# Communications to the Editor

Organic Synthesis by Means of Metal Complexes. XIII.[1] Efficient, Nonenzymatic Oxidation of Catechol with Molecular Oxygen Activated by Cuprous Chloride to cis,cis-Muconate as the Model Reaction for Pyrocatechase

Sir:

Oxidative cleavage reaction of aromatic rings is a widespread occurrence in nature. Typically, the enzyme pyrocatechase catalyzes the oxidative cleavage of the aromatic ring of catechol to give cis,cis-muconic acid.[2] In this reaction, an oxygen molecule is incorporated into the product.[3] Pyrocatechase and other related oxygenases are known to require either Cu or Fe ion for maximum activity.[4] In connection with chemical studies on the biological oxidation, the activation of molecular oxygen is a crucial problem of research. Several studies on *in vitro* oxidation of catechol derivatives as a nonenzyme model reaction for pyrocatechase have been attempted. But these studies have been carried out mostly with 3,5-di-*tert*-butylcatechol, rather than catechol itself. For example, oxidation of dibutylcatechol catalyzed by several metal salts gave the corresponding quinone.[5] Oxidation with oxygen in an alkaline solution gave γ-lactone of 2,4-di-*tert*-butyl-4,5-dihydroxy-α-hydromuconic acid as a main product.[5] Photooxidative cleavage of the same catechol involving singlet oxygen gave the similar lactonic acid in 24% yield.[6] So far no successful oxidative cleavage of catechol itself with oxygen has been reported. Besides oxygen, peracetic acid was used for the oxidation of catechol, or better of phenol, to cis,cis-muconic acid, but the yields were not satisfactory.[7,8]

We now wish to report smooth oxidative cleavage of catechol with molecular oxygen activated by cuprous chloride at room temperature. This is the first successful example of the model reaction for pyrocatechase. The attempted oxidation of catechol in the presence of cuprous chloride in pyridine produced only a trace of cis,cis-muconic acid. We found that the addition of methanol to the reaction system has a profound effect on the reaction. The product isolated in a high yield was monomethyl ester of cis,cis-muconic acid. Neither dimethyl ester nor free muconic acid was obtained.
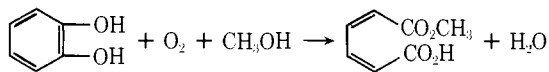

The following experimental procedure is illustrative of the reaction. Powdered cuprous chloride (1.98 g, 0.01 mol) was added in several portions to a stirred mixture of pyridine (40 ml) and methanol (1 ml, 0.025 mol) in a three-neck flask under nitrogen. Next the flask was connected to a gas buret filled with oxygen. The stirred solution absorbed 130 ml of oxygen, forming a deep green, somewhat heterogeneous mixture. Then catechol (1.10 g, 0.01 mol) dissolved in a mixture of pyridine (20 ml) and methanol (1 ml) was added slowly over 1 hr at 25° with efficient stirring. During the addition of catechol, absorption of 280 ml of oxygen was observed. Pyridine was removed under reduced pressure and the residue was extracted with *n*-hexane, evaporation of which gave nearly pure monomethyl ester of cis,cis-mu-

conic acid as white solid (1.2 g, 77%). Recrystallization from hexane gave the pure ester as long needles (1.1 g, 70%) mp 80–81° (reported 80°).[9] *Anal.* Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16; mol wt, 156.14. Found: C, 53.78; H, 5.22; mol wt, 156. Nmr (CCl_4, δ) 4.17 (s, 3 H), 6.30–6.55 (m, 2 H), 8.3–8.65 (m, 2 H), 12.55 (s, 1 H). The monoester was converted into dimethyl cis,cis-muconate by treating with diazomethane and identified by melting point (73°) and a characteristic nmr pattern.[10]

There are several characteristic features in this reaction. The product of the reaction was the unexpected monomethyl ester. The diester or free acid was not obtained although the reaction was carried out with various concentrations of methanol. The addition of only 1.5 molar equiv of methanol gave a 72% yield of the mono ester. Higher concentration of methanol is not favorable and the yield dropped to 42% with 20 molar equiv of methanol. As the catalyst for the reaction, cuprous chloride seems to be the best one. Other metal salts such as cupric chloride showed no activity. This oxidation reaction appears to be quite delicate. Persistence of the deep green color of the reaction mixture throughout the reaction is important. When the reaction mixture turns to black or purplish, the yield of the muconate decreases drastically. In order to carry out the reaction smoothly, efficient stirring and slow addion of catechol seem to be essential.

