silver nitrate solution to remove olefinic impurities. It was then washed with water, dried over magnesium sulfate, and finally passed through a column of alumina to remove hydroperoxide impurities. All other materials were commercially available in >98% purity (GC analysis) and were used without further purification.

Instruments. The apparatus used in this work has been described in detail elsewhere. Briefly, the laser flash photolysis system employed pulses from a nitrogen laser (10 mJ, 10 ns, 337 nm) for sample photolysis. Transient absorptions were detected with a monochromator and photomultiplier tube, and signals from the latter were fed to a transient digitizer-computer system for storage and kinetic analysis.

Qualitative analyses of reaction mixtures were carried out on a Hewlett-Packard 5995 GC/MS. Quantitative analyses were made on a Varian 3500 gas chromatograph. Both instruments were fitted with capillary columns.

Response factors for unavailable halides were calculated on the basis of an assumed zero mass response for chloride (correct to within a few percent for the alkyl chlorides measured) with the assumption that a similar correction factor can be applied to chlorinated organometallics to obtain a response factor from the (measured) Et_4M response factors.

Assignment of Structure of Chlorinated Organometallics. Mass spectral analysis distinguished between the isomers of the chlorinated organometallic compounds on the basis of the fragmentation products (more Et_3M^+ and Et_2MH^+ from the α-compound, more Et_2MCl^+ from the β-compound). These assignments indicate that the β-isomer should

have the longer retention time and accord with the EPR results. Individual mass spectral results follow in the order m/e (relative abundance) assignment. For Ge and Sn compounds, only the ^{74}Ge and ^{120}Sn peaks in the pattern are listed.

$Et_3SiCHClCH_3$: 87 (100) Et_2SiH, 121 (84) $Et_2Si^{35}Cl$, 115 (76) Et_3Si, 93 (67) $EtSiH^{35}Cl$, 59 (40) $SiEtH_2$, 123 (30) $Et_2Si^{37}Cl$.

$Et_3SiCH_2CH_2Cl$: 121 (100) $Et_2Si^{35}Cl$, 93 (67) Et $SiH^{35}Cl$, 123 (36) $Et_2Si^{37}Cl$, 95 (25) $EtSiH^{37}Cl$, 65 (17) $Si^{35}ClH_2$, 87 (11) Et_2SiH.

$Et_3GeCHClCH_3$: 133 (100) Et_2GeH, 161 (71) Et_3Ge, 103 (61) $EtGe$, 167 (45) $Et_2Ge^{35}Cl$, 139 (41) $EtGe^{35}ClH$, 109 (29) $Ge^{35}Cl$.

$Et_3GeCH_2CH_2Cl$: 167 (100) $Et_2Ge^{35}Cl$, 139 (80) $EtGe^{35}ClH$, 109 (37) $Ge^{35}Cl$, 103 (28) $EtGe$, 133 (18) Et_2GeH, 75 (18) GeH.

$Et_3SnCHClCH_3$: 149 (100) $EtSn$, 151 (80) $EtSnH_2$, 179 (70) Et_2SnH, 155 (67) $Sn^{35}Cl$, 207 (65) Et_3Sn, 121 (61) SnH, 213 (52) $Et_2Sn^{35}Cl$.

$Et_3SnCH_2CH_2Cl$: 155 (100) $Sn^{35}Cl$, 149 (97) $EtSn$, 151 (97) $EtSnH_2$, 207 (81) Et_3Sn, 179 (68) Et_2SnH, 213 (64) $Et_2Sn^{35}Cl$, 121 (47) SnH [$EtSn$, $EtSnH_2$, and $SnCl$ have overlapping isotope patterns].

(25) Mintz, M. J.; Walling, C. "Organic Syntheses"; Wiley: New York, 1975; Collect. Vol. V, p 184.

