Singlet Oxygen Sources in Ozone Chemistry. Chemical Oxygenations Using the Adducts between Phosphite Esters and Ozone[1]

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Abstract: The adduct between ozone and triphenyl phosphite provides a convenient method of chemical oxygenation for synthetic or mechanistic purposes. Control experiments, esr results, and the nature of the chemistry observed lead to the conclusion that the oxygenation agent is free singlet oxygen.

The highly significant report by Foote and Wexler[3] that the reaction of sodium hypochlorite and hydrogen peroxide produces an oxidizing species which gives products identical with those of dye-sensitized oxygenations has initiated an intensive investigation of the chemistry of the species suggested[3] as being the common oxidizing agent in these apparently diverse systems, namely, $^1\Delta$-oxygen. While many of these reports have been concerned with demonstrating further the likely involvement of $^1\Delta$-oxygen in dye-sensitized oxygenations,[4] others have described additional methods of producing $^1\Delta$-oxygen either for use in chemical oxygenation or as evidence for its intermediacy. Other such methods reported include the use of a radiofrequency discharge in gaseous oxygen,[5,6] the reaction of bromine and hydrogen peroxide,[7] the decomposition of alkaline solutions of peracids,[7] the decomposition of photoperoxides,[8] and the self-reaction of *sec*-butylperoxy radicals.[9]

We previously reported in preliminary form that the adduct between triphenyl phosphite and ozone can be used to accomplish typical singlet oxygen oxidations both in solution[1] and in the gas phase.[1] It has also been reported that the oxygen produced in the decomposition of the triphenyl phosphite–ozone adduct contains $^1\Delta$-oxygen as demonstrated by its characteristic epr absorptions.[10] In this paper we describe further the use of phosphite ester–ozone adducts in chemical oxygenations as well as some additional evidence on the nature of the oxidizing species and the stability of the adduct. This work provides additional evidence that $^1\Delta$-oxygen is indeed the oxygenation reagent and indicates that the triphenyl phosphite–ozone adduct is a convenient and versatile source of singlet oxygen for use in chemical oxygenation. It further suggests that there may be many additional sources of singlet oxygen in ozone chemistry and that such a possibility has important consequences not only to synthetic and mechanistic ozone chemistry studies but also to such areas as air pollution and biological oxidations.

Results and Discussion

A number of cases are known in which ozone reacts with a substrate in such a way that only one oxygen atom of the ozone is incorporated in the oxidized product. The remaining two oxygen atoms of the ozone are usually evolved as molecular oxygen. Examples include the oxidation of tertiary amines to amine oxides, phosphines to phosphine oxides, sulfides to sulfoxides, and sulfoxides to sulfones.[11] Even in ozonolysis, where the usual reaction leads to all three oxygen atoms of ozone being incorporated in products, there are a number of cases reported where again only one of the ozone oxygen atoms is accounted for by the major reaction products. These latter cases are usually 1-olefins with special structural features which lead to the corresponding epoxide as the ozonization product.[12–15]

A consideration of the conservation of spin principle suggested to us some time ago that the oxygen involved in some or all of these reactions probably has singlet multiplicity. This possibility has also been considered by Corey and Taylor.[5] The recent intensive investigations of singlet oxygen beginning with the work of Foote and Wexler[3] provided us with the additional incentive to examine the general question of singlet oxygen sources in ozone chemistry.

The case examined in our initial investigation in this area was reported first in 1961 by Thompson.[16] Thompson had observed that ozone and triaryl phosphites formed 1:1 adducts which were stable at low temperatures. When these adducts were allowed to warm the corresponding phosphates were produced and molecular oxygen was evolved. In such cases, we would be able to purge the reaction solution of excess ozone and use reactions diagnostic of singlet oxygen to examine the evolved oxygen while avoiding the added complexity which accompanying ozone oxidations would bring to product analysis. This latter complication still remains in other cases we have attempted or contemplated.

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[1] Preliminary accounts of this work have appeared: R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **90**, 537, 4161 (1968).

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[3] C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879 (1964).

[4] For a recent summary of this aspect of $^1\Delta$ oxygen work, see C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *ibid.*, **90**, 975 (1968).

[5] E. J. Corey and W. C. Taylor, *ibid.*, **86**, 3881 (1964).

[6] A. M. Winer and K. D. Bayes, *J. Phys. Chem.*, 70, 302 (1966).

[7] E. McKeown and W. A. Waters, *J. Chem. Soc.*, *B*, 1040 (1966).

[8] H. H. Wasserman and J. R. Scheffer, *J. Am. Chem. Soc.*, **89**, 3073 (1967).

[9] J. A. Howard and K. U. Ingold, *ibid.*, **90**, 1956 (1968).

[10] E. Wasserman, R. W. Murray, M. L. Kaplan, and W. A. Yager, *ibid.*, **90**, 4160 (1968).

[11] P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[12] R. C. Fuson, M. D. Armstrong, W. E. Wallace, and J. W. Kneisley, *J. Am. Chem. Soc.*, **66**, 1274 (1944).

[13] P. D. Bartlett and M. Stiles, *ibid.*, 77, 2806 (1955).

[14] R. Criegee, Advances in Chemistry Series, No. 21, American Chemical Society, Washington, D. C., 1959, p 133.

[15] P. S. Bailey and A. G. Lane, *J. Am. Chem. Soc.*, **89**, 4473 (1967).

[16] Q. E. Thompson, *ibid.*, **83**, 846 (1961).

In the general procedure the adduct is formed from triphenyl phosphite and ozone at −78° by passing ozone into a methylene chloride solution of the phosphite until the blue color of ozone persists. Excess ozone is then removed by nitrogen purging. A cold methylene chloride solution of the acceptor is then added. The adduct is then permitted to warm and evidence for reaction with the acceptor is then sought.

Singlet Oxygen Acceptors

Largely because of their importance in dye-photosensitized oxidations two general types of acceptor molecules have become useful for diagnosing the presence of singlet oxygen. These are (1) conjugated dienes which undergo a Diels–Alder type reaction to give 1,4-*endo*-peroxides and (2) olefins with allylic hydrogens available for undergoing an "ene" reaction to an allylic hydroperoxide.

