Aromatic Oxygenation with Diisopropyl Peroxydicarbonate–Cupric Chloride

Sir:

According to prior disclosures aromatic oxygenation with peroxides has commonly been effected by radical attack[1] *via* homolytic cleavage, or through electrophilic substitution[2] resulting from heterolytic fission usually under the agency of a Friedel–Crafts catalyst. This communication provides the first recognized case entailing apparent oxidation of an oxy radical to a species exhibiting oxonium ion character, which then effects aromatic substitution. These transformations occur from interactions involving diisopropyl peroxydicarbonate, cupric chloride, and aromatic substrate in acetonitrile. Since the discovery of the copper-catalyzed reactions of peroxides with organic substrates,[3] a considerable amount of work has been devoted to delineation of the mechanistic aspects.[4] Although, in general, oxygen radicals formed initially from the peroxides served to produce carbon radicals which were subsequently oxidized by cupric salts, analogous oxidation of oxy radicals *per se* had not been noted.

In the present case, the homogeneous reaction mixture yielded tolyl isopropyl carbonates from toluene in 78–97% yield after 2 hr at 60° (Table I). The over-all stoichiometry of the reaction is expressed in eq 1. In a control experiment with the peroxide and toluene in solvent, less than 1% of the nuclear oxygenation product was found. Acetone, isopropyl alcohol, and materials

$$(i\text{-PrOCO}_2)_2 + C_6H_5CH_3 \xrightarrow{Cu^{II}} CH_3C_6H_4OCO_2Pr\text{-}i + i\text{-PrOH} + CO_2 \tag{1}$$

arising from free radical processes involving toluene constituted the major reaction products (Table I). The presence of small amounts of benzyl chloride and acetone in the $CuCl_2$-catalyzed system indicated minor competition from chain-transfer reactions of the oxygen radical.[5]

Table I. Oxygenation of Toluene with Diisopropyl Peroxydicarbonate–Copper (II) Salts[a]

	Products, %[b]						
				Tolyl isopropyl carbonates			
					Isomer distribution		
Catalyst	Acetone	Isopropyl alcohol	Benzyl-X[c]	Yield	*ortho*	*meta*	*para*
$CuCl_2$	13	108	5[d]	92	57	15	28
$CuBr_2$	43	125	18[e]	39	55	21	24
None	68	120	15[f]	<1	51	13	36

[a] Toluene:peroxide:CuX_2 = 17.2:1:0.3; acetonitrile solvent, 60°, 2 hr. [b] Based on the peroxide, see eq 1. [c] X = Cl, Br, or $CH_2C_6H_5$. [d] Benzyl chloride, 4%. [e] Benzyl bromide, 16%. [f] Bibenzyl, 12%.

The indicated experimental observations apply to the copper-catalyzed transformations of diisopropyl peroxydicarbonate–toluene: (a) decompositions in the presence of cupric salts were faster than the uncatalyzed reaction; (b) substitution of cuprous chloride or bromide for the cupric salts evoked an even more pronounced rate enhancement, but low yields (4 and 14%, respectively) of the aryl isopropyl carbonates resulted; (c) cuprous chloride produced a shorter induction period than cupric chloride; (d) a minimal $CuCl_2$:peroxide ratio of 0.3 was necessary to effect the maximum involvement of aromatic substitution; (e) carbonates were obtained in decreased amounts when ratios of aromatic:peroxide of less than 15 were employed.

The illustrated scheme (eq 2 and 3) is consistent with the experimental findings. Although eq 4 provides a

$$(i\text{-PrOCO}_2)_2 + Cu^{I} \longrightarrow Cu^{II}OCO_2Pr\text{-}i + i\text{-PrOCO}_2\cdot \tag{2}$$

$$i\text{-PrOCO}_2\cdot + ArH + Cu^{II}OCO_2Pr\text{-}i \longrightarrow ArOCO_2Pr\text{-}i + i\text{-PrOH} + CO_2 + Cu^{I} \tag{3}$$

$$i\text{-PrOCO}_2\cdot + Cu^{II} \longrightarrow i\text{-PrOCO}_2^{+} + Cu^{I} \tag{4}$$

convenient portrayal of the oxidation step, there is uncertainty concerning the exact nature of the electrophile. The induced decomposition of peroxides by copper(I) is a well-known reaction.[4,6] When cupric salts are used, copper(I) formed in oxidation of the oxy radicals then initiates the chain reaction (eq 2 and 3). Because of the ease associated with the competitive pathways, it was necessary to employ a relatively high concentration of copper(II) in order to favor the oxidation process (eq 3 and 4). Presumably the poor yields of aryl isopropyl carbonates obtained with cuprous salts were due to the low concentration or modified nature of the copper(II) species. Large amounts of aromatic reactant also appear to be crucial to the success of the oxygenation aspect. Even though the isomer distributions from the control and cupric chloride systems are somewhat similar, quite different oxygenating species may well be involved. It is relevant to compare the orientation resulting from attack on toluene by hydroxyl radical (*ortho*:*meta*:*para* = 78:2:20) with that by hydroxonium ion (*ortho*:*meta*:*para* = 71:5:24).[7]

