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Singlet Oxygen Reactions from the Adducts of Ozone with Heterocyclic Substrates

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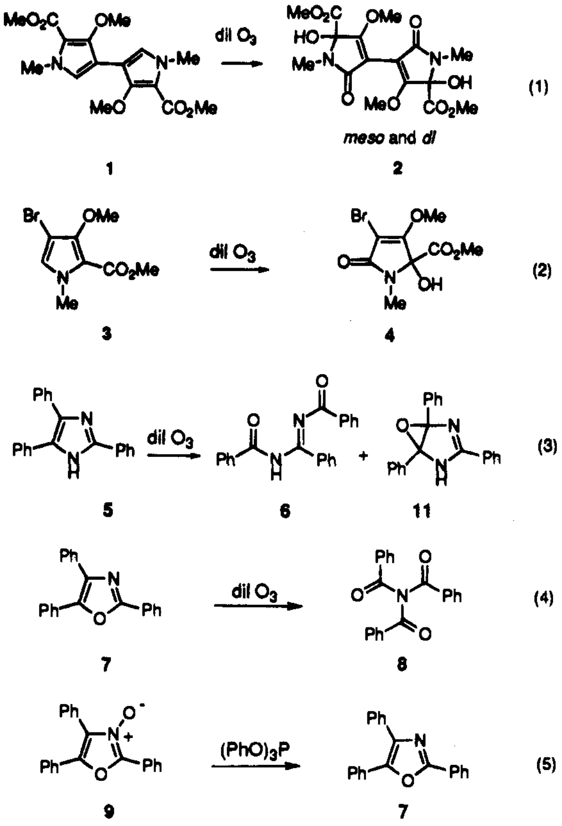
There has been continuing interest in the reactions of ozone with certain organic substrates in which the substrate incorporates one atom of oxygen, releasing singlet molecular oxygen for the oxidation of a suitable acceptor. In early work on this phenomenon, Knowles and Thompson investigated the reactions of ozone with triaryl phosphites leading to ozone−phosphite adducts.[1] This work was followed by the studies of Murray[2] and, later, of Bartlett,[3] who showed that triphenyl phosphite ozonide could bring about typical singlet oxygen reactions with a variety of acceptors. Other species which appear to react with ozone by removal of one atom of oxygen and the generation of singlet oxygen include sulfides, phosphines, sulfoxides, tertiary amines, ethers, trialkylsilanes, and highly hindered olefins.[4]

We now report that a number of heterocyclic systems undergo reactions with low concentrations of ozone, forming products typically associated with oxygenation by singlet oxygen. As outlined below, the pyrrole, oxazole or imidazole reactants appear to form complexes with dilute ozone at −78 °C. In the breakdown of these complexes, one atom of oxygen is incorporated in the heterocyclic system, while molecular oxygen is released in singlet form for reaction with the uncomplexed heterocycle present in excess. These results are analogous to those encountered the early studies of Knowles and Thompson on the reactions of phosphites with ozone, which were interpreted in terms of the initial formation of an ozone−phosphite adduct, which could react with substrate phosphite to produce phosphate.[1]

We first observed this phenomenon in our studies on the oxidative conversion of a bipyrrole precursor (**1**) to the highly oxygenated isochrysohermidine (**2**) using a stream of nitrogen containing a very dilute concentration of ozone (eq 1) (Scheme 1).[5,6] Related results were then obtained with methyl *N*-methyl-3-methoxy-4-bromopyrrole-2-carboxylate (**3**). In the reaction with dilute ozone, the unsaturated lactam **4** could be isolated (25%) along with other unidentified material (eq 2). A control dye-sensitized photooxidation of **3** in methanol showed that the same unsaturated lactam **4** was the major product. Under the traditional conditions of ozonolysis of **3**, none of the lactam **4** could be isolated.