Using the general procedure described above we have shown that when the triphenyl phosphite–ozone adduct is allowed to warm up in the presence of 1,3-cyclohexadiene a 67% yield of 5,6-dioxabicyclo[2.2.2]octene-2 ("norascaridole") is produced. This product is identical with that produced in photooxygenations[17] and with the hypochlorite–hydrogen peroxide system[4] and attributed to a singlet oxygen reaction.[4]

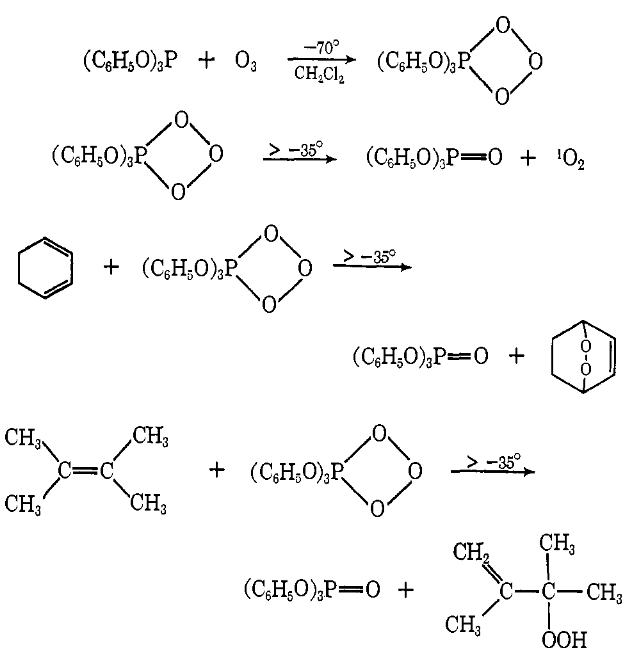
A number of variations on the general experimental procedure were attempted in order to optimize product yield. The yield of *endo*-peroxide was found to be consistently about 67% regardless of whether acceptor and adduct were present in equimolar amounts or whether one or the other were present in excess.

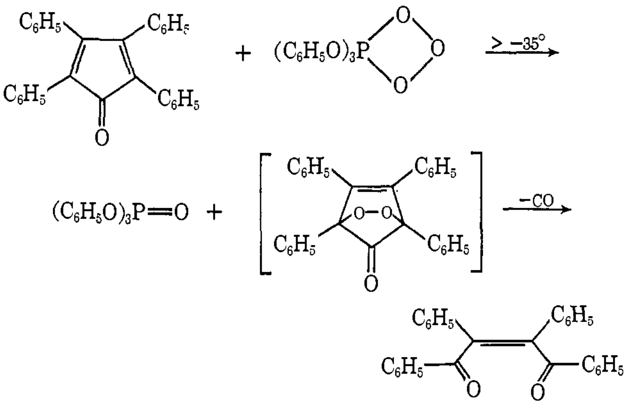
Part of the difficulty encountered in improving the yield may be the nucleophilic attack of the substrate phosphite on the phosphite–ozone adduct as suggested by Thompson.[16] Thus, while in all cases we observe a quantitative yield of phosphate, a portion of this may have been produced prior to the addition of acceptor and subsequent warm-up. This possibility is being investigated.

Using the same general procedure described above the phosphite–ozone adduct was prepared and then allowed to warm up in the presence of an equimolar amount of 2,3-dimethylbutene-2. In this case a 53% yield of the allylic hydroperoxide, 2,3-dimethyl-3-hydroperoxybutene-1, was obtained. This product had the same properties as that reported by Foote and Wexler[3] and that obtained in a photosensitized oxidation.

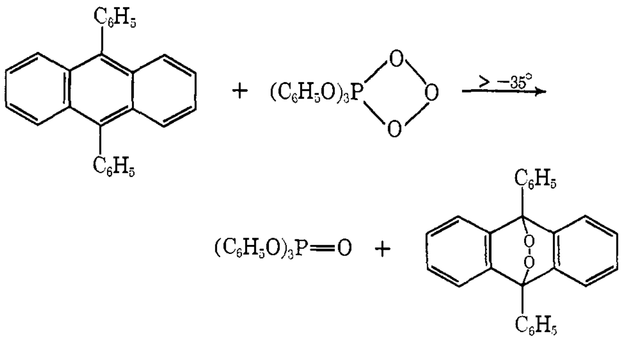
The phosphite–ozone adduct was capable, therefore, of giving both general types of singlet oxygen reactions.

Other systems known to undergo chemical oxygenations were then treated with the phosphite–ozone adduct. A methylene chloride solution of tetraphenylcyclopentadienone was added to a 2:1 excess of the triphenyl phosphite–ozone adduct at −78° with subsequent warm-up. This procedure gave a 38.2% yield of *cis*-dibenzoylstilbene. This product is reported to be formed in photooxygenation[18–20] and has also been obtained using the hypochlorite–hydrogen peroxide system.[4]





While generally less reactive as a singlet oxygen acceptor than tetramethylethylene or 9,10-dimethylanthracene,[21] 9,10-diphenylanthracene has also been observed to give the *endo*-peroxide. When treated with a 2:1 excess of the triphenyl phosphite–ozone adduct in the usual manner, 9,10-diphenylanthracene gave a 77% yield of the *endo*-peroxide which had properties identical with those for the photochemically obtained material.



Finally the oxygenation of α-terpinene to ascaridole was accomplished in 60% yield using the triphenyl

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(17) G. O. Schenck and W. Willmund, reported by R. Criegee in Houben-Weyl, "Methoden der organischen Chemie," Vol. VIII, E. Müller, Ed., 4th ed, Georg Thieme Verlag, Stuttgart, 1952, p 16.

