Electron Transfer Photooxygenation of 8-Methoxypsoralen

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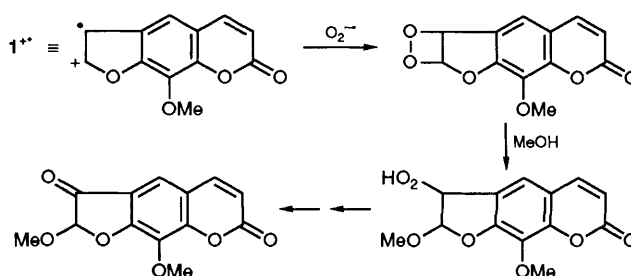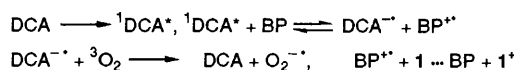*Department of Chemistry, Nanjing University, Nanjing 210008, P.R. China*

9,10-Dicyanoanthracene (DCA) and chloranil sensitized electron transfer photooxygenation of 8-methoxypsoralen in MeOH–MeCN (7 : 3, v/v) gave the furan ring oxidized product 4'-oxo-5',8-dimethoxypsoralen {2,9-dimethoxy-7H-furo[3,2-g][1]benzopyran-3,7(2H)-dione} in 38 and 74% yield, respectively, while in HOAC–MeCN (2 : 8, v/v), similar photooxygenation gave 4'-oxo-5'-acetoxy-8-methoxypsoralen {2-acetoxy-9-methoxy-7H-furo[3,2-g][1]benzopyran-3,7(2H)-dione} as product in 30 and 73% yield, respectively.

The photochemistry of 8-methoxypsoralen, an effective sensitizer widely used in the treatment of psoriasis and other diseases, has received intensive research.[1] The photochemocerapic mechanism is commonly attributed to two successive (2 + 2) cycloaddition reactions of the thymine residue of two strands of DNA with the 3,4-pyrone and 4',5'-furan double bonds of the furocoumarin, leading to the crosslinking of the two strands of DNA. As a model process to simulate these reactions, photoinduced cycloaddition reaction of the pyrone 3,4-double bond with simple alkenes on direct and triplet sensitized photolysis has been widely reported.[2–4] In sharp contrast is the situation with the furan 4',5'-double bond which shows very low photochemical reactivity and photoinduced addition with simple alkenes and other reactions at this double bond have rarely been reported.[5] We have also noticed that the photochemistry of psoralens involving a single electron-transfer process (SET) has not so far been reported.

We report here the 9,10-dicyanoanthracene (DCA) and chloranil sensitized electron transfer photooxygenations of the 8-methoxypsoralen 1 to give the furan ring oxidized products.
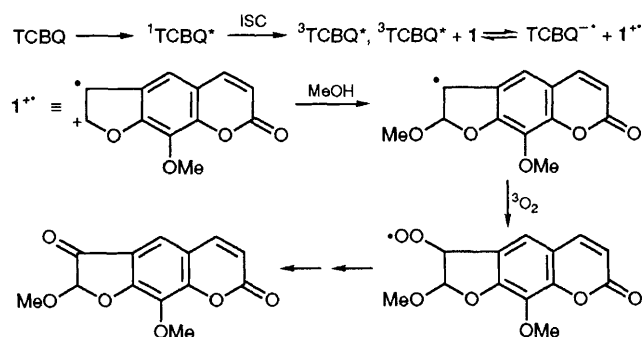
Although 1 quenches the ¹DCA* fluorescence with near diffusion controlled rate constant in acetonitrile,[6]† it was