Nitrosation of Organic Hydroperoxides by Nitrogen Dioxide/Dinitrogen Tetraoxide

William A. Pryor,* Laurence Castle, and Daniel F. Church*

Contribution from the Departments of Chemistry and Biochemistry, Louisiana State University, Baton Rouge, Louisiana 70803. Received June 28, 1984

Abstract: Cumyl and *tert*-butyl hydroperoxides react rapidly with NO_2/N_2O_4 in organic solvents in the presence of a base to form the organic nitrate ($RONO_2$) as the major product, together with smaller amounts of the corresponding nitrite (RONO), alcohol, and carbonyl compound (acetophenone or acetone from cumyl and *tert*-butyl hydroperoxide, respectively). The products from *tert*-butyl hydroperoxide are similar whether a base is present or not but those from cumyl hydroperoxide are more complex. We have formulated the initial reaction as a nitrosation of the hydroperoxide by N_2O_4 to give the pernitrite ester. This latter species is unstable and either rearranges to give the nitrate or dissociates to form alkoxyl radicals and nitrogen dioxide that ultimately give the other observed products. The kinetics of the reaction were studied by stopped flow and are complex, but we conclude the kinetics are consistent with the nitrosation mechanism. The rate constants at 30 °C are 2.4 × 10^4 and 8.1 × 10^3 M^{-1} s^{-1} for *tert*-butyl and cumyl hydroperoxides, respectively. We suggest that this facile reaction of NO_2/N_2O_4 with hydroperoxides may have important consequences with respect to the pulmonary toxicity of NO_2 in smoggy air.

Nitrogen dioxide (NO_2) is one of the most important toxic components of photochemical smog,[1] and understanding the reactions that NO_2 undergoes in the lungs of persons exposed to smoggy air is, therefore, of considerable importance. Previous work has shown that NO_2 initiates the autoxidation of polyunsaturated fatty acids[2] and oxidizes thiols to disulfides.[3] At the higher levels present in cigarette smoke, NO_2 reacts with simple olefins in the gas phase to give scavengeable oxygen-centered radicals.[4,5,6]

The gas-phase reactions of NO_2 and nitric oxide (NO) with hydrogen peroxide have been studied by atmospheric chemists[7,8] and are believed to produce hydroxyl radicals by a homolytic displacement reaction at the O–O bond by NO_x. There is one brief report of the reaction of NO with an organic hydroperoxide in solution;[9] a radical mechanism was proposed that also involves

(1) Pryor, W. A. In "Environmental Health Chemistry"; McKinney, J. D., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 445–467.

(2) Pryor, W. A. In "Lipid Peroxides in Biology and Medicine"; Yagi, K., Ed.; Academic Press: New York, 1982; p 1–22.

(3) Pryor, W. A.; Church, D. F.; Govindan, C. K.; Crank, G. *J. Org. Chem.* **1982**, *47*, 156.

(4) Pryor, W. A. In "Molecular Basis of Environmental Toxicity"; Bhatnagar, R. S. Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 3–36.

(5) Pryor, W. A.; Lightsey, J. W. *Science (Washington, D.C.)* **1981**, *214*, 435.

(6) Pryor, W. A.; Lightsey, J. W.; Church, D. F. *J. Am. Chem. Soc.* **1982**, *104*, 6685.

(7) Audley, G. J.; Baulch, D. L.; Campbell, I. M. *J. Chem. Soc. Chem. Commun.* **1982**, 1053.

(8) Gray, D.; Lissi, E.; Heicklen, J. *J. Chem. Phys.* **1972**, *76*, 1919.

212   *J. Am. Chem. Soc., Vol. 107, No. 1, 1985*

Pryor, Castle, and Church

homolytic displacement on oxygen.

In view of the environmental importance of NO_2, it is rather surprising that the reaction of NO_2 with organic hydroperoxides in solution has escaped attention. In this paper we report a product and kinetic study of this reaction and we conclude that the mechanism involves a nitrosation of the hydroperoxide.