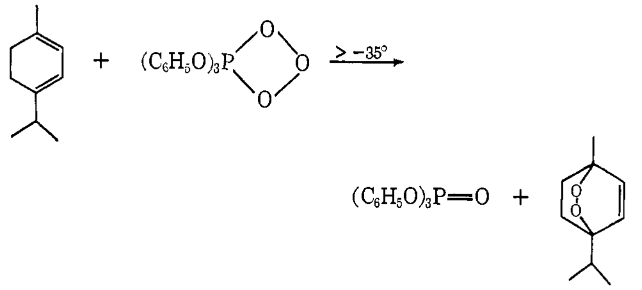
(18) C. F. Wilcox, Jr., and M. P. Stevens, *J. Am. Chem. Soc.*, **84**, 1258 (1962).

(19) G. O. Schenck, *Z. Elektrochem.*, **56**, 855 (1952).

(20) N. M. Bikales and E. I. Becker, *J. Org. Chem.*, **21**, 1405 (1956).

(21) T. Wilson, *J. Am. Chem. Soc.*, **88**, 2898 (1966).

phosphite–ozone adduct. This reagent is thus seen to be a very useful one for accomplishing a variety of chemical oxygenations in good yield and under very mild conditions.



Use of Other Phosphites

Thompson[16] had found that only the triaryl phosphites appeared to be capable of giving stable adducts. This conclusion was based primarily on the stoichiometry of the ozone–phosphite reaction. We have attempted to detect formation of such an adduct by use of the acceptor oxygenation technique. When triethyl phosphite was ozonized at −78° and then cyclohexadiene-1,3 added with subsequent warm-up no oxygenation of the olefin was observed. However, when this same experiment was carried out at −95° a low yield (~10%) of cyclohexadiene *endo*-peroxide could be obtained.

This result suggests that there may be a range of stabilities of ozone adducts and that under the proper conditions, *i.e.*, very low temperatures, other species which undergo one oxygen atom oxidations with ozone, may give stable adducts. Such other species might include, in principle at least, phosphines, sulfides, sulfones, tertiary amines, and perhaps even suitably substituted 1-olefins.

The relationship of such potential ozone adducts to the moloxide concept is perhaps worth pointing out. While the recent work of Foote and Wexler[3] and others strongly suggest that the species involved in photosensitized oxygenations is free singlet oxygen as opposed to the sensitizer–oxygen complex concept originally advocated by Schönberg,[22] the ozone adducts referred to here could, formally, be regarded as moloxides which are capable of causing oxygenations. The adduct between triphenyl phosphite and ozone, for example, might also be regarded as a moloxide of triphenyl phosphate. While this adduct was observed to decompose to give molecular oxygen and triphenyl phosphate, the question remained as to whether the oxygenation reagent was the adduct itself or the molecular oxygen evolved. This point is examined further below.

Nature of the Oxygenation Reagent

In order to test for any oxygenation activity of the phosphite–ozone adduct we have treated a solution of rubrene with a 200-fold excess of the adduct. Rubrene is one of the most active singlet oxygen acceptors[21] and, in addition, its bright orange color compared with the colorless *endo*-peroxide permits visible evidence of reaction.

A −78° solution of the adduct and rubrene showed no evidence of bleaching of the rubrene color after 30-min storage at this temperature. When the solution was permitted to slowly warm up, however, some color loss was evident at −35° and by −25° the solution was colorless. Continued warm-up to −10° gave vigorous gas evolution. Since our procedure calls for nitrogen purging of unreacted ozone prior to addition of acceptor it became necessary to verify the adequacy of the nitrogen purge. This was done by adding ozone to methylene chloride at −78°, purging with nitrogen, adding rubrene, and then warming. No bleaching of the rubrene occurred. When a cold solution of rubrene was treated with ozone the color was immediately bleached. These experiments indicate that there is little, if any, bimolecular reaction between the phosphite–ozone adduct and rubrene. On the other hand when the adduct is allowed to decompose and evolve oxygen then reaction with the rubrene is rapid.[23]

Further evidence on the nature and degree of freedom of the oxygenation species was obtained by observing gas phase reactions of the molecular oxygen evolved in the decomposition of the phosphite–ozone adduct. In an earlier experiment we attempted to transfer the gas evolved in the solution decomposition of the adduct to an adjacent flask containing a solution of rubrene. Even under conditions of vigorous gas evolution, no bleaching of the rubrene was observed. Apparently collisional deactivation of the $^1\Delta$-oxygen is far too rapid to permit transfer.

We then devised an apparatus to permit gas phase evolution and reaction of the oxygen. The phosphite–ozone adduct was prepared in dichlorodifluoromethane solvent which was subsequently removed at low temperature to give the solid adduct. It was necessary to add crushed chalk sticks to the adduct prior to solvent removal in order to moderate the subsequent decomposition of the solid adduct. The solid adduct was then attached to the apparatus shown in Figure 1. This apparatus was constructed in such a way as to prevent acceptor molecules from undergoing a heterogeneous reaction on the surface of the solid adduct.

Using this system it was possible to observe gas phase oxygenation of 1,3-cyclohexadiene to the *endo*-peroxide. The yield is small, *i.e.*, ~0.01% based on theoretically available oxygen. Again this could be due to collisional deactivation. The pressure during the decomposition reaction phase was ~0.2–0.6 mm. In a similar experiment α-terpinene was converted into ascaridole in ~0.01% yield. In both experiments the products were analyzed by flame ionization glpc. In both cases the starting materials were free of products. Likewise use of ground-state molecular oxygen in control experiments gave no *endo*-peroxide products.

A similar experiment using tetramethylethylene was less conclusive because of a failure to remove completely the allylic hydroperoxide product from starting material.

The combined weight of the esr results,[10] rubrene solution results, and gas phase oxygenations leads us to conclude that the oxygenation reagent in this system is excited molecular oxygen and not the phosphite–ozone adduct itself.

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(22) A. Schönberg, *Ann.*, **518**, 299 (1935).

(23) Professor P. D. Bartlett has observed a bimolecular reaction between the triphenylphosphite–ozone adduct and tetramethylethylene at low temperature. He has confirmed the absence of such a reaction in diene-type acceptors: P. D. Bartlett, paper presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, Abstract R2O.