found that DCA (10^{-4} mol dm^{-3}) sensitized photolysis of 1 (2 × 10^{-2} mol dm^{-3}) in acetonitrile with light longer than 400 nm under oxygen atmosphere led only to sluggish reaction and resulted in a complicated intractable reaction mixture with low overall conversion. The addition of biphenyl (BP, 2 × 10^{-2} mol dm^{-3}) as cosensitizer[6] remarkably accelerate the reaction but still gave a tarry mixture. To suppress the polymerization reaction and simplify the product, methanol–acetonitrile (7:3, v/v) were used as solvents and it was found that simplified products with much less tarry material were obtained of which the main product isolated was 4'-oxo-5',8-dimethoxypsoralen {2,9-dimethoxy-7H-furo[3,2-g][1]benzo-

$$\text{DCA} \longrightarrow {}^1\text{DCA*}, \quad {}^1\text{DCA*} + \text{BP} \rightleftharpoons \text{DCA}^{-\cdot} + \text{BP}^{+\cdot}$$

$$\text{DCA}^{-\cdot} + {}^3\text{O}_2 \longrightarrow \text{DCA} + \text{O}_2^{-\cdot}, \quad \text{BP}^{+\cdot} + 1 \cdots \text{BP} + 1^+$$

Scheme 1

Scheme 2

pyran-3,7(2H)-dione} 2. In a typical example a MeOH–MeCN (7:3, v/v, 100 ml) solution of DCA (6.3 mg, 0.027 mmol), 1 (637 mg, 2.95 mmol) and BP (270 mg, 1.75 mmol) was photolysed under oxygen atmosphere with light longer than 400 nm (500 W medium pressure mercury lamp, 20% aqueous $NaNO_2$ solution filter) for 12 h to lead to total conversion of 1. After removing the solvent, the reaction mixture was chromatographed on silica gel column to give 2 in 38% yield.‡ DCA (10^{-4} mol dm^{-3}) sensitized a similar photooxygenation of 1 in acetic acid–acetonitrile (2:8, v/v) and gave 4′-oxo-5′-acetoxy-8-methoxypsoralen {2-acetoxy-9-methoxy-7H-furo[3,2-g][1]benzopyran-3,7(2H)-dione} 3 as the main product (30%).§

The DCA sensitized reaction could not proceed in less polar solvents, e.g. C_6H_6–MeOH (7:3, v/v). High polarity of acetonitrile and methanol and the hydrogen bonding ability of methanol promote the dissociation of the ion radical pairs formed in the initial electron transfer step. This profound solvent polarity effect, together with the observed rate acceleration by the addition of cosensitizer BP which served as a relay in the electron transfer between ^{1}DCA* and 1 to suppress back electron-transfer and lead to enhanced SET efficiency, provided further support for the involvement of a SET process in the reaction. To identify the active oxygen species in the reaction, tetraphenylporphine (TPP; 1 × 10^{-3} mol dm^{-3}), an effective $^1O_2$ sensitizer, was used to sensitize the oxygenation of 1 (2 × 10^{-2} mol dm^{-3}) in benzene but no reaction was observed after 6 h irradiation with constant oxygen purging. A DCA sensitized photooxygenation of 1 in heavy-atom solvent, tetrachloromethane, was also carried out but again without observing any obvious reaction. Since DCA sensitized photooxygenation of $^1O_2$ active substrate in CCl_4 proceeds with high efficiency via $^1O_2$ mechanism,[7] failure in observing photooxygenation in both TPP sensitized reaction and DCA sensitized reaction in CCl_4 eliminated the possibility of any significant $^1O_2$ involvement in the above reactions. The effect of added benzoquinone (BQ), a known superoxide (O_2^-·) trap[8] was then tested and it was found that the oxygenation was totally quenched by 2.5 ×

10^{-3} mol dm^{-3} of BQ. This indicated that O_2^-· is the active oxygen species responsible for the oxygenaton. The reaction mechanism is proposed based on the above facts as in Scheme 1.