Experimental Section

Instruments. Infrared spectra were recorded on a Perkin-Elmer Model 621 spectrophotometer using a solution cell with a pathlength of 0.2 mm. Proton NMR spectra were obtained at 60 MHz on a Varian A-60A or at 200 MHz on a Brucker WP-200. UV/vis absorption spectra were taken on a Varian/Cary 219 spectrophotometer. GC analyses were done on a Varian Model 3700 gas chromatograph with flame ionization detection; areas were determined with a Varian CDS111 integrator. Durobond and Durowax capillary GC columns from J & W (15 m long × 0.25 mm i.d.) were used; these bonded phases are comparable to SE-30 and Carbowax, respectively.

Kinetic experiments were performed using a Hitech stopped-flow spectrophotometer Model SF-3L interfaced to an On-Line Instrument Systems Model 3820 data system. The mixing chamber/optical cell has a 2-mm light path and a combined mixing/dead time of approximately 6 ms. Reaction temperatures for kinetic experiments were controlled to ±0.1 °C.

Materials. *tert*-Butyl hydroperoxide (Aldrich, 70%) was distilled before use. The distillate was 97% active as determined by reduction with PPh_3, followed by estimation of the alcohol formed by GC. The only impurity detected was di-*tert*-butyl peroxide (^1H NMR). Cumyl hydroperoxide (Pfaltz & Bauer) was 89% active, determined as above; the impurity was cumene (^1H NMR).

Pentane (Aldrich, Gold Label), hexane (Mallinckrodt, Nanograde), cyclohexane (Aldrich), decane (MCB, 98%), dodecane (MCB, 99%), and dichloromethane (Mallinckrodt, Nanograde) were each purified by stirring with concentrated H_2SO_4 several days, washing with water, drying over anhydrous $MgSO_4$, and distillation. Chloroform (Fisher, ACS Cert.) was distilled from CaH_2, passed through a neutral alumina column, and redistilled from CaH_2. Carbon tetrachloride (MCB, ACS Reagent) was treated with ozone overnight. It was then washed several times with aqueous carbonate followed by water and then dried over and distilled from anhydrous sodium carbonate.

Dinitrogen tetraoxide (Matheson, 99.5%) was used as supplied. Nitrosyl chloride (NOCl) was prepared by passing N_2O_4 in a carrier stream of argon through a column packed with solid potassium chloride containing 2% surface water.[10] Dinitrogen pentaoxide was prepared by the dehydration of anhydrous nitric acid[11] with phosphorus pentoxide in a stream of ozone.[12]

Cumyl and *tert*-butyl nitrites were prepared from the corresponding alcohols using nitrosyl chloride in CCl_4 and anhydrous sodium carbonate as an acid scavenger.[13] Cumyl nitrate was prepared likewise from the alcohol and dinitrogen pentaoxide.[14] *tert*-Butyl nitrate was obtained by esterification of nitric acid with the alcohol.[15] These four organic esters of nitrous and nitric acids were used as standards for the identification and quantitation of products from the reaction of hydroperoxides with NO_2/N_2O_4. They were not isolated, but the concentrations of the esters in CCl_4 were determined by integration of their proton NMR spectra using toluene as an internal standard. Each ester gave satisfactory mass spectra and proton NMR spectra.

Spectral Titrations. Titrations of NO_2/N_2O_4 with both hydroperoxides were done in hexane at room temperature in 1-cm cuvettes. The volume of the headspace in the cuvettes was kept small to ensure that the fraction of NO_2 in the vapor phase was negligible. After establishing the optical base line for pure solvent, NO_2 gas was added to the sample cuvette by syringe through a septum cap. The amount of NO_2 added was found by weight difference; typically 3.0 ± 0.1 mg was used. The contents of the cuvette were then titrated by syringe with aliquots of hydroperoxide in hexane. The concentration of NO_x (= $[NO_2] + 2[N_2O_4]$) remaining after each addition was determined from the absorbance at 357 nm. This wavelength represents an isosbestic point for the NO_2/N_2O_4 equilibrium.[16]