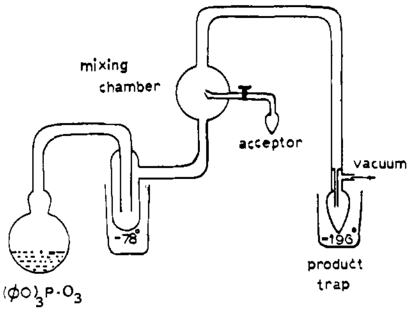

Figure 1. Diagrammatic representation of the Pyrex gas phase reactor.

Nature and Stability of the Triphenyl Phosphite–Ozone Adduct

On the basis of the ^{31}P nmr spectrum Thompson[16] concluded that the triphenyl phosphite–ozone adduct must have a cyclic structure and finally settled on the four-membered ring representation used here by analogy with other pentacovalent phosphorus compounds. Thompson also pointed out that such a structure is formally analogous to the initial adduct or molozonide formed in olefin–ozone systems.

We have measured the stability of the adduct by following its rate of decomposition by means of the oxygen evolved. Oxygen evolution was found to follow a typical first-order rate law (Figure 2). This method was used to calculate the rate of decomposition of the adduct in methylene chloride at a series of temperatures as shown in Table I. These data were then used to obtain the activation energy for decomposition and the transition-state parameters shown in Table II. The value for E_a of 14.1 ± 1.8 kcal/mole would appear to be a reasonable one for the assigned structure. The four-membered ring structure containing three oxygen atoms would be expected to have considerable steric strain and resultant instability. In fact few data are available for comparison. Benson has estimated[24] the bond strength of the oxygen–oxygen bond in the 1,2,3-trioxalane produced as the initial adduct in an olefin–ozone system to be about 15 kcal/mole. Also, Criegee and Schröder[25] have found the heat of rearrangement of the initial olefin–ozone adduct in the case of *trans*-1,2-di-*t*-butylethylene to be 37 kcal/mole in pentane. These authors also reported that this value was lower in halide-containing solvents.

Table I. Rate Constants at Several Temperatures for the Evolution of Oxygen from Triphenyl Phosphite–Ozone Adduct

T, °C	k, sec^{-1}
−17.0	1.58×10^{-3}
−24.0	5.97×10^{-4}
−33.5	2.27×10^{-4}
−41.0	7.90×10^{-5}
−44.0	6.24×10^{-5}

Table II. Activation Energy and Transition-State Parameters for Triphenyl Phosphite–Ozone Adduct Decomposition

E_a, kcal mole	14.1 ± 1.8
Log A	9.167
$\Delta F^{\ddagger}$, kcal mole (−24°)	17.5
$\Delta H^{\ddagger}$, kcal mole (−24°)	13.6
$\Delta S^{\ddagger}$, eu (−24°)	−3.9

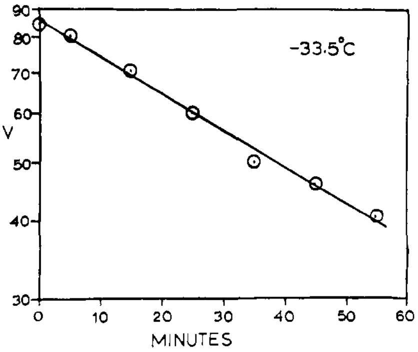

Figure 2. Typical first-order rate plot for the evolution of oxygen from the triphenyl phosphite–ozone adduct at −33.5°.

On the other hand it has been reported that the initial olefin–ozone adduct for hexene-1 has an E_a for decomposition in ethanol of 7 ± 2 kcal/mole.[26]

We have also attempted to determine the effect of solvent structure on the rate of decomposition of the adduct. These results are shown in Table III. As with the initial adduct in the olefin–ozone system,[25] the halogen-containing solvent methylene chloride leads to a more rapid rate of decomposition of the phosphite–ozone adduct than does ether. Also the hydrogen-donating solvents methanol and isopropyl alcohol gave higher rates of decomposition of the phosphite–ozone adduct.

Table III. Effect of Solvent on Rate of Decomposition of the Triphenyl Phosphite–Ozone Adduct (−24°)

Solvent	Rate constant, sec^{-1}	Relative rate
CH_2Cl_2	5.97×10^{-4}	1.0
CH_3OH	2.07×10^{-3}	3.5
$(CH_3)_2CHOH$	5.73×10^{-4}	0.96
$C_6H_5CH_3$	7.40×10^{-5}	0.12
CH_3COCH_3	1.60×10^{-4}	0.27
$(CH_3CH_2)_2O$	1.55×10^{-4}	0.26

Nature of Singlet Oxygen

A final point regarding the nature of the oxygenation reagent in this system needs to be considered, that is, the possibility that both Σ and Δ singlet oxygen are involved. This possibility has been recently discussed for dye-photosensitized oxygenations.[27,28] An experimental discussion of this possibility requires an acceptor which is presumably able to discriminate between $^1\Sigma$- and $^1\Delta$-oxygen in product formation. Kearns and coworkers have presented such a discussion[27,28] in the case of the dye-sensitized photooxygenation of cholest-4-en-3β-ol reported earlier by Nickon and Mendelson.[29]

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[24] S. W. Benson, Advances in Chemistry Series, No. 77, Vol. III, American Chemical Society, Washington, D. C., 1968, p 74.

[25] R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).

[26] S. D. Razumousky and L. V. Berezova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 1, 207 (1968).

[27] D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Am. Chem. Soc.*, **89**, 5455 (1967).

[28] D. R. Kearns, R. A. Hollins, A. U. Khan, and P. Radlick, *ibid.*, **89**, 5456 (1967).