This postulate parallels the mechanism set forth for oxidation by metal salts when the carbon radical participates,[4,6] the major difference being the virtual elimination of the commonly observed chain-transfer step which gives rise to the carbon radical. Perhaps enhanced stability of the alkoxycarboxy radical[8] and ion-type entity is an important factor contributing to the predominance of oxidation over chain transfer. It is interesting that the onium moiety displays considerably higher activity than that formed from diisopropyl peroxydicarbonate in the presence of aluminum chloride.[2]

Not only the concentration but also the nature of the oxidant appears to play a crucial role. Differences in the yields and isomeric constitution of the tolyl isopropyl carbonates were noted when cupric bromide was

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(1) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960, Chapter 7.

(2) P. Kovacic and S. T. Morneweck, *J. Am. Chem. Soc.*, **87**, 1566 (1965); P. Kovacic and M. E. Kurz, *ibid.*, **87**, 4811 (1965); for additional examples see references contained therein.

(3) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **23**, 324, 325 (1958); M. S. Kharasch and G. Sosnovsky, *J. Am. Chem. Soc.*, **80**, 756 (1958).

(4) J. K. Kochi and H. E. Mains, *J. Org. Chem.*, **30**, 1862 (1965); J. K. Kochi, *Tetrahedron*, **18**, 483 (1962); G. Sosnovsky and S. O. Lawesson, *Angew. Chem., Intern. Ed. Engl.*, **3**, 269 (1964); J. K. Kochi and R. V. Subramanian, *J. Am. Chem. Soc.*, **87**, 4855 (1965).

(5) H. C. McBay and O. Tucker, *J. Org. Chem.*, **19**, 869 (1954); W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *J. Am. Chem. Soc.*, **86**, 4237 (1964).

(6) J. K. Kochi, *ibid.*, **84**, 774 (1962).

(7) A. J. Davidson and R. O. C. Norman, *J. Chem. Soc.*, 5404 (1964).

(8) S. G. Cohen and D. B. Sparrow, *J. Am. Chem. Soc.*, **72**, 611 (1950); G. A. Razuvaev, L. M. Terman, and D. M. Yanovskii, *Dokl. Acad. Nauk SSSR*, **161**, 614 (1965); *Chem. Abstr.*, **63**, 1869 (1965).

employed (Table I). Preliminary evidence suggests that factors other than the nature of the metal halide may also influence the character of the electrophile.

It would be advisable at this stage to seriously consider an alternative interpretation entailing attack of the oxy radical upon the aromatic nucleus followed by oxidation of the resulting complex through the influence of cupric halide. Analogy may be found in the enhancement by cupric salt of intramolecular

$$i\text{-PrOCO}_2\cdot + \text{ArH} \rightleftarrows i\text{-PrOCO}_2\text{ArH}\cdot \xrightarrow{\text{Cu}^{\text{II}}} i\text{-PrOCO}_2\text{Ar} + \text{H}^+ + \text{Cu}^{\text{I}} \quad (5)$$

oxygenation in the decomposition of di-*o*-phenylbenzoyl peroxide,[9] the role of ferric ion in hydroxylation with Fenton's reagent,[10] and the increased yield of biaryl effected by oxygen in phenylation of benzene with benzoyl peroxide.[11] Since the present investigations constitute the initial probings into unexplored areas, we deem it important to label the interpretations as tentative, and to defer a more detailed and rigorous treatment until our factual knowledge has advanced to a greater extent.

The procedural simplicity and extremely high yields of monooxygenated materials obtained by this novel method of aromatic substitution suggest possible synthetic usefulness. Further studies concerning the scope and mechanism of this intriguing reaction are underway.[12,13]

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[9] J. K. Kochi and R. D. Gilliom, *J. Am. Chem. Soc.*, **86**, 5251 (1964).

[10] J. R. Lindsay Smith and R. O. C. Norman, *J. Chem. Soc.*, 2897 (1963).

[11] M. Eberhardt and E. L. Eliel, *J. Org. Chem.*, 27, 2289 (1962).

[12] The products were characterized by comparison with authentic substances.

[13] Relevance of this report to the analogous ferric chloride system [G. A. Razuvaev, N. A. Kartashova, and L. S. Boguslavskaya, *J. Gen. Chem. USSR*, 34, 2108 (1964)] is treated in a separate communication.