Table I. Reactivity of Peroxo Compounds (XOOY) toward NO_2/N_2O_4 in CCl_4

X	Y	reaction[a]
Me_3C	H	+
$EtMe_2C$	H	+
$PhMe_2C$	H	+
3-ClPhCO	H	+
$4\text{-}NO_2PhCO$	H	+
Me_3C	Me_3C	−
$EtMe_2C$	$EtMe_2C$	−
$n\text{-}C_{11}H_{23}CO$	$n\text{-}C_{11}H_{23}CO$	−
PhCO	PhCO	−
PhCO	Me_3C	−

[a] + indicates that decoloration of the NO_2/N_2O_4 solution occurred within seconds of mixing; a dash indicates no decoloration after several hours.

Reactions. Hydroperoxide $((1-2) \times 10^{-4}$ mol) in the solvent of choice (2–3 mL) was stirred rapidly at 25 ± 1 °C in a 4-mL septum-capped vial. Approximately 3 equiv of an NO_2/N_2O_4 gas mixture (4–8 mL) was rapidly injected into the headspace of the tube by gas syringe; reaction occurs as the gas diffuses into the solution of hydroperoxide. For reaction in the presence of an acid trap, finely powdered, anhydrous sodium carbonate (ca. 0.1 g) was suspended in the hydroperoxide solution. Reactions were over in a matter of seconds, as evidenced by the rapid decrease in the characteristic color of NO_2 in the headspace. Unreacted NO_2/N_2O_4 was removed by the application of a gentle vacuum after a 5-min interval. When not present during the reaction, sodium carbonate was added at this time. The reaction solutions were then examined for products as described below.

In the "reverse addition" protocol, the nitrogen dioxide was first dissolved in the reaction solvent. Hydroperoxide was then added as the neat liquid by syringe over ca. 30 s with the tip of the syringe needle below the surface of the stirred solution.

NMR and IR Analysis. The solutions of products were examined directly after the removal of sodium carbonate by filtration. The position of absorbances in the proton NMR spectra are reported as parts per million downfield from Me_4Si internal standard.

Gas Chromatography. The products from the reaction of *tert*-butyl hydroperoxide with NO_2 and NOCl were determined by gas chromatography using both polar and nonpolar capillary columns. A Durobond column at 30 °C allowed the analysis of *tert*-butyl nitrite (RONO), *tert*-butyl nitrate ($RONO_2$), *tert*-butyl alcohol, and *tert*-butyl hydroperoxide; a Durowax column at 40 °C was used to determine the nitrite, nitrate, and acetone. Ethyl acetate was used as an internal GC standard for the determination of the influence of reaction solvent on product distribution. It was added to product mixtures after the removal of unreacted NO_2/N_2O_4. Chloroform was the internal standard for reactions in CCl_4 where the influence of reaction protocol on product distribution was studied.

The analysis of acetophenone formed from reaction of cumyl hydroperoxide used a Durobond column programmed from 70 to 250 °C or a Durowax column from 120 to 195 °C. 2-Phenyl-1-ethanol, added after reaction, was used as an internal standard.

Kinetics Experiments. Stopped-flow experiments were done using the organic hydroperoxide in large excess relative to NO_2/N_2O_4 and were followed at 410 nm. The extinction coefficient of NO_2 at this wavelength was taken as 160 M^{-1} cm^{-1} and was assumed to be invariant with temperature.[17] The N_2O_4 is transparent at this wavelength,[17] but its concentration can be calculated from that of NO_2 using the equilibrium constant for the dissolution of N_2O_4. This equilibrium constant was calculated for various temperatures using the thermodynamic parameters reported by Redmond and Wayland for the equilibrium in noncoordinating solvents.[18] To prevent loss of NO_2 from solution during experiments, the open reservoir of the stopped-flow apparatus was replaced by a 50-mL syringe.[19]