We have attempted oxygenations of this same acceptor using the triphenyl phosphite–ozone adduct in order to examine the possibility of a distribution between $^1\Sigma$- and $^1\Delta$-oxygen in this system. While the results are as yet inconclusive it is clear that the product distribution is complex and make a definite conclusion difficult. We are presently considering other simpler acceptors to be used for this purpose. In addition we are attempting to determine the product selectivity of the singlet oxygen produced from the phosphite–ozone adduct. This method has been used effectively by Foote and coworkers.[30]

Experimental Section

All melting points and boiling points are uncorrected unless otherwise stated. Ir spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrometer, and are reported as τ values relative to external TMS.

Preparative gas chromatography utilized the Aerograph A-700 Autoprep instrument. Analytical gpc was performed with flame ionization detection cells on either the Aerograph Hi-Fi Model 600D or Aerograph Model 200. These units were used in conjunction with an Aerograph 471 digital integrator.

Ozonizations. Phosphite esters were dissolved in methylene chloride for ozonization unless otherwise stated. The solutions were placed in a two-necked, round-bottomed flask fitted with a gas inlet tube emerging near the bottom of the flask and a calcium sulfate drying tube. The flask was cooled in a Dry Ice–acetone bath at −78° and then ozonized using a Welsbach Model T-23 ozonator. Ozone was supplied at the rate of approximately 100 mmoles/hr. During ozonization the temperature of the solution rose to about −70°. When the blue color of excess ozone was observed the ozone stream was disconnected and replaced by a stream of dry nitrogen. Nitrogen purging was carried on well beyond the time necessary for the solution to loose its blue color.

Bleaching of Rubrene. A solution of triphenyl phosphite (3.1 g, 0.01 mole) was ozonized in methylene chloride (100 ml) in a flask fitted with a gas inlet tube, a drying tube, and a low-temperature thermometer. After nitrogen purging ($\sim$20 min) a cold solution of rubrene (Eastman, 0.025 g, 4.7×10^{-5} mole) in methylene chloride (50 ml) was added. Mixing was effected with the nitrogen stream. The bright red-orange solution appeared to remain unchanged during 30 min at −78°. When the cooling bath was removed and the mixture permitted to warm up, a slight color loss was apparent at −35° and by −25° the solution was colorless. Vigorous gas evolution was evident at −10°. No attempt was made to identify the oxidized product.

In a separate experiment a flask containing methylene chloride (100 ml) was ozonized at −78°. The blue color of ozone was observed after a very short time. A nitrogen purge was continued for $\sim$25 min after which time a cold solution of rubrene (0.025 g, 4.7×10^{-5} mole) in methylene chloride (50 ml) was added. The bright color of the rubrene persisted even when the bath was removed and the solution warmed to room temperature. When the solution was recooled to −78° and treated with ozone the rubrene color was immediately bleached.

Attempted Transfer of Singlet Oxygen Produced in Solution. Triphenyl phosphite (9.3 g, 0.03 mole) was ozonized in methylene chloride and purged with nitrogen. The drying tube was replaced with a gas transfer tube, the open end of which was introduced below the surface of a solution of rubrene ($\sim$10 mg) in methylene chloride. The −78° bath was removed and the solution warmed to room temperature. At −10° vigorous gas evolution proceeded. When the reaction was complete no color change was observed in the rubrene solution.

Oxidation of 1,3-Cyclohexadiene. A solution of triphenyl phosphite (Aldrich, 9.3 g, 0.03 mole) was ozonized in methylene chloride (100 ml). After nitrogen purging a cold solution of 1,3-cyclohexadiene (Aldrich, 1.60 g, 0.02 mole) in methylene chloride (45 ml) was added by funnel. Thorough mixing was achieved with the nitrogen stream. The Dry Ice–acetone bath was removed and the mixture was permitted to warm to room temperature. The solution was concentrated on a rotary evaporator and distilled *in vacuo* (<0.1 torr), with a short-path still. The product, 1.51 g, was a pale yellow semisolid (yield 67.4% based on olefin). After three recrystallizations from pentane the mp was 90–91°, with some gas evolution (lit.[17] mp 88.5°). The nmr and ir spectra were identical with those obtained from photochemically produced material.[4,31]

Several other variations were attempted in order to determine optimum oxidation conditions.

Method A. Triphenyl phosphite (6.2 g, 0.02 mole) was ozonized in methylene chloride (150 ml), purged with nitrogen, and followed by the addition of cyclohexadiene-1,3 (1.60 g, 0.02 mole) in cold methylene chloride solution (25 ml). The −78° bath was removed and replaced with a −25° bath (methanol–ice). The reaction remained at this temperature for 1.5 hr and was then permitted to warm to room temperature. A work-up identical with that above was used and the yield of product was 1.50 g (67%).

Method B. Triphenyl phosphite (6.2 g, 0.02 mole) was ozonized and purged with nitrogen as in method A. A cold solution of cyclohexadiene-1,3 (8.0 g, 0.1 mole) in methylene chloride (25 ml) was added and the −78° bath removed and the solution warmed to room temperature. A work-up identical with that used in method A gave 1.51 g (67.4%) of *endo*-peroxide.

Oxidation of 2,3-Dimethylbutene-2. A solution of triphenyl phosphite (6.2 g, 0.02 mole) in methylene chloride (100 ml) was ozonized and purged with nitrogen at −78°. A cold solution of 2,3-dimethylbutene-2 (1.68 g, 0.02 mole) in methylene chloride (45 ml) was added and mixing effected with the nitrogen stream. The −78° bath was removed and replaced with a −25° bath (ice–methanol). After about 16 hr the temperature had risen to −10°. At this point the reaction mixture was warmed to room temperature, concentrated on a rotary evaporator, and distilled *in vacuo* on a short-path still. The product was a colorless liquid boiling at 52–54 (9 mm) (lit.[32] bp 55° (12 mm)) and its ir and nmr spectra were identical with those for the product from a photooxygenation reaction.[4,31]

Oxidation of Tetraphenylcyclopentadienone. A solution of triphenyl phosphite (3.1 g, 0.01 mole) in methylene chloride was ozonized at −78° and purged with nitrogen. A cold deep red solution of tetraphenylcyclopentadienone (1.92 g, 0.005 mole) in methylene chloride (50 ml) was then added. A slow stream of nitrogen mixed the reactants and was continued after removal of the cold bath. After reaching room temperature the resulting mixture had lost most of its color. The solution was concentrated on a rotary evaporator and chromatographed on neutral alumina. A pale pink solid was eluted with benzene and was recrystallized from absolute ethyl alcohol. The yield of small pale pink needles was 0.71 g (38.2%). The mp of recrystallized material was 218–220° cor (lit.[33] mp 216–217°) and its ir spectrum was identical with that previously reported[33] for *cis*-dibenzoylstilbene.