Scheme 1



The following is a typical procedure for the dilute ozone reaction. Methylene chloride at −78 °C was saturated with O_3 until a dark blue color persisted. The solution was then purged with N_2 at −78 °C until only a pale blue color remained.[7] The reaction flask was then connected through a glass tube to another flask containing the heterocycle in CH_2Cl_2 (0.01 M) at 0 °C. Nitrogen was bubbled through the dilute O_3 solution transferring a low concentration of O_3 to the substrate in CH_2Cl_2 until the reaction was complete (5−20 min) as shown by TLC analysis. The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography (SiO_2). In this way, lophine (2,4,5-triphenylimidazole) (**5**) was converted to *N,N'*-benzoylbenzamidine (**6**) (21%) (eq 3). The benzamidine **6** is the same product formed from lophine by singlet oxygen oxidation.[8]

The reactions of oxazole derivatives with singlet oxygen have been extensively studied in our earlier work.[9] In particular, the formation of triamides in this reaction has been noted as one of the definitive tests for the involvement of singlet oxygen in the oxidation. Thus 2,4,5-triphenyloxazole (**7**) yields tribenzamide (**8**) in nearly quantitative yield under typical dye-sensitized photooxidation conditions.[10] When, in the present work, oxazole **7** was subjected to the reaction with dilute ozone in the nitrogen sweep setup, tribenzamide (**8**) was isolated (31%) as the major product along with an unstable byproduct (eq 4). It is pertinent to mention that recent studies by Kashima on the reactions of ozone with aryl-substituted oxazoles including **7** under conventional ozonolysis conditions at −78 °C have led to a variety of oxygenated products, none of which have been triamides.[11]

Under slightly different conditions, the oxazole−ozone complex could be employed as a singlet oxygen source for reaction with other substrates. After the complex was formed at −78 °C, the solution was swept free of any excess ozone and then treated with the acceptor. With rubrene, no decolorization took place initially at −78 °C, but as the solution was allowed to warm to room temperature, it underwent gradual decolorization. Similarly, addition of 1,3-diphenylisobenzofuran to the complex at −78 °C followed by warming produced *o*-dibenzoylbenzene (70%). Further definitive evidence for the

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[1] Knowles, W. S.; Thompson, Q. E. *Chem. Ind.* **1959**, 121.

[2] Murray, R. W.; Kaplan, M. L. *J. Am. Chem. Soc.* **1969**, *91*, 5358.

[3] Bartlett, P. D.; Mendenhall, G. D. *J. Am. Chem. Soc.* **1968**, *90*, 4161.

[4] (a) Murray, R. W. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press Inc.: New York, 1979; p 106. (b) Corey, E. J.; Mehrotra, M. M.; Kahn, A. U. *J. Am. Chem. Soc.* **1986**, *108*, 2472.

[5] Wasserman, H. H.; DeSimone, R. W.; Boger, D. L.; Baldino, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 8457.

[6] In our first report on this transformation,[5] we incorrectly assumed that triphenylphosphine or triphenyl phosphite served as the scavenger of oxygen from ozone, releasing singlet oxygen into the nitrogen stream.

[7] Analysis of the ozone solution by the titrimetric method of Treadwell and Anneler (*Z. Anorg. Chem.* **1905**, *48*, 86) showed that the pale blue solution had an ozone concentration of 0.006 M.

[8] Sonnenberg, J.; White, D. M. *J. Am. Chem. Soc.* **1964**, *86*, 5686.

[9] Wasserman, H. H.; McCarthy, K. E.; Prowse, K. S. *Chem. Rev.* **1986**, *86*, 845.

[10] Wasserman, H. H.; Floyd, M. B. *Tetrahedron, Suppl. 7* **1966**, 441.

[11] Kashima, C.; Arao, H.; Hibi, S. *J. Chem. Res. Miniprint* **1991**, 347.

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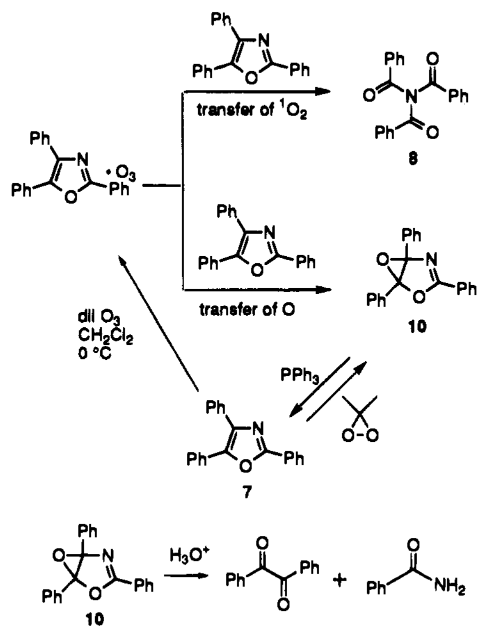
Scheme 2



involvement of singlet oxygen in the above processes was obtained by the addition of tetramethylethylene to the complex at −78 °C. Workup of the reaction mixture at room temperature after the addition of triphenylphosphine produced 2,3-dimethyl-3-hydroxy-1-butene, the expected reduction product of the $^1O_2$ ene oxidation of TME.