A typical stopped-flow run consisted of 100 points collected over a sufficiently long time interval so that at least 90% of the NO_2/N_2O_4 was consumed during the observation period, plus one point at least 4 times longer than this time interval. The raw data from 5–10 such runs were

(9) Shelton, J. R.; Kopczewski, R. F. *J. Org. Chem.* **1967**, *32*, 2908.
(10) "Handbook of Preparative Inorganic Chemistry"; Brauer, G., Ed.; Academic Press: New York, 1965; Vol. I, p 551.
(11) Stern, S. A.; Mullhaupt, J. T.; Kay, W. B. *Chem. Rev.* **1960**, *60*, 185.
(12) *Inorg. Synth.* **1950**, *3*, 78.
(13) Beckham, L. J.; Fessler, W. A.; Kise, M. A. *Chem. Rev.* **1951**, *48*, 319.
(14) Caesar, G. V.; Goldfrank, M. *J. Am. Chem. Soc.* **1946**, *68*, 372.
(15) Lucas, G. R.; Hammett, L. P. *J. Am. Chem. Soc.* **1942**, *64*, 1928.

(16) Isosbestic points were determined by varying the temperature of a hexane solution of NO_2/N_2O_4 thermostated in the spectrophotometer.
(17) Hall, T. C., Jr.; Blacet, F. E. *J. Phys. Chem.* **1952**, *20*, 1745.
(18) Redmond, T. F.; Wayland, B. B. *J. Phys. Chem.* **1968**, *72*, 1626.
(19) Bennet, J. E.; Brunton, G.; Cruse, H. W.; Higgins, F. V.; Smith, T. M., Verbal presentation to the 1979 meeting of the Fast Reactions in Solution Discussion Group of the Chemical Society, University of Kent, UK, July 13, 14, 1979.
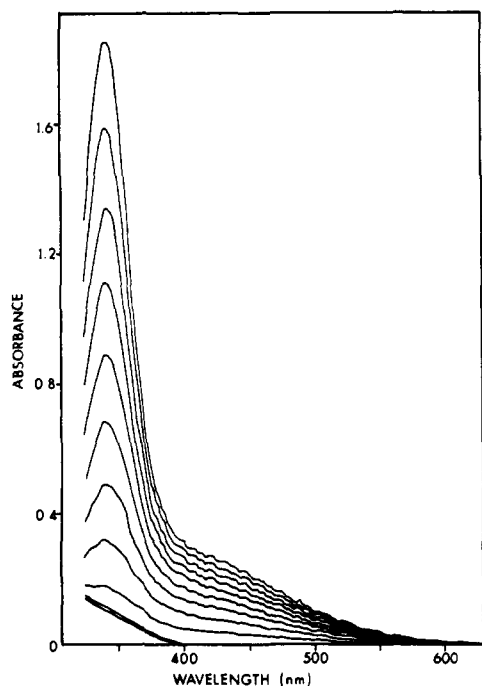
Figure 1. Spectral titration of 6.74×10^{-5} mol of NO_2 in 3.5 mL of hexane with successive 3.43×10^{-6} mol aliquots of cumyl hydroperoxide at ambient temperature.

averaged to obtain a single kinetic trace of absorbance vs. time. An exponential fitting procedure was then used to obtain a smooth trace.[20] The analysis of the fitted curves is described under Results.

Results

Reactivity of Organic Peroxides toward NO_2/N_2O_4. A number of representative organic peroxo compounds have been screened for reactivity toward NO_2/N_2O_4 in CCl_4 solution at room temperature; the results are shown in Table I. Of the ten compounds in the five classes tested, only hydroperoxides and peroxy acids were found to decolor solutions of NO_2/N_2O_4 within seconds. In contrast, peresters and diacyl and dialkyl peroxides did not cause significant decoloration even after standing several hours at room temperature. These results imply that NO_2/N_2O_4 reacts at O–H bonds and not by homolytic displacement at the O–O bond as has been proposed for the gas-phase reaction of NO_2 with hydrogen peroxide.[8] The reaction is clearly a facile one, and we have chosen to study the reactions of *tert*-butyl (TBH) and cumyl (CHP) hydroperoxides in detail.

