl substitution on the pyrrole rings is crucial and intend to measure polarographic half-wave potentials of 1-4 and 14-16 in an effort to develop a clearer rationale for the exhibited differences in behavior.

We are currently studying the reactivity of ene-amide C=C's in other systems and are attempting to understand the factors influencing their variable reactivity toward $^1O_2$. In the work to date it is important to note that ene-amide C=C's are probably not generally reactive toward $^1O_2$ in the same way that enamine C=C's are.

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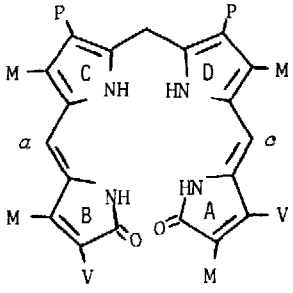
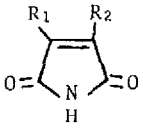


M = CH_3

V = $CH{=}CH_2$

E = CH_2CH_3

P = CH_2CH_2COOH



5 R_1 = M, R_2 = V

6 R_1 = R_2 = E

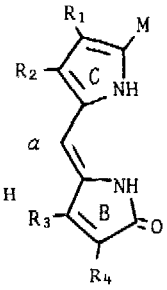
7 R_1 = R_2 = H

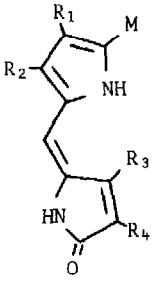
1 Bilirubin IXα

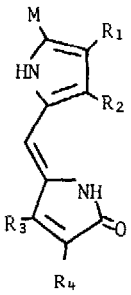
2 R_1 = R_3 = R_4 = E, R_2 = M

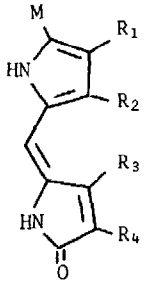
3 R_1 = R_2 = H, R_3 = R_4 = E

4 R_1 = E, R_2 = M, R_3 = R_4 = H

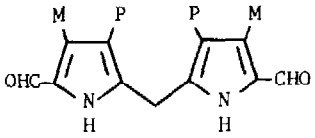


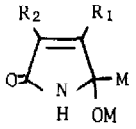


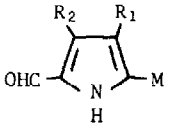


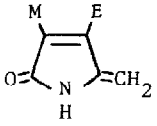


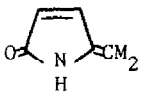
Configurational Isomers: *syn*-Z *anti*-E *anti*-Z *syn*-E











8

9 R_1=E, R_2=M

10 R_1 = R_2 = H

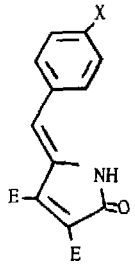
12 R_1=E, R_2=M

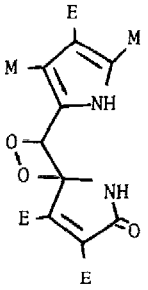
13 R_1 = R_2 = H

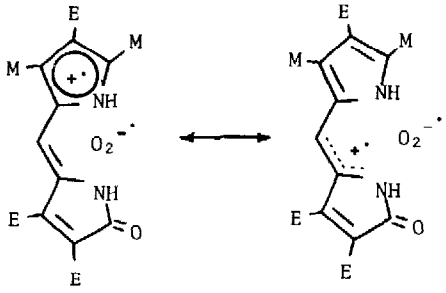
14

15

Z







16

11

17

References and Footnotes

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2. Final Report of the Committee on Phototherapy in the Newborn, National Academy of Sciences (1974).

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8. Sylvania Quartz-iodine lamp, 500 W, no. 500 Q/CL, 120V run at 100V.

9. C. S. Foote and G. Uhde, *Org. Photochem. Syn.*, 1, 70 (1971).

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11. The yields are isolated yields and are doubtless minimal as material losses are encumbered with the chromatographic separation and solvent evaporation, *e.g.* diethylmaleimide sublimes.

12. D. A. Lightner and G. B. Quistad, *J. Heterocyc. Chem.*, 10, 273 (1973).

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15. Z $\rightleftarrows$ E photoisomerization of this type has been reported recently by H. Falk, K. Grubmayr, O. Hofer and F. Neufingrl, *Montash*, 106, 991 (1975).

16. G. Rio and D. Masure, *Bull. Soc. Chim. Fr.*, 4610 (1972).

17. D. L. Cullen, P. S. Black and E. F. Meyer, Jr., unpublished data.

18. Curiously, the *syn*-E configuration is the most commonly found representation for BR in the literature, but it is clearly the most sterically hindered, and is doubtless an inaccurate representation for the stable configuration. The *syn*-Z configuration at *a* and *c* of BR is more probable. For example, see P. Manitto and D. Monti, *Chem. Comm.*, 122 (1976).

19. The compound related to 3 with R_3=R_4=M has been shown to photoisomerize *syn*-Z $\rightleftarrows$ E. H. Falk, K. Grubmayr, U. Herzig and O. Hofer, *Tetrahedron Lett.*, 559 (1975).

20. (Photo)isomerizations of BR involving the various *syn* and *anti* Z and E configurations at *a* and *c* are possible and would require the breaking of intramolecular H-bonds [C. C. Kuenzle, M. H. Weible, R. R. Pelloni and P. Hemmerich, *Biochem. J.*, 133, 304 (1973)] between the P groups and opposite end rings A and B. Such photo-induced H-bond breaking would be expected to alter the solubility of BR, perhaps make it more H_2O soluble and thus explain the excretion of unconjugated BR during phototherapy.

21. In the unsensitized photooxidation, 2 is irradiated with monochromatic light (417 nm, 10 nm bandpass) at its intense long wavelength absorption. In the Rose Bengal-sensitized photooxidation of 2, the solution is irradiated with monochromatic light (557 nm, 10 nm bandpass).