Oxidation of 9,10-Diphenylanthracene. A solution of triphenyl phosphite (3.1 g, 0.01 mole) was ozonized in methylene chloride (100 ml) and purged with nitrogen in the usual way A cold solution of 9,10-diphenylanthracene (1.65 g, 0.005 mole) in methylene chloride (50 ml) was then added. A nitrogen stream mixed the solution during warm-up of the reaction to room temperature. The reaction mixture was concentrated on a rotary evaporator and chromatographed on neutral alumina (Fisher). The pale yellow solid which was eluted with pentane was recrystallized twice from acetone. The nearly white needles which resulted, yield 1.33 g (77%), decomposed rapidly at $\sim$200° (lit.[34] dec pt 180°) to give a higher melting yellow solid whose ir spectrum was identical with that of 9,10-diphenylanthracene. The ir spectrum of the peroxide in a KBr pellet was identical with that for the product formed in a photooxidation.[35]

Oxidation of α-Terpinene. α-Terpinene was prepared from α-terpineol by the oxalic acid dehydration procedure of von Rudloff.[36] The products were distilled on a Nester-Faust Teflon auto-

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(29) A. Nickon and W. L. Mendelson, *J. Am. Chem. Soc.*, **85**, 1894 (1963); **87**, 3921 (1965).

(30) C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Lett.*, 4111 (1965).

(31) We gratefully acknowledge the gift of photochemically produced norascaridole and 2,3-dimethyl-3-hydroperoxybutene-1 from Mrs. S. R. Fahrenholtz.

(32) G. O. Schenck and K. H. Schulte-Elte, *Ann.*, **618**, 185 (1958).

(33) D. R. Berger and R. K. Summerbell, *J. Org. Chem.*, **24**, 1881 (1959).

(34) C. Dufraisse and J. LeBras, *Bull. Soc. Chim. Fr.*, 4 [5], 349 (1937).

(35) We thank Mrs. V. Kuck for a sample of the photochemically produced product.

(36) E. von Rudloff, *Can. J. Chem.*, **39**, 1 (1961).

annular still and the fractions boiling at 76–77° (25 mm) were collected. Their ir spectra were identical with the published spectrum of α-terpinene.[37] Gpc analysis of the fractions on a 10 ft × $^3/_8$ in. 10% XE-60 column at 105° and 200 cc/min carrier gas showed them to contain from 83 to 93% α-terpinene (by comparison with retention time of analytical standard grade α-terpinene)[38] and the main impurity was shown to be *p*-cymene.

A cold solution of α-terpinene (2.72 g, 0.02 mole; material was 93% pure) in methylene chloride (50 ml) was added to the ozonized and nitrogen-purged solution of triphenyl phosphite (6.2 g, 0.02 mole) in methylene chloride (125 ml). A slow nitrogen stream was allowed to continue after the −78° bath was removed and until room temperature was reached. After concentration on a rotary evaporator a vacuum distillation on a short-path still gave 2.35 g of a pale yellow liquid (bp 40–50° (<0.4 mm)). The nmr spectrum of the crude material (aromatic impurities) showed it to be ~85% ascaridole. This corresponds to an over-all yield of ascaridol of 60%. A portion of the crude material was purified by gpc on a 10 ft × $^3/_8$ in. 10% XE-60 column at 135° with helium at 200 cc/min (retention time 28 min). The nmr spectrum of the pure material was identical with the published spectrum of ascaridole.[39]

Oxygenation with Triethyl Phosphite–Ozone Adduct. A solution of triethyl phosphite (Eastman Practical, 1.66 g, 0.01 mole) in dichlorodifluoromethane (Freon 12) (~100 ml) was ozonized at −95° (frozen acetone bath). After purging with nitrogen a cold solution of cyclohexadiene-1,3 (0.8 g, 0.01 mole) in Freon 12 was added. The nitrogen stream was used to mix the reactants. The cold bath was removed and the solution permitted to warm to room temperature. When all the solvent had boiled away the remaining viscous liquid was distilled *in vacuo*. The material boiling at 40–63° and 1 torr was collected. The nmr spectrum of this material showed it to be mainly oxidized triethyl phosphite with about 10% cyclohexadiene *endo*-peroxide.

When triethyl phosphite was ozonized at higher temperatures (*e.g.*, −78°) with subsequent addition of olefin no oxidation products were observed.

General Procedure for Gas Phase Reactions. The triphenyl phosphite-ozone adduct was typically prepared by ozonizing triphenyl phosphite (3.1 g, 0.01 mole) in dichlorodifluoromethane followed by nitrogen purging and then adding cold crushed chalk sticks as moderator (100 g/0.01 mole of adduct) to the ozonized solution and solvent removal by pumping on the cold (−78°) reaction vessel for ~20 hr. The flask containing the solid adduct and moderator was kept at −78° and transferred to the Pyrex gas phase reaction apparatus (Figure 1). The system was evacuated to $<10^{-3}$ torr (while acceptor was kept frozen). A trap at −78°, between the adduct flask and mixing chamber, ensured that acceptor molecules, cyclohexadiene-1,3, α-terpinene, or 2,3-dimethylbutene-2, could not diffuse back to the adduct and possibly undergo a heterogeneous reaction. With the acceptor bleed-in valve closed the temperature of the adduct was raised gradually (by adding water to a methanol–ice bath) until it was ~0°. The pressure in the system usually rose to between 0.2 and 0.6 torr and remained there during the course of a run. When the pressure had stabilized, olefin was permitted to enter the mixing chamber by opening the needle valve leading to the acceptor flask. In the case of 1,3-cyclohexadiene and 2,3-dimethylbutene-2, the rate of introduction of the olefins was adequate when room temperature of the acceptor flask was maintained. In the case of α-terpinene some external warming was necessary. The product materials were condensed and frozen in a trap kept at liquid nitrogen temperature.