Stoichiometry of Reaction of NO_2 with Hydroperoxides. The stoichiometries of the reactions of NO_2/N_2O_4 with CHP and TBH were determined by experiments in which the disappearance of the absorption due to NO_2/N_2O_4 was followed as a function of added hydroperoxide. The family of absorption curves obtained from CHP are shown in Figure 1. An overall reaction stoichiometry of $ROOH/NO_2$ of (44–48):100 was found for both CHP and TBH.

Products of the Reaction of TBH with NO_2/N_2O_4 and NOCl. The major product of the reaction of TBH with NO_2/N_2O_4 is *tert*-butyl nitrate, $RONO_2$. Analysis of the mixture obtained from the reaction of TBH with NO_2/N_2O_4 by IR reveals new bands at 1300, 1615, and 1655 cm^{-1} for reaction in chloroform and at 1295, 1625, and 1655 cm^{-1} for reaction in hexane. These absorbances are characteristic of alkyl nitrates[21,22] and were seen for authentic *tert*-butyl nitrate. Proton NMR confirmed the presence of *tert*-butyl nitrate (1.55 pm) and also showed acetone

Table II. Products from the Reaction of TBH with NO_2/N_2O_4 and NOCl

condtns[a]	% yields			
	t-BuONO₂	*t*-BuONO	*t*-BuOH	Me₂CO
NO_2/N_2O_4				
A	78	12		9
B	78	9	4	9
C	85	9		6
D	74		22	4
NOCl				
A	77	18		5
B	74	19	3	3
C	76	19		5
D	69	4	23	4

[a] For the reaction of TBH in CCl_4 solution with nitrogen species indicated according to four reaction protocols: (A) NO_2/N_2O_4 or NOCl diffused into a solution of TBH; (B) hydroperoxide rapidly added to a solution of the nitrogen species; (C) protocol A, except that Na_2CO_3 was suspended in solution before and during reaction; (D) protocol B, except that Na_2CO_3 was suspended in solution before and during reaction.

(2.23 ppm), *tert*-butyl alcohol (1.25 ppm), and *tert*-butyl nitrite (1.57 ppm) as minor products. These assignments were confirmed by spiking experiments with each authentic compound.

All four of these products could also be determined by GC. This method was used to investigate the effect of varying the reaction conditions and protocol; the results are shown in Table II. Hydroperoxide was completely consumed in each experiment; the four products tabulated account for 100 ± 10 mol % of the hydroperoxide reacted. The results indicate that reaction protocol does not significantly affect the product ratio except in the last case where the NO_2/N_2O_4 solution was stirred with suspended Na_2CO_3 before the hydroperoxide was added. This latter result may be due to complexation between the carbonate and dinitrogen tetraoxide that alters the nature and reactivity of the reactive species.

A similar product distribution was found when nitrosyl chloride was substituted for nitrogen dioxide; these results are also shown in Table II. As we will suggest below, both of these nitrogen species react with hydroperoxides to give the same initial intermediate.

The formation of acetone clearly must be accompanied by the loss of a one-carbon fragment; we, therefore, have attempted to identify this fragment. Closer examination of the NMR spectrum of the TBH–NO_2/N_2O_4 reaction mixture in CCl_4 revealed a small amount of nitromethane (4.27 pm); the yield was about 19% of the acetone formed. Absorbances due to MeOH, MeONO, $MeONO_2$, $MeOONO_2$, HCHO, or HCOOH could not be detected.