The mechanism of this unique reaction and its relevance to the mechanism of pyrocatechase are interesting problems. Although a few mechanisms have been proposed for the pyrocatechase reaction, none of them seems to be conclusive. The formation of the cyclic peroxide (1) was proposed by Hayaishi based on $^{18}O_2$ incorporation[3] and the intermediate (2) was given by Grinstead,[5] but the formation of the mono ester in the present study cannot be explained by these intermediates. The more likely intermediate is the anhydride (3) formed *via* the electrophilic attack of oxygen on the aromatic ring suggested by Norman and Smith.[4c] Methanolysis of the anhydride gives the monomethyl ester, but it is somewhat difficult to explain by this mechanism the experimental fact that the reaction carried out in pyridine containing aqueous methanol gave the monomethyl ester and no free acid. Thus further systematic studies are necessary in order to give satisfactory mechanistic interpretation of the reaction.
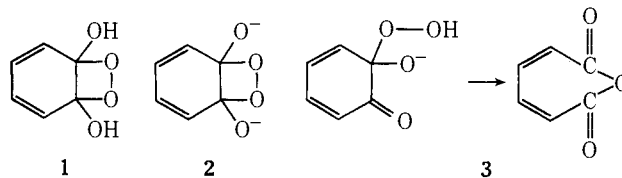
This reaction has not only a theoretical interest as the nonenzyme model reaction for pyrocatechase but also a considerable synthetic use as a simple method of cis,cis-muconate preparation. In addition, this reaction gives an additional example showing that cuprous chloride in pyridine is a good system for activating molecular oxygen under mild condition. We reported before the smooth oxidation of *o*-phenylenediamine to cis,cis-mucononitrile,[11] and α-dihydrazones to acetylenes[1] in very high yields by using the same catalyst system.

References and Notes

(1) For part XII see J. Tsuji, H. Takahashi, and T. Kajimoto, *Tetrahedron Lett.*, 4573 (1973).
(2) O. Hayaishi and K. Hashimoto, *J. Biochem. (Tokyo)*, **37**, 371 (1950).
(3) O. Hayaishi, M. Katagiri, and S. Rothberg, *J. Amer. Chem. Soc.*, **77**, 5450 (1955); *J. Biol. Chem.*, **229**, 905 (1957).
(4) For reviews see (a) A. E. Martell and M. M. Taqui Khan in "Inorganic Biochemistry," Vol 2, G. L. Eichhorn, Ed., Elsevier, New York, N.Y., 1973, p 654; (b) K. Bloch and O. Hayaishi, "Biological and Chemical Aspects of Oxygenases," Maruzen, Tokyo, 1966; (c) R. O. C. Norman and J. R. L. Smith in "Oxidases and Related Redox Systems," Vol. 1, T. E. King, H. S. Mason, and M. Morrison, Ed., Wiley, New York, N.Y., 1965, p 131; (d) O. Hayaishi, ref 4c, p 286; (e) H. S. Mason, *Advan. Enzymol. Relat. Subj. Biochem.*, **19**, 79 (1957); (f) G. A. Hamilton, *ibid.*, **32**, 55 (1969).
(5) R. R. Grinstead, *Biochemistry*, **3**, 1308 (1964).
(6) T. Matsuura, H. Matsushima, S. Kato, and I. Saito, *Tetrahedron*, **28**, 5119 (1972).
(7) J. Böeseken and C. L. M. Kerkhoven, *Recl. Trav. Chim. Pays-Bas*, **51**, 964 (1932).
(8) J. A. Elvidge, R. P. Linstead, B. A. Orkin, P. Sims, H. Baer, and D. B. Pattison, *J. Chem. Soc.*, 2228 (1950).
(9) J. A. Elvidge, R. P. Linstead, and P. Sims, *J. Chem. Soc.*, 1973 (1953).
(10) J. A. Elvidge and P. D. Ralph, *J. Chem. Soc. C*, 387 (1966).
(11) H. Takahashi, T. Kajimoto, and J. Tsuji, *Syn. Commun.*, **2**, 181 (1972).