Gas Phase Oxidation of Cyclohexadiene-1,3. The cyclohexadiene-1,3 used for the gas phase oxidations was purified by passing it through Woelm neutral alumina and distilling (spinning band column) under nitrogen (bp 80°). The pure material was stored under nitrogen at −20°. The product trapping flask was tared, to allow determination of the amount of product during each run. After a run was completed the product flask was warmed to room temperature and the solution weighed and immediately analyzed by gpc[19] using a flame ionization detector. A standard solution of cyclohexadiene *endo*-peroxide in heptane was used to calibrate the detector. The glpc conditions used to analyze for *endo*-peroxide were a 5 ft × $^1/_8$ in. 5% XF-1150 on Chromosorb G column, with nitrogen carrier gas at 40 cc/min, hydrogen flow at 20 cc/min, and oven temperature of 110°. An average of ten digital integrator determinations gave 46,500 counts/μg of *endo*-peroxide. The retention time of the *endo*-peroxide was 29 min. Analysis of the product solution gave a yield figure of 116 μg (0.01% based on theoretically available oxygen). In an identical separate experiment the yield of *endo*-peroxide was 118 μg. In both cases a smaller peak was evident with a retention time of 24 min. If the product solution was permitted to stand for even a few hours this peak at 24 min grew considerably. No attempt was made to identify it. In neither of these cases was *endo*-peroxide present in the starting material. A control experiment was performed in which tank oxygen at a pressure of 0.35 mm was maintained in the oxidation system (Figure 1). Acceptor molecules were introduced into the system for 1.5 hr. Flame ionization gpc analysis of both starting material and product showed the absence of *endo*-peroxide.

Gas Phase Oxidation of α-Terpinene. Immediately before use in the gas phase oxidations α-terpinene[36] was purified by gas chromatography on a 10 ft × $^3/_8$ in. 10% XE-60 column at 90° and a 200 cc/min flow rate of helium. Introduction of the α-terpinene into the acceptor vessel (Figure 1) was accomplished by passing it through a neutral alumina (Woelm) column. After oxidation the product was immediately analyzed by flame ionization gpc. The column used was 5 ft × $^1/_8$ in., 5% XF-1150 on Chromosorb G. The carrier gas was nitrogen at a flow of 40 cc/min, the hydrogen was at a flow of 20 cc/min, and the oven temperature was 130°. Ascaridole prepared by liquid phase oxidation of α-terpinene was purified by preparative gpc (10 ft × $^3/_8$ in., 10% XE-60 column at 135° and carrier gas at 200 cc/min) and made up into a standard solution with dodecane as solvent in order to calibrate the flame ionization detector. An average of several determinations gave 61,470 counts/μg of ascaridole. The retention time of ascaridole was 25 min. The analysis of the product indicated a yield of 60 μg of ascaridole (0.01% based on the α-terpinene utilized). Two minor products, one with a retention time of 8 min and one with a retention time of 39 min, were also present. The peak at 39 min is also present in a pure ascaridole solution which has stood several days at room temperature. Analysis of the starting material showed it to contain no product peaks.

Gas Phase Oxidation of 2,3-Dimethylbutene-2 (**Tetramethylethylene**). The olefin was purified by first passing it through neutral alumina (Woelm) and distilling on a spinning band column (bp 72°) under nitrogen. It was stored under nitrogen at −20°. Gas phase oxidation with singlet oxygen was followed by analysis by flame ionization gpc on a 10 ft × $^1/_8$ in., 10% Dow 710 on a Chromosorb W column at 45°. The carrier gas (nitrogen) flow rate was 40 cc/min and the hydrogen flow was 20 cc/min. The chromatogram of the starting material was not significantly different from that of the product. It was not possible by our techniques to remove all traces of allylic hydroperoxide from the starting material.

Kinetic Experiments in the Liquid Phase. The rate of decomposition of the triphenyl phosphite-ozone adduct was measured by following the evolution of oxygen with time. The apparatus for preparation of the adduct consisted of a 300-ml, two-necked, round-bottomed Pyrex flask initially fitted with a gas bubbling tube exiting near the bottom of the flask and a calcium sulfate drying tube. The flask was charged with triphenyl phosphite (1.55 g, 0.005 mole) and 200 ml of solvent. The phosphite was ozonized to completion at −78° and then purged with dry nitrogen. The gas inlet tube was removed and replaced with a combination thermowell gas delivery exit tube. The reaction flask was then connected to a calibrated gas buret and associated leveling tube. The gas buret was allowed to fill with mercury at the start of each experiment. When the reaction solution had reached the desired temperature[40] (the cooling baths used consisted of ice-methanol and varying amounts of Dry Ice) the flask was sealed with a Teflon-coated stopper. The system was found to be leak free. At the same instant the system was sealed a stop watch was activated. The body of the flask containing the adduct was always completely submerged in the cooling bath and shaken vigorously before each reading of oxygen volume. During the course of each run the leveling tube was used to keep the system as close to atmospheric pressure as possible and adjusted more precisely immediately before

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(37) B. M. Mitzner, E. T. Theimer, and S. K. Freeman, *Appl. Spectrosc.*, **19**, 169 (1965).

(38) We gratefully acknowledge a gift of this material from the Hercules Powder Co.

(39) "High Resolution NMR Spectra Catalogue," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 276.

