Ozonation of Monosubstituted Diazomethanes

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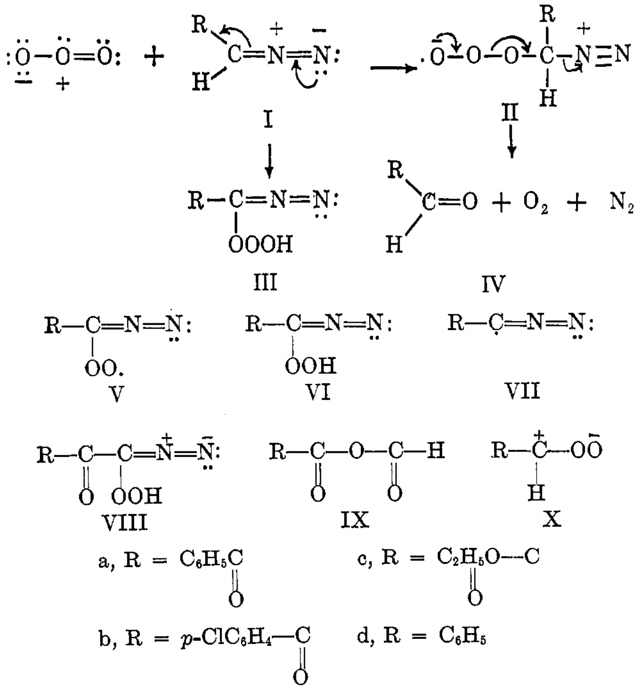
Ozone attack on diazoacetophenone, *p*-chlorodiazoacetophenone, ethyl diazoacetate, and phenyldiazomethane occurred both on the carbon–nitrogen bond and on the carbon–hydrogen bond associated with the carbon–nitrogen bond. In the presence of oxygen, some autoxidation occurred. In their behavior toward ozone, therefore, these compounds bear an analogy both to disubstituted diazomethanes and to aromatic aldehydes.

Recently, we reported on the ozonation of disubstituted diazomethanes[1] and of aromatic aldehydes.[2] In the case of the disubstituted diazomethanes[1] ozone attack occurred *via* two routes, one with 1:1 and the other with 2:1 diazomethane–ozone stoichiometry, and each route resulted in cleavage of the carbon–nitrogen bond. Ozone attack on the aromatic aldehydes[2] occurred at the carbon–hydrogen bond to give the peracid, which slowly converted unreacted aldehyde to the corresponding carboxylic acid. In the presence of molecular oxygen the aroylperoxy radical precursors to the peracid initiated autoxidation.

In the present study the diazomethanes ozonized were diazoacetophenone (Ia), *p*-chlorodiazoacetophenone (Ib), ethyl diazoacetate (Ic), and phenyldiazomethane (Id), compounds which are similar to aldehydes in that they have a hydrogen atom attached to the carbon–nitrogen double bond. Consequently, the ozone attack could occur either, or both, on the carbon–nitrogen double bond and on the carbon–hydrogen bond of the diazomethane system.



p-Chlorodiazoacetophenone (Ib) reacted more slowly with ozone than did any of the seven diazomethanes so far studied, while diazocetophenone (Ia) absorbed ozone only slightly less quantitatively than did diphenyldiazomethane or diazofluorene.[1] In methanol solution diazoacetophenone (Ia) and *p*-chlorodiazoacetophenone (Ib) reacted with 1 mole equiv. of ozone to produce the methyl hemiacetal of the corresponding glyoxals (IVa and IVb). About 0.85 mole equiv. of molecular oxygen was evolved, using ozone–nitrogen[1,3,4] and 0.05–0.10 equiv. of active oxygen was present in the reaction mixture. The phenylglyoxal (IVa) methyl hemiacetal was identified by comparison of its infrared spectrum with that of an authentic sample. It was isolated from the reaction mixture in 76% yield in the form of mandelic acid.[5] The infrared spectrum of *p*-chlorophenylglyoxal (IVb) methyl hemiacetal was similar to that of the corresponding derivative of IVa. It was isolated in good yield in the form of *p*-chlorophenylglyoxal hydrate.