Washing the reaction solution with sodium carbonate solution gave a yellow aqueous extract. The absorption spectrum of this solution showed a symmetrical peak with a sharp maximum at 362 nm. This absorption was reversibly bleached on the addition of acid; titration with sulfuric acid gave a pK_a of 3.9 for this material. On the basis of these observations, we suggest that this acidic material is dinitromethane.[23,24] Using the literature value of the molar extinction coefficient ($=20\,000$) for dinitromethane at 362 nm,[23] we estimate its yield to be 9% relative to the yield of acetone formed. Dinitromethane appears to arise as a secondary product from nitromethane since increased yields were seen when reactions of TBH with NO_2/N_2O_4 in CCl_4 were spiked with 10% nitromethane (relative to TBH).

Products of the Reaction of CHP with NO_2/N_2O_4. With CHP as the substrate, simple product mixtures are obtained when sodium carbonate is present as an acid trap. Only cumyl nitrate (1.81 ppm), cumyl nitrite (1.91 ppm), cumyl alcohol (1.55 ppm), and acetophenone (2.56 ppm) were detected by proton NMR; the percent yields are 58, 13, 11, and 17, respectively. No acetone was observed. In the absence of an acid trap; however, the product

(20) The analysis algorithm was written by Dr. K. Johnson (Pennsylvania State University, Department of Biochemistry, University Park, PA) using a method of moments procedure. See: Dyson, R. D.; Isenberg, I. *Biochemistry* **1971**, *10*, 3233.
(21) Kornblum, N.; Ungnade, H. E.; Smiley, R. A. *J. Org. Chem.* **1956**, *21*, 377.
(22) Brown, J. F., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6341.

(23) Kamlett, M. J.; Glover, D. J. *J. Org. Chem.* **1962**, *27*, 537.
(24) Pearson, R. G.; Dillon, R. L. *J. Am. Chem. Soc.* **1953**, *75*, 2439.
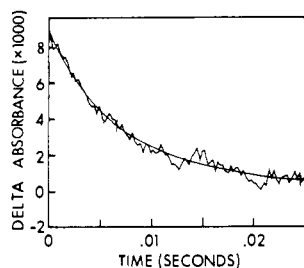
Figure 2. Decay curve observed at 410 nm for the reaction between NO_2/N_2O_4 (initial concentration ca. 1.5×10^{-3} M, expressed as NO_2) and *tert*-butyl hydroperoxide (0.015 M) in hexane at 19.8 °C. The smooth curve is the fitted data.

mixtures are more complex. By NMR, cumyl nitrate is seen to decompose over 20–30 min to form mainly acetone; reverse-phase HPLC showed phenol and the isomeric nitrophenols (>80% ortho) to be the aromatic products corresponding to side-chain loss as acetone. This decomposition did not produce additional aceto-phenone, the concentration of which remained constant. Authentic cumyl nitrate was found to undergo this acid-catalyzed decom-position when exposed to anhydrous nitric acid in CCl_4.

Kinetic Measurements by Stopped Flow. The rates of reaction between TBH and CHP and NO_2/N_2O_4 were measured using the stopped-flow technique to follow the disappearance of NO_2 in the presence of excess hydroperoxide. In any reaction involving NO_2 or N_2O_4 in solution, kinetic measurements are complicated by the presence of the NO_2/N_2O_4 equilibrium, eq 1.[18]

$$2NO_2 \rightleftharpoons N_2O_4 \qquad (1)$$

The rate of attainment of the equilibrium in eq 1 has been reported to be much faster than the rates of reaction of NO_2/N_2O_4 with the hydroperoxides studied here.[25] We confirmed this by a solvent-jump relaxation experiment. On mixing a hexane so-lution of NO_2/N_2O_4 with an equal volume of pure solvent, the absorbance at 410 nm, due solely to NO_2, will at first be halved on dilution and will then increase as eq 1 shifts toward NO_2 to reestablish equilibrium. With $[NO_2] + 2[N_2O_4]$ equal to 2×10^{-2} M before dilution and a temperature of 25 °C, the absorbance observed immediately after mixing was 67% of the absorbance of the NO_2/N_2O_4 solution before dilution; the absorbance did not change within the time resolution of our stopped-flow system. This absorption observed after mixing is just what would be calculated for the diluted solution after equilibrium has been reestablished. We conclude that the system relaxes to the new equilibrium concentrations within the mixing/dead time of our instrument (6 ms) and therefore is not rate limiting in the reactions of NO_2/N_2O_4 with hydroperoxide described below.[26]