(40) A copper–constantan thermocouple inserted into a thermowell in the flask, in conjunction with a Leeds and Northrup Co. millivolt potentiometer, No. 8690, was used to monitor temperature throughout a run.

volume readings were made. The volume of gas evolved at infinite time (V_∞) was determined by removing the reaction flask from the cooling bath, warming it to room temperature, and allowing it to remain there for some time (15–30 min). The flask was then recooled to the temperature of the experiment and the gas volume read. Plots of the log ($V_\infty - V$) *vs.* time were made and slopes were determined by a least-squares treatment of the data. A typical first-order rate plot is shown in Figure 2. Most runs were followed for about 2 half-lives and all were followed at least 1 half-life. In the experiments where the amount of initial adduct was quite small, due to decomposition during the warm-up of the adduct flask to the temperature of the experiment, it was found that the slope of the line changed somewhat at the end of the run. These points were neglected when calculating the rate constants. Temperature control in all cases was better than ±1° and in most cases better than ±0.5°

Determination of Transition-State Parameters. Rate constants for the decomposition of the triphenyl phosphite–ozone adduct were determined at five different temperatures using methylene chloride as solvent. A summary of the results of these experiments appears in Table I. An Arrhenius plot of log *k vs.* $1/T$°K was treated by least squares to determine the slope, the intercept, and the probable error in the slope. From these were calculated the energy of activation (E_a) and the transition-state parameters for the decomposition of the adduct. These results are tabulated in Table II.

Effect of Solvent. Rate constants for the decomposition of the triphenyl phosphite–ozone adduct were determined at −24° in a variety of solvents. These results are collected in Table III.

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A Synthesis of Prostaglandin $F_{1\alpha}$ and Related Substances

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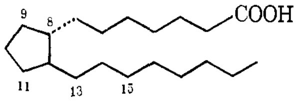
Abstract: The synthesis of prostaglandins $F_{1\alpha}$, $F_{1\beta}$, and a number of related products is described. The key step of the syntheses involves the acid-catalyzed opening and rearrangement of epoxybicyclo[3.1.0]hexanes of the type **28**.

The prostaglandins consist of a family of C_{20} acids of widespread occurrences in animal tissues and of varied, extremely potent, biological activities. Several recent reviews[2] adequately summarize the extensive literature on this important class of natural products. Syntheses of compounds containing the prostanoic acid carbon skeleton (**1**) have been accomplished,[3] and three groups[4] have reported syntheses of racemates of naturally occurring prostaglandins or their derivatives. The first of these reported[4a] a multistep synthesis of the ethyl ester of 13,14-dihydroprostaglandin E_1, a metabolite of prostaglandin E_1 (PGE_1) (**2**). The second[4b] carried out the autoxidation of 8,11,14-eicosatrienoic acid, which was reported to give a 0.1% yield of noncrystalline PGE_1. Crystalline racemic PGE_1, $PGF_{1\alpha}$, and $PGF_{1\beta}$ (as well as several other members of the prostaglandin family) have recently been made by Corey and his group at Harvard.[4c]



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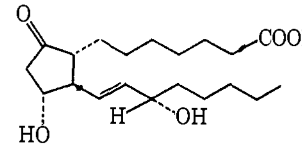

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In this paper, we give details of a synthesis of prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$), prostaglandin $F_{1\beta}$ ($PGF_{1\beta}$), and several other prostaglandins isomeric with these, *via* bicyclo[3.1.0]hexane derivatives. A portion of this work has been published in a preliminary fashion.[5a,b] Recently, another group has reported[5c] failure to obtain PGE_1 or $PGF_{1\alpha}$ by this route or modifications of it.

3-Cyclopentenol[6] (**3**) was converted to its tetrahydropyranyl ether (**4**), which was then treated[7] with ethyl diazoacetate in the presence of copper powder (Chart I). Two major products were formed in 75% total yield which were assigned the *exo* structures **5a** and **6a**. Treatment of the mixture with methanolic sodium methoxide to isomerize *endo* isomers, if present, to *exo* also resulted in ester exchange to give the two methyl esters, **5b** and **6b**. That these differed only in configuration at the carbinolic carbon was shown by removal of the tetra-

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(1) (a) McGill University; (b) The Upjohn Co.

(2) S. Bergström, *Science*, **157**, 382 (1967); S. Bergström, L. A. Carlson, and J. R. Weeks, *Pharmacol. Rev.*, **20**, 1 (1968); "Nobel Symposium 2, Prostaglandins," S. Bergström and B. Samuelsson, Ed., Almqvist and Wiksell, Stockholm, Sweden, 1967; V. R. Pickles, *Biol. Rev.*, **42**, 614 (1967); U. S. von Euler and E. Eliasson, "Medicinal Chemical Monographs," Vol. 8, Academic Press, New York, N. Y., 1967, p 1; J. W. Hinman, *Bioscience*, **17**, 779 (1967).

(3) (a) B. Samuelsson and G. Stallberg, *Acta Chem. Scand.*, **17**, 810 (1963); (b) J. F. Bagli, T. Bogri, R. Degenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966); J. F. Bagli and T. Bogri, *ibid.*, 5 (1967); J. F. Bagli, 10th Annual Medicinal Chemistry Symposium, Bloomington, Ind., June 1966.

(4) (a) P. F. Beal, J. C. Babcock, and F. H. Lincoln, *J. Am. Chem. Soc.*, **88**, 3131 (1966); (b) D. H. Nugteren, H. Vonkeman, and D. A. van Dorp, *Rec. Trav. Chim.*, **86**, 1 (1967). (c) Following the completion of this work, two other total syntheses of *dl*-prostaglandins were described: E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968); E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *ibid.*, **90**, 3247 (1968).

(5) (a) G. Just and C. Siminovitch, *Tetrahedron Lett.*, 2093 (1967); *Chem. Canada*, **19** (1), 41 (1967); (b) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *J. Am. Chem. Soc.*, **90**, 5895 (1968); (c) K. G. Holden, B. Hwang, K. R. Williams, J. Weinstock, M. Harman, and J. A. Weisbach, *Tetrahedron Lett.*, 1569 (1968). It is difficult for us to evaluate this report or compare results with ours since intermediate isomeric mixtures were not separated, and melting points of the crystalline products obtained in the attempted PGF synthesis were not given.

(6) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960).

(7) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, **85**, 582 (1963).