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Sulfur Dioxide Trapping of Photochemically Generated 1,4-Biradicals

Sir:

The oxidative photoaddition of *p*-benzoquinone (*p*-BQ) to olefins under aerobic conditions to form 1,2,4-trioxanes (**1**) (Scheme I) has recently emerged as a new and general photochemical reaction.[1] This reaction is believed to proceed through the quinone-olefin intermediate, probably the 1,4-biradical, which has traditionally been invoked as the intermediate in oxetane formation.[2] Since these trapping reactions can be realized in surprisingly high yield,[3] we have initiated a program to determine if substances other than oxygen might also efficiently trap biradicals.

Sulfur dioxide is known to be an efficient radical trapping agent[4] which forms polymeric sulfones[5] and unstable sulfinic acids[6] in radical reactions with olefins and hydrocarbons. Farid[7] has reported that 1,4-biradicals generated photochemically through intramolecular γ-hydrogen abstraction in *tert*-butylquinones can be trapped by sulfur dioxide to yield labile sulfinic acids. Therefore, we have examined the photochemistry of *p*-BQ in the presence of sulfur dioxide and olefins that are known to form trioxanes in trapping experiments with oxygen.

The trioxanes **1a-c** can be isolated following argon ion laser irradiations[8] of the appropriate *p*-BQ-olefin mixture in carbon tetrachloride solution under an atmosphere of high pressure oxygen (159 psi). Cyclohexene affords **1a**, bp 95° at 10^{-6} mm, *tert*-butylethylene affords **1b**, mp 78.4–78.7°,[1c] and vinyl acetate affords a mixture of trioxanes from which **1c** can be isolated as a viscous oil[9] (Scheme I).[10] The structure of trioxane **1b** has been established by oxygen-18 labeling studies.[1c] Trioxanes **1a** and **1c** both exhibit the characteristic dienone patterns in the nmr spectra as well as the appropriate number of signals for protons on carbon bearing oxygen. In **1c** the methylene protons are deshielded by 0.4–0.5 ppm relative to the methylene protons in the unstable isomer which indicates that the methylene protons in **1c** are adjacent to the more highly deshielding peroxide linkage.[11]

Argon ion laser irradiation for 20 min of the same *p*-BQ-olefin mixtures in a 10–20% carbon tetrachloride solution of sulfur dioxide at −11° affords the following sulfones: from cyclohexene, **2a**, mp 171.0–173.9°; from *t*-butylethylene, **2b**, mp 254.0–255.3°; and from vinyl acetate, **2c** and **2d**, mp 182.9–184.5° and 164.1–169.2°, respectively. All of these substances were 1:1:1 adducts of *p*-BQ, sulfur dioxide, and olefin as judged by their molecular ions and elemental analysis. They all exhibited strong hydroxyl absorption in the infrared as well as the characteristic intense sulfone bands in the 1295–1270 and 1135–1130-cm^{-1} regions. The nmr spectra each displayed very similar patterns in the aromatic region consisting of a one-proton doublet at low field (δ 7.3–7.1 ppm, J = 2–3 Hz), and a complex two-proton signal at higher field (δ 7.1–6.95 ppm). These data are only consistent with the proposed 7-hydroxy-4,1-benzoxythian 1,1-dioxide ring system. The location of the acetoxyl and *tert*-butyl substituents follows from the nmr spectra and the predominance of the McLafferty rearrangement observed in the mass spectrum of **2b**.[12]

Clearly, biradical trapping by sulfur dioxide closely parallels trapping by oxygen. The two differ in that the sulfur dioxide series affords rearranged products. Presumably, sulfur dioxide trapping leads initially to the spirosulfone **3** which undergoes a dienone-phenol rearrangement to **2**. This rearrangement must be extremely facile, since it has not been possible to detect **3**. Perhaps the excess sulfur dioxide, which is required in order to realize efficient trapping, serves as a Lewis acid[13] catalyst for this rearrangement. Dienones such as **3** would be expected to rearrange very readily with the sulfonyl group undergoing migration.[14]

These results demonstrate that biradical trapping is not peculiar to oxygen, but in fact may be a general technique of broad synthetic utility. Finally, it must be noted that sulfur dioxide offers several distinct advantages over oxygen as a trapping agent for biradicals that have been generated photochemically. It is much easier to obtain the requisite

Scheme I

1a, R and R' = −(CH$_2$)$_4$−; 58%
b, R = H, R' = *t*-Bu; 66%
c, R = H, R' = OAc; 12%

2a, R and R' = −(CH$_2$)$_4$−; 58%
b, R = H, R' = *t*-Bu; 81%
c, R = H, R' = OAc; 20%
d, R = OAc, R' = H; 16%

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