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PHOTOSENSITIZED OXYGENATION OF PHENYLPYRUVIC ACID DERIVATIVES AS A MODEL FOR *p*-HYDROXYPHENYLPYRUVATE DIOXYGENASE[1]

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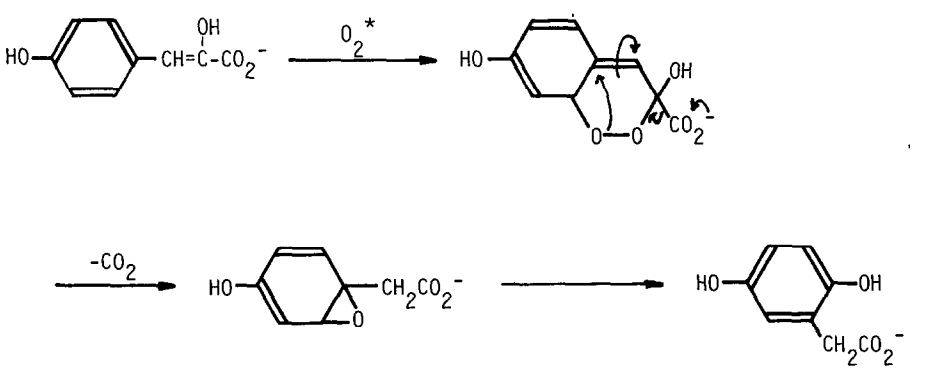
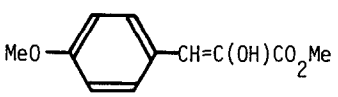
Summary: *Dye-sensitized photooxygenation of enol ethers of methyl phenylpyruvates (3) produced diendoperoxides 4 in aprotic solvents, whereas in methanol hydroxylated product 6 was obtained. The reaction scheme is discussed in comparison with that for the enzymic transformation.*

The mechanism of the conversion of *p*-hydroxyphenylpyruvate into homogentisate catalyzed by dioxygenase has been a subject of current interest.[2,3] At least three different reaction sequences have been proposed for the mechanism of the enzymic reaction on the basis of related chemical model reactions.[2,3] We previously proposed a mechanism involving 1,4-addition of molecular oxygen to the enol tautomer of *p*-hydroxyphenylpyruvate as exemplified in Scheme 1.[3b] In order to obtain a chemical support for the proposed mechanism, we have investigated the reaction of the enol ethers with singlet oxygen.

Scheme 1



Methylene blue- or rose bengal-sensitized photooxygenation of methyl *p*-methoxyphenylpyruvate (1) in methanol proceeded sluggishly with the bleaching of dye to give *p*-methoxybenzaldehyde (2) and monomethyl oxalate as reported previously.[4] However, photooxygenation of enol ether derivatives 3 resulted in smooth formation of diendoperoxides 4. For example, photooxygenation of 3a (7.5 mM) in CCl_4 in the presence of tetraphenylporphyrin (TPP) at 0 °C followed by rapid preparative TLC (silica gel) provided an unstable endoperoxide 4a (15%) together with a minor amount of 2 (6%). The structure of 4a was assigned on the basis of spectral data including ^1H and ^{13}C NMR.[5] The chemical shifts and coupling constants of the proton signals are in good agreement with those of the model compounds reported by Matsumoto *et al.*[6] TPP-sensitized photooxygenation of 3b and 3c in CCl_4 under similar conditions gave 4b[7] (20%) and 4c[7] (15%), respectively. Attempts to obtain monoendoperoxide 5 at low conversion or at low-temperature photooxygenation have been unsuccessful. An analogous type of 1,4-cycloaddition of singlet oxygen to vinyl-substituted aromatics has been extensively studied by Foote and Matsumoto *et al.*[8]



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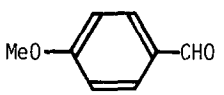

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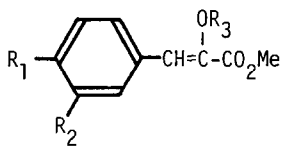
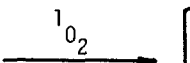
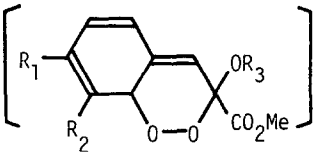
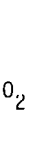


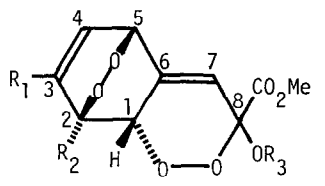




5

3 a, R_1 = OMe, R_2 = H, R_3 = Me
b, R_1 = R_2 = H, R_3 = Me
c, R_1 = R_2 = OMe, R_3 = Me
d, R_1 = OMe, R_2 = H, R_3 = $Si(Me)_2$-*t*-Bu