In carbon tetrachloride or methylene chloride solution 1 mole equiv. of ozone from ozone–nitrogen[1,3,4] was required to react with diazoacetophenone (Ia), and 0.3–0.5 mole equiv. of molecular oxygen was evolved. An infrared spectrum of the reaction mixture showed bands at 5.6, 5.7, 9.55, and 9.8 μ, typical of benzoic formic anhydride (IXa).[6] In addition, there were bands at 5.8 and 5.9 μ which may have been due to phenylglyoxal (IVa). From the reaction mixture was isolated 42–49% yields of benzoic acid and, in one instance, a 16% yield of mandelic acid (from sodium hydroxide treatment of phenylglyoxal, IVa).[5] A small amount of nonacidic material remained in the reaction mixture; the infrared spectrum of this material from the carbon tetrachloride ozonation mixture indicated it to be an acyl halide. Using ozone–oxygen mixtures, only 0.65 or less mole equiv. of ozone was required to react with diazoacetophenone (Ia) in carbon tetrachloride solvent, and the benzoic acid yields were larger, 52–58%. The infrared spectrum of the reaction mixture slowly changed over a period of 39 days from that of benzoic formic anhydride (IXa) to that of benzoic acid.

p-Chlorodiazoacetophenone (Ib) behaved similarly upon ozonation in carbon tetrachloride or methylene chloride solution, except that higher yields of *p*-chlorobenzoic acid were isolated (58% from a reaction using ozone–nitrogen, and 96% from a reaction using ozone–oxygen). Carbon monoxide (from decomposition of IXb perhaps) was found in the exit gases.

These data suggest that in methanol solution the two diazoacetophenones (Ia and b) reacted by the route

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[2] H. M. White and P. S. Bailey, *ibid.*, **30**, 3037 (1965).

[3] P. S. Bailey and A. M. Reader, *Chem. Ind.* (London), 1063 (1961).

[4] P. S. Bailey, P. Kolsaker, B. Sinha, J. B. Ashton, F. Dobinson, and J. E. Batterbee, *J. Org. Chem.*, **29**, 1400 (1964).

[5] P. S. Bailey, S. B. Mainthia, and C. J. Abshire, *J. Am. Chem. Soc.*, **82**, 6136 (1960).

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involving 1:1 stoichiometry described in the earlier paper for the disubstituted diazomethanes[1] (*i.e.*, I → II → IV). The results in methylene chloride or carbon tetrachloride, however, are strikingly similar to the results described for the ozonation of the aromatic aldehydes.[2] Thus, we believe that in these solvents ozone not only attacks the carbon–nitrogen double bond of Ia and Ib, but also the carbon–hydrogen bond, to give IIIa and IIIb. Decomposition of III to peroxy V and/or oxy radicals then occurs and these initiate autoxidation (*e.g.*, V + I → VI + VII; VII + O_2 → V; etc.). The fact that less ozone was required to use up the starting material with ozone–oxygen than with ozone–nitrogen mixtures is indicative of the autoxidation side reaction. In the absence of oxygen and the presence of carbon tetrachloride, radicals such as VII could abstract chlorine[2] and eventually give the aroyl chloride found in the reaction mixture. Benzoic formic anhydride (IXa), and its analog IXb, could come from various routes, such as a rearrangement of VIIIa, involving a 1,2-carbon-to-oxygen shift and loss of molecular nitrogen. More of VIII should be produced when ozone–oxygen rather than ozone–nitrogen is used (because of autoxidation), thus accounting for the higher carboxylic acid yields under these conditions.

An alternative route to anhydride IX involves cyclization of, and loss of nitrous oxide from II to give X, followed by rearrangement of X.[1] If, however, such a reaction occurred in the case of Ia and Ib, there is no reason why it should not have occurred with azibenzil to give benzoic anhydride, but neither benzoic anhydride nor benzoic acid was found among the products from ozonation of azibenzil.[1]

Ethyl diazoacetate (Ic) reacted quantitatively with ozone (from ozone–oxygen) until about 0.7 mole equiv. of ozone had reacted; a total of 0.86 mole equiv. of ozone finally reacted. Although an infrared spectrum of the reaction mixture showed the presence of nothing but ethyl glyoxalate (IVc), only a 33% yield was isolated. As in the case of Ia and Ib, the results indicate a mechanism involving IIIc competing with the mechanism involving IIc. Decomposition of IIIc or its hydroperoxy analog (VIc) might be expected to give largely gaseous products.