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Oxidation by Molecular Oxygen. IV. A Possible Model Reaction for Some Amine Oxidases[1-3]

Sir:

Recent work has clearly shown that some amine oxidases[4] which catalyze the over-all reaction: $R_2CHNH_2 + O_2 + H_2O \rightarrow R_2CO + NH_3 + H_2O_2$, require pyridoxal phosphate and a metal ion (apparently copper) as cofactors.[5] During a search for a model reaction whose mechanism might be readily investigated we found that a number of amines, especially amino acids, are oxidized readily by O_2 at room temperature in slightly basic solution if catalytic amounts of both pyridoxal and manganese ions are present.[6] Some typical reaction conditions and results are shown in Figure 1. In other experiments it was found that the rate increases with pH and with increasing concentrations of alanine and pyridoxal (if the Mn^{2+} concentration is greater than the pyridoxal concentration), but is essentially unchanged when the oxygen pressure is changed from 0.2 to 1.0 atm. A complexed form of Mn^{3+} is probably the catalyst. On mixing solutions of Mn^{2+} and pyridoxal (yellow) in the absence of O_2, very little color change occurs, but in the presence of O_2 the solution rapidly turns brown (but not turbid), and takes up 1 mole of O_2/4 moles of Mn^{2+}.

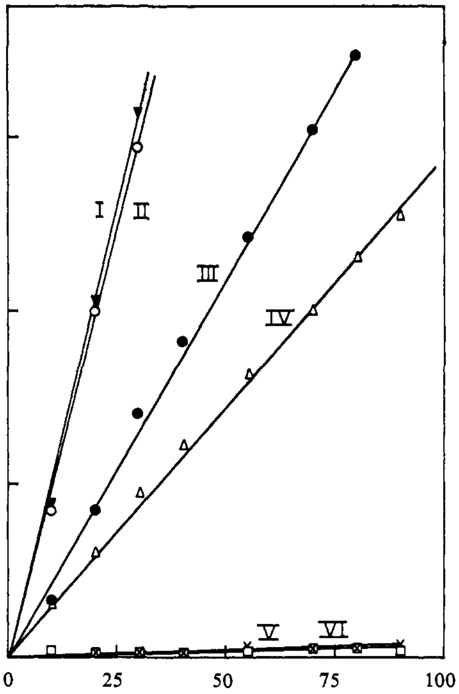

Figure 1. The oxidation of alanine by oxygen in the presence of pyridoxal and manganese ions. The oxygen uptake was measured by standard Warburg techniques. In each experiment the reaction solution was homogeneous, the temperature was 25.0°, the total volume was 3.0 ml, the oxygen pressure was 0.2 atm, the alanine concentration was 0.08 *M*, and the pH was 9.1. In expt II, III, IV, and V (×) the pyridoxal concentration was 5×10^{-3} *M*; in expt I it was 2×10^{-3} *M*; and in expt VI (□) there was no pyridoxal present. The concentration of $Mn(NO_3)_2$ in I, II, and VI was 1.7×10^{-4} *M*; in III, 6.7×10^{-5} *M*; in IV, 3.3×10^{-5} *M*, and in V no manganese was present. In each experiment except VI the reaction was initiated at zero time by adding an aliquot of a pyridoxal solution; in expt VI the reaction was initiated by adding a Mn^{2+} solution. Experiments similar to I–V but initiated by adding an aliquot of a Mn^{2+} solution gave essentially the same rates of uptake of oxygen.

The stoichiometry of the oxidation (Table I), which is similar to the enzymic reactions, indicates that H_2O_2 should be another product. However, H_2O_2 rapidly reacts when added to the reaction mixture; some O_2

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[2] This research was supported by Public Health Service Research Grant GM-09585 from the Division of General Medical Sciences, Public Health Service.

[3] Part III: G. A. Hamilton and J. R. Giacin, *J. Am. Chem. Soc.*, **88**, 1584 (1966).

[4] For reviews of diamine and monoamine oxidases see E. A. Zeller, *Enzymes*, **8**, 313 (1963); H. Blaschko, *ibid.*, 337 (1963); also H. Blaschko, *Advan. Comp. Physiol. Biochem.*, **1**, 67 (1962).

[5] (a) H. Yamada and K. T. Yasunobu, *J. Biol. Chem.*, **238**, 2669 (1963); (b) H. Blaschko and F. Buffoni, *Proc. Roy. Soc.* (London), **B163**, 45 (1965); (c) B. V. Goryachenkova and E. A. Ershova, *Biokhimiya*, **30**, 165 (1965); (d) B. Mondovi, A. Scioscia-Santoro, G. Rotilio, and M. T. Costa, *Enzymologia*, **28**, 228 (1965); (e) J. M. Hill and P. J. G. Mann, *Biochem. J.*, **91**, 171 (1964); (f) R. Kapeller-Adler, *Federation Proc.*, **24**, 757 (1965); (g) C. M. McEwen, Jr., *J. Biol. Chem.*, **240**, 2003 (1965); and references contained in these publications.

[6] M. Ikawa and E. E. Snell, *J. Am. Chem. Soc.*, **76**, 4900 (1954), had observed a much less efficient oxidation with other metal ions.