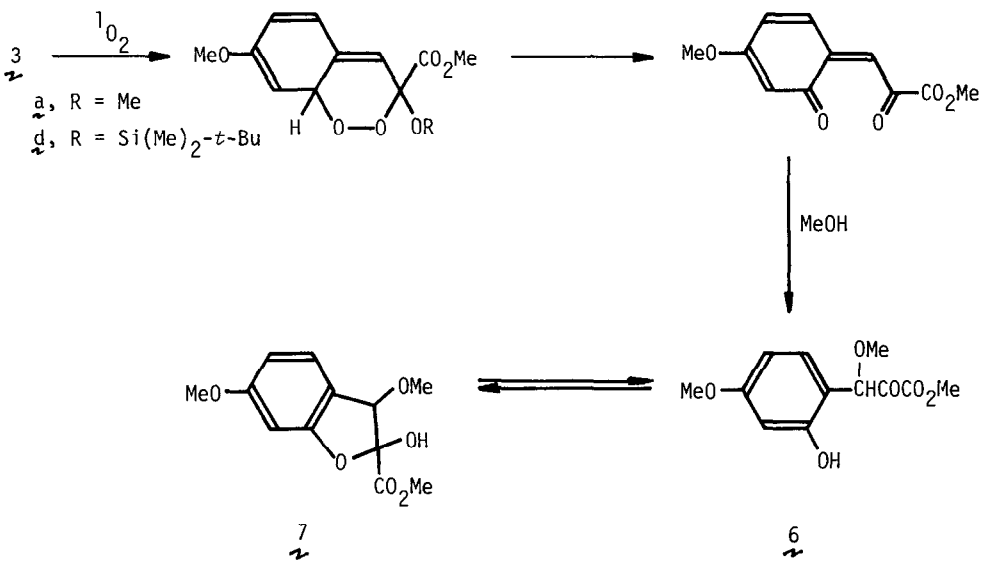




4

The photooxygenation in methanol, however, produced a different type of product. Methylene blue-sensitized photooxygenation of 3a (7 mM) in methanol at 0 °C afforded 6[7] (50% based on consumed 3a): none of the endoperoxides such as 4a has been detected. The product 6 exists in an equilibrated mixture of 6 and 7 in d_6-acetone as evidenced by ^{1}H NMR. Likewise, photooxygenation of *tert*-butyldimethylsilyl ether 3d in methanol afforded 6 (20%) and 2 (20%). The formation of 6 may be rationalized by the mechanism shown in Scheme 2 as proposed previously.[9]

Scheme 2



The present work described here indicates that the enol tautomer of *p*-hydroxyphenylpyruvate is capable of undergoing 1,4-addition with singlet oxygen under proper conditions when the enol is protected. However, the reaction sequence of Scheme 2 is quite different from that for the enzymic transformation, *i.e.*, the foregoing chemical oxygenation results in *meta*-hydroxylation, whereas the enzymic reaction induces *para*-hydroxylation with the migration of the alkyl side chain. Nevertheless, the present result does not necessarily rule out the mechamism of Scheme 1 for the enzymic reaction.

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5. Mp 79 - 80 °C; ^{1}H NMR ($CDCl_3$) δ 3.46 (s, 3 H), 3.61 (s, 3 H), 3.78 (s, 3 H), 4.72 (m, 1 H, C-2H), 5.24 (dd, 1 H, J = 3.3, 2.0 Hz, C-1H), 5.31 (1 H, d, J = 8 Hz, C-5H), 5.51 (dd, 1 H, J = 8 Hz, 2.5 Hz, C-4H), 5.68 (d, 1 H, J = 2 Hz, C-7H); ^{13}C NMR ($CDCl_3$) δ 52.6 (q), 52.8 (q), 55.4 (q), 72.7 (d), 73.7 (d), 73.9 (d), 96.8 (d), 101.2 (s), 110.6 (d), 145.5 (s), 156.6 (s), 167.1 (s).
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7. All new compounds exhibited consistent spectral data (^{1}H and ^{13}C NMR, MS) and elemental analyses. Selected spectral data follow. 4b: mp 123 - 124.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.41 (s, 3 H), 3.71 (s, 3 H), 4.76 (m, 1 H, C-2H), 5.08 (dt, 1 H, J = 6.5, 1.2 Hz, C-5H), 5.17 (dd, 1 H, J = 3, 2 Hz, C-1H), 5.71 (d, 1 H, J = 2 Hz, C-7H), 6.40 (ddd, 1 H, J = 8.3, 5.8, 1.2 Hz, C-3H), 6.79 (ddd, 1 H, J = 8.3, 6.5, 1.7 Hz, C-4H). 4c: mp 120 - 121.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 3 H), 3.66 (s, 3 H), 3.77 (s, 3 H), 3.78 (s, 3 H), 5.26 (d, 1 H, J = 7 Hz, C-5H), 5.38 (d, 1 H, J = 2 Hz, C-1H), 5.53 (d, 1 H, J = 7 Hz, C-4H), 5.71 (d, 1 H, J = 2 Hz, C-7H). 6: mp 112 - 113 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3 H), 3.76 (s, 3 H), 3.84 (s, 3 H), 5.01 (s, 1 H), 5.18 (br, 1 H, OH), 6.44 (d, 1 H, J = 2.5 Hz), 6.53 (dd, 1 H, J = 8, 2.5 Hz), 7.24 (d, 1 H, J = 8 Hz).
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9. (a) M. Matsumoto and K. Kuroda, Tetrahedron Lett., 1607 (1979); (b) D. S. Steichen and C. S. Foote, ibid., 4363 (1979).

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