Two mole equivalents of ozone (from ozone–nitrogen[1,3,4]) were absorbed quantitatively by phenyldiazomethane (Id) in ethyl acetate solution; about 0.9 mole equiv. of molecular oxygen was evolved. An infrared spectrum of the product showed only benzoic acid and benzaldehyde (IVd) in approximately a 4:1 proportion; a 67% yield of benzoic acid was isolated. The results could be explained by Id → IId → IVd, followed by ozonation of benzaldehyde (IVd) to benzoic acid,[2] or by a combination of this route and the route involving IIId.

There is no doubt, either from the results reported here or those reported earlier by us[1,7,8] and others,[9–13] that carbon–nitrogen double bonds are attacked, and often cleaved, by ozone. However, there is a question, in cases where a hydrogen atom is present on the carbon atom of the carbon–nitrogen bond, whether the initial ozone attack is on the carbon–nitrogen or the carbon–hydrogen bond, or whether both types of attack occur. For this reason we are reinvestigating our earlier work with Schiff bases.[7]

Experimental

The ozonation setup and procedures were described in earlier publications.[1,3,4,14] Solvents were pure and anhydrous, unless otherwise stated. Diazoacetophenone[15] (Ia), *p*-chlorodiazoacetophenone[15] (Ib), and phenyldiazomethane[16] (Id) were synthesized by published methods and possessed physical properties identical with those recorded in the literature. Ethyl diazoacetate (Ic) was purchased from K & K Laboratories, Jamaica, N. Y.

Ozonation of Diazoacetophenone (Ia) in the Presence of Methanol. A.—Several ozonations were run using 5–10 mmoles of Ia in 50–75 ml. of a 3:1 solution of carbon tetrachloride and methanol at −35°. The reaction mixture absorbed 1 mole equiv. of ozone from ozone–nitrogen,[1,3,4] almost quantitatively. Molecular oxygen yields[1,3,4] averaged 0.85 mole. equiv. The active oxygen content of the reaction mixtures ranged from 0.05 to 0.10 equiv. The reaction mixture was evaporated under reduced pressure. An infrared spectrum of the residue in carbon tetrachloride showed almost complete identity with a spectrum of a carbon tetrachloride solution of phenylglyoxal (IVa) methyl hemiacetal, prepared by dissolving phenylglyoxal[5] in methanol, evaporating the solution under reduced pressure, and dissolving the residue in carbon tetrachloride. Characteristic peaks were present at about 2.9 (hydroxyl), 3.25 (phenyl hydrogens), 3.45 (methyl hydrogens), 3.52 (hydrogen of former aldehyde group), 5.92 (keto carbonyl), 6.25 (phenyl unsat.), and 7.82, 8.5–8.6, and 9.0–9.4 μ (probably methoxyl). No diazo band (4.75 μ) was present. Similar results were obtained when the ozonation was carried out with ozone–oxygen.

B.—In another instance the ozonation was carried out with ozone–nitrogen, after which 50 ml. (per 10 mmoles of Ia) of 8% aqueous sodium hydroxide solution was added to the reaction mixture and the resulting mixture was refluxed for 2 hr. and stirred for 14 hr. The aqueous layer was separated, acidified, saturated with sodium chloride, and exhaustively extracted with ether. Evaporation gave a 76% crude yield of *dl*-mandelic acid[5] melting at 115–118°, recrystallized from benzene to m.p. 117–118° (64% yield), no depression in a mixture melting point with an authentic sample.

Ozonation of *p*-chlorodiazoacetophenone (Ib) in carbon tetrachloride–methanol gave results similar to those with Ia, including molecular oxygen and active oxygen yields. Evaporation of the reaction mixture gave a 96% yield of a low-melting solid which is thought to be crude *p*-chlorophenylglyoxal (IVb) methyl hemiacetal because of the similarity of its infrared spectrum (in carbon tetrachloride) with that of phenylglyoxal (IVa) methyl hemiacetal (preceding experiment). Treatment of the material with boiling water converted it to *p*-chlorophenylglyoxal (IVb) hydrate melting at 121–122°.[17]

Ozonation of Diazoacetophenone (Ia) in Carbon Tetrachloride or Methylene Chloride. A. With Ozone–Nitrogen.—A solution of 10 mmoles of Ia in 50 ml. of carbon tetrachloride was ozonized at 0° with an ozone–nitrogen stream containing 10 mmoles of ozone. Ozone absorption was almost quantitative. The molecular oxygen yield was 3.8 mmoles.[18] An infrared spectrum of the reaction mixture showed that no Ia remained (characteristic diazo band at 4.75 μ); strong bands found at 5.6, 5.7, 9.55, and 9.8 μ are characteristic of benzoic formic anhydride.[6]

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[17] P. Karrer and C. Musante [*Helv. Chim. Acta*, **18**, 1140 (1935)] reported m.p. 122°.