We further investigated the chloranil [TCBQ, $E_{1/2}^{red}$ −0.02 V, saturated calomel electrode (SCE)[9]] sensitized oxygenation of 1 in the above solvent systems. In this case, O_2^-· is not to be considered as the active oxygen form since the secondary electron-transfer between TCBQ$^-$· and ground state oxygen, which leads to the formation of O_2^-·, is a large endothermic process with a ΔG_{ET} of 88 kJ mol^{-1} and is thermodynamically very unfavourable.[10] The only oxygen species that has to be taken into account is the ground state oxygen $^3O_2$.

It was found that in the TCBQ (5 × 10^{-3} mol dm^{-3}) sensitized oxygenation of 1 (5 × 10^{-2} mol dm^{-3}) in MeOH–MeCN (7:3, v/v) and in HOAC–MeCN (2:8, v/v), the same products 2 and 3 as in the DCA sensitized runs were formed, albeit in significantly higher yields (74 and 73%, respectively). In a typical example, a HOAC–MeCN (2:8, v/v, 100 ml) solution of TCBQ (120 mg, 0.49 mmol) and 1 (550 mg, 2.54 mmol) was photolysed under the same conditions as in the DCA sensitized reactions for 25 h to lead to a conversion of 89% of 1. Column chromatographic separation of the reaction mixture gave 3 in 73% yield (based on consumed 1). Rate acceleration by the addition of BP was also observed in the TCBQ sensitized reactions, providing evidence for the SET process involved in the oxygenation. The higher yield of products 2 and 3 could be rationalized according to the reaction mechanism shown in Scheme 2.

Nucleophilic attack on the cation centre of the intermediate cation radical I by methanol (acetic acid) and trapping of the radical centre by ground state oxygen led directly to the products, averting such side reactions as polymerization induced by the decomposition of the intermediate dioxetane in the DCA sensitized reactions.

The above mentioned photooxygenation reactions show that, in contrast to the direct and triplet sensitized photolyses, the 4′,5′-double bond of the furan ring rather than the pyrone 3,4-double bond in 1 is the reactive site under photoinduced electron-transfer conditions. Photo SET reactions therefore provide new ways for the structural modification of the furocoumarins at the furan ring and the possibility to induce (2 + 2) cycloaddition with simple alkenes at the furan 4′,5′ double bond under photo SET conditions is to be further investigated.

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References

1 C. D. Cimino, H. B. Gamper, S. T. Isaacs and J. E. Hearst, *Ann. Rev. Biochem.*, 1985, **54**, 1151 and the references cited therein.
2 M. H. Zhang and J. Y. An, *Acta Chim. Sin.*, 1983, **41**, 182.
3 J. Y. An, Y. X. Lei, M. H. Zhang and L. J. Jiang, *Sci. Sin., B*, 1983, 779.
4 T. Otsuki, *Chem. Lett.*, 1987, 453.
5 S. H. Shim, Y. Z. Kim and H. K. Shim, *J. Chem. Soc., Chem. Commun.*, 1982, 22; S. H. Shim, Y. Z. Kim and H. K. Shim, *Photochem. Photobiol.*, 1983, **38**, 265.
6 A. P. Schaap, S. Siddiqui, G. Prasad, E. Palomino and L. Lopes, *J. Photochem.*, 1984, **25**, 167.
7 B. W. Zhang, J. X. Chen and Y. Cao, *Acta Chim. Sin.*, 1986, **44**, 1244; K. Gollnick and A. Schnatterer, *Photochem. Photobiol.*, 1986, **43**, 365.
8 L. E. Manring, M. K. Kramer and C. S. Foote, *Tetrahedron Lett.*, 1984, **25**, 2523.
9 L. Meites and P. Zuman, *CRC Handbook Series in Organic Electrochemistry*, CRC Press, Inc., Cleveland, 1977, vol. 1.
10 Calculated by $\Delta G_{ET} = 23.06[E_{1/2}(Sens^-/Sens) - E_{1/2}(O_2^-/O_2)]$. $E_{1/2}(O_2^-/O_2)$ was taken as −0.94 V (SCE). See J. Eriksen and C. S. Foote, *J. Am. Chem. Soc.*, 1980, **102**, 6083.