In the course of our studies on oxazoles, we attempted to isolate and identify the unstable side product which was consistently formed in the dilute ozone oxidation of **7**. The possibility that this substance was the *N*-oxide of the oxazole was ruled out by experiments in which authentic *N*-oxide was prepared and its TLC behavior compared with that of the unknown intermediate. We also observed that the reaction mixture containing this intermediate underwent ready reaction with triphenylphosphine to yield the starting oxazole **7**. This reduction was not shown by the authentic oxazole *N*-oxide, which yielded **7** only when treated with triphenyl phosphite (eq 5).

A likely alternative structure for the unstable intermediate was considered to be the 4,5-epoxide (**10**). This monooxygenated derivative would be expected to revert to the original oxazole on treatment with triphenylphosphine. Strong evidence supporting this structure was obtained in the following way (Scheme 2). When oxazole **7** was treated with dimethyldioxirane (DMD),[12] a labile product was formed which showed TLC behavior identical with that of the unstable intermediate. This product could be converted to the starting oxazole with triphenylphosphine. Most significantly, when the reaction mixture from the dilute ozonolysis of **7** was treated with aqueous acid, benzil and benzamide were obtained in approximately equal amounts (~32%). Formation of these hydrolysis products (which are also generated by the reaction of **7** with DMD followed by aqueous acid) points convincingly to the 4,5-epoxide structure **10** for the unstable intermediate[13] (Scheme 2). In the same way, we showed that the labile byproduct formed along with **6** from the reaction of lophine with dilute ozone yielded benzil on treatment with dilute acid. With this evidence in hand, we suggest structure **11** for the lophine monooxygenated product.

We now come to the question of the difference between the results of conventional ozonolyses of heterocyclic systems such as oxazoles and the reactions of the same heterocyclic substrates with dilute ozone. One explanation pictures both ozonolytic processes as taking place through the formation of an initial complex between ozone and the heterocycle at low temperature. Under the normal circumstances, this complex or adduct[14] would react with excess ozone to form the traditional ozonolysis products. However, with low concentrations of ozone and in the presence of excess heterocyclic substrate, the adduct could break down on warming, forming the monooxidation product of the heterocycle while releasing singlet oxygen for typical $^1O_2$ reactions with the hetero system.[2] Alternatively, the reactions of these adducts with typical acceptors may take place by a direct bimolecular process without release of singlet oxygen.[3] On the basis of this work, one may now look on the adducts of heterocyclic systems with ozone as singlet oxygen sources taking part in Murray[2] or Bartlett[3] oxidations analogous to those observed with the adduct of triphenyl phosphite and ozone.

In further work, we are extending our studies to other heterocyclic systems and to electron-rich substrates which may form related adducts with ozone, leading to the formaton of singlet oxygen.

Acknowledgment. Financial support from the National Institutes of Health and the National Science Foundation is gratefully acknowledged. We thank Drs. Kieseung Lee and Steven Coats for help in identifying the tetramethylethylene oxidation product.

Supporting Information Available: Experimental procedures for the oxidation of **3**, **5** and **7**, ^1H, IR, and mass spectral data for **4**, descriptions of $^1O_2$ reactions with rubrene, 1,3-diphenylisobenzofuran, and tetramethylethylene, and studies on the characterization of unstable intermediates **10** and **11** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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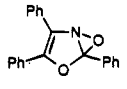
(12) For recent reviews on the reaction of DMD, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, Chapter 1. (c) Adam, W., Hadjiarapoglou, L.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, **1993**; Chapter 4, pp 195−219. (d) Adam, W.; Hadjiarapoglou, L. In *Topics in Current Chemistry*; Herrmann, W. A., Ed.; Springer-Verlag: Berlin, 1993, Vol. 164, pp 45−62.

(13) Our evidence does not eliminate the less likely oxaziridine structure **12** for the oxazole monooxygenated product.



12

(14) At this stage, we cannot rule out the possibility of an initial addition product of the heterocyclic system with ozone.