[18] In several experiments the molecular oxygen yield varied from 2.7 to 3.8 mole equiv., with most of the values being closer to the latter.

The resulting suspension was stirred with 25 ml. of water for 2 hr. and then extracted with several portions of sodium bicarbonate solution. The organic layer was dried and evaporated, leaving 0.24 g. of a yellow oil which had the pungent odor of an acid chloride. An infrared spectrum of the oil showed a carbonyl band at 5.9, which could be due to phenylglyoxal (IVa), no band at 5.6, showing that benzoic formic anhydride (IXa) was no longer present, and a band at 5.7 μ which could be due to an acid chloride. Acidification of the bicarbonate layer with hydrochloric acid, extraction with ether, evaporation of the ether extract, and recrystallization of the residue from water gave a 47% yield of benzoic acid melting at 121–122°; identification was by infrared spectrum.

In another experiment the carbon tetrachloride reaction mixture was worked up by extraction with four 10-ml. portions of 30% sodium hydroxide solution. Acidification, extraction with ether, evaporation of the ether, and recrystallization of the residue from water gave a 42% yield of benzoic acid (m.p. 120–121° alone and in admixture with an authentic sample). Evaporation of the aqueous filtrate and recrystallization of the residue from benzene gave a 16% yield of *dl*-mandelic acid[5] (m.p. 117–118° alone and in admixture with an authentic sample).

In another experiment only 0.7 mmole of ozone was employed in an ozonation of 10 mmoles of Ia in carbon tetrachloride at 0°. An immediate infrared spectrum of the reaction mixture indicated that approximately 3 mmoles of unreacted Ia (diazo band at 4.75 μ) remained in the reaction mixture. Work-up as in the first experiment described with Ia gave 3.4 mmoles of benzoic acid (m.p. 120–121°, identified by infrared spectrum), which is a 49% yield based on 0.7 mmole of Ia reacting. The molecular oxygen yield was 3.4 mole equiv. based on 0.7 mmole of Ia reacting.

B. **With Ozone–Oxygen.**—A solution of 10 mmoles of diazoacetophenone (Ia) in 50 ml. of carbon tetrachloride was ozonized as in the preceding experiments, except with 10 mmoles of ozone from ozone–oxygen (9.8 mmoles actually reacted). The reaction mixture was worked up as described in this first experiment with Ia using ozone–nitrogen. The neutral layer weighed 0.21 g.; it did not have the characteristic pungent acyl halide odor, and its infrared spectrum was more complex in the carbonyl region than was that of the neutral fraction from the ozone–nitrogen experiment. From the basic extract, a 52% yield of benzoic acid was obtained (m.p. 122°, identification by infrared spectrum). From a similar experiment using methylene chloride solvent, the benzoic acid yield was 58%. In another instance, using methylene chloride solvent at 25°, the infrared spectrum of the reaction mixture closely resembled that of the carbon tetrachloride ozonation mixture, with the characteristic benzoic formic anhydride bands at 5.6, 5.7, 9.55, and 9.8 μ.[6] The reaction mixture was allowed to stand for 39 days, during which time it changed gradually, as indicated by infrared spectra, to a solution of benzoic acid.

In another experiment, using carbon tetrachloride solvent at 0°, 0.75 mole equiv. of ozone from ozone–oxygen was passed through the reaction mixture (0.65 mole equiv. actually reacted, as found by titration of the iodide trap). An infrared spectrum of the reaction mixture was almost identical with that of the reaction mixture obtained with 1 mole equiv. of ozone from ozone–nitrogen. No starting material (Ia) was present (diazo band at 4.75 μ), indicating that less ozone was required when ozone–oxygen was employed than when ozone–nitrogen was used and, therefore, that some autoxidation had occurred.

Ozonation of *p*-Chlorodiazoacetophenone (Ib). A. In Carbon Tetrachloride.—A solution of 9.2 mmoles of Ib in 120 ml. of carbon tetrachloride was ozonized at 0° with an ozone–oxygen stream containing 1.43 mmoles of ozone/liter. Excess ozone was delivered, and titration of the iodide trap showed that about 1.0 mole equiv. reacted. The ozonation mixture which contained a small amount of white precipitate (*p*-chlorobenzoic acid) was extracted four times with a saturated aqueous sodium bicarbonate solution. Acidification of the basic extract gave a precipitate of *p*-chlorobenzoic acid (66% yield, m.p. 238–240°), identified by comparison of infrared spectra and by mixture melting point with an authentic sample. From similar runs using ozone–nitrogen, 0.4–0.5 mole equiv. of molecular oxygen was evolved, and a 58% yield of *p*-chlorobenzoic acid (m.p. 240–242°) was obtained.

In another run, a low ozone content (0.8 mmole/l.) ozone–oxygen stream was employed and ozone absorption was quantitative until 0.5 mole equiv. of ozone had reacted. Less than 1.0 mole equiv. reacted in total after passage of excess ozone through the reaction mixture. An infrared spectrum of the reaction mixture was very similar to that of the diazoacetophenone (Ia) ozonation mixture; no diazo band appeared at 4.77, but typical anhydride bands of 5.6, 5.7, 9.5, and 9.8 μ were present. The solvent was removed by evaporation, the residue was dissolved in methylene chloride, and this solution was allowed to stand for 1 week. *p*-Chlorobenzoic acid was periodically filtered off, giving a total yield of 82% (m.p. 239–241°, alone and in admixture with an authentic sample).

B. **In Methylene Chloride.**—An ozonation carried out and worked up in the manner described for the last experiment, except in methylene chloride at 0°, gave a 96% yield of *p*-chlorobenzoic acid (m.p. 239–241° alone and in admixture). In another run at 0°, palladium chloride test papers were suspended above the reaction mixture. As the ozonation neared completion, the palladium chloride papers turned black, indicating the evolution of carbon monoxide.

Ozonation of Ethyl Diazoacetate (Ic).—A solution of 5.24 g. (45.9 mmoles) of ethyl diazoacetate (Ic) in 53 ml. of methylene chloride was ozonized at 0° with ozone–oxygen containing 1.45 mmoles of ozone/liter. Ozone absorption was initially quantitative but fell off rapidly after about 0.7 mole equiv. of ozone had reacted. Titration of the iodide trap after passage of 1 mole equiv. of ozone showed that only 0.86 mole equiv. had reacted. The molar ratio of Ic to O_3 reacting was approximately 1.2. An infrared spectrum of the colorless reaction mixture showed that all of the ethyl diazoacetate (Ic, typical diazo band at 4.7 and carbonyl band at 5.9 μ) had reacted. The carbonyl band had shifted to 5.7 μ, which is characteristic of α-keto esters. The solution was evaporated at room temperature under reduced pressure and 11 g. of semicarbazide hydrochloride and 10 g. of sodium acetate in 50 ml. of water were immediately added to the residue, giving a 33% yield of the semicarbazone of ethyl glyoxalate (IVc) melting at 223–226° dec.[19]

Ozonation of Phenyldiazomethane (Id).—A solution of 1.14 g. (9.66 mmoles) of Id in 100 ml. of ethyl acetate was ozonized at 0° with an ozone–nitrogen stream containing 19.2 mmoles of ozone. Ozone absorption was quantitative and 8.7 mmoles of molecular oxygen was evolved. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in 11 ml. of methylene chloride. Comparison of the infrared spectrum of this solution with those of 10% solutions of Id, benzoic acid, and benzaldehyde (IVd) indicated that the product contained no starting material (Id) and consisted of 80% benzoic acid and 20% benzaldehyde. The methylene chloride solution was evaporated and the residue was recrystallized from water (charcoal), giving a 67% yield of benzoic acid melting at 121–122°, showing no depression in a mixture melting point with an authentic sample.

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(19) L. J. Simon and G. Chavanne, [*Compt. Rend.*, **143**, 904 (1906)] reported m.p. 228° dec. Since they also reported that IVc rapidly polymerizes, the semicarbazone was made immediately after the reaction mixture was evaporated.