The kinetics of the reaction of NO_2/N_2O_4 with excess hydro-peroxide were determined by following the decay of NO_2 at 410 nm; a typical decay trace and the corresponding fit line[20] are shown in Figure 2. Since the NO_2/N_2O_4 ratio varies with their total concentrations, the reaction progress is most clearly expressed in terms of product formation, eq 2. We can use the relationship

$$[P]_t = ([N_2O_4]_0 - [N_2O_4]_t) + \frac{1}{2}([NO_2]_0 - [NO_2]_t) \qquad (2)$$

of eq 2 if we assume that the reaction stoichiometry of $NO_2/$ ROOH is 2:1 throughout the course of the reaction. To evaluate eq 2, the concentration of NO_2 at time $= t$ is taken as the ab-sorbance of the reaction solution divided by the extinction coef-ficient for NO_2 at 410 nm.[17] The concentration of N_2O_4 is then calculated from the equilbrium constant from eq 1 (K_1).[18] We can safely use the literature values for extinction coefficient and K_1 since the spectral titrations show no product absorption at 410 nm and the solvent-jump experiment confirms that equilibrium 1 is maintained.

---

(25) Brass, P. D.; Tolman, R. C. *J. Am. Chem. Soc.* **1932**, *54*, 1003.
(26) This experiment allows us to estimate a lower limit for the rate of dissociation of N_2O_4. The rate of association of $2NO_2$ can be estimated from the dissociation rate and K_1.
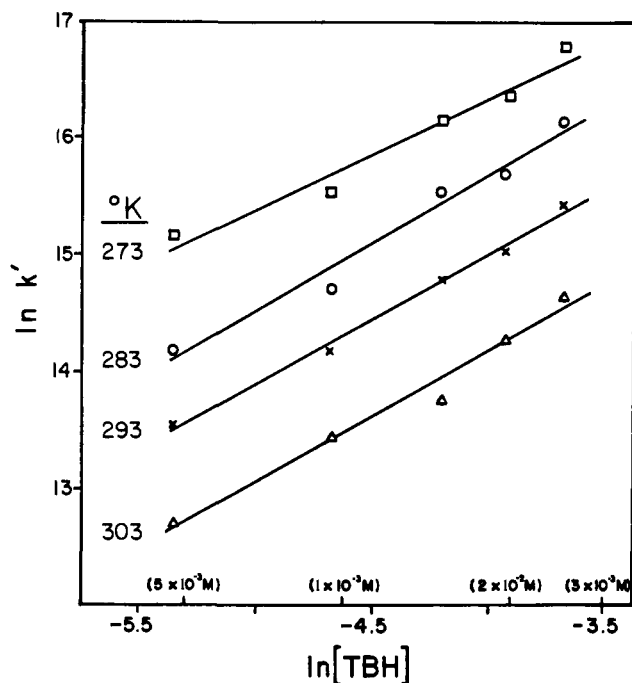

Figure 3. Plot of ln k' vs. ln [TBH] for the reaction of TBH with NO_2/N_2O_4 in hexane at temperatures from 0 to +30 °C.

Table III. Rate Constants for the Reaction of NO_2/N_2O_4 with ROOH in Hexane at Various Temperatures

ROOH	temp, K	$k_6 \times 10^{-7}$ [a]	$K_{10} \times 10^{-3}$ [b]	$k_{11} \times 10^{-3}$ [c]
Me$_3$COOH	273	73.5	54.6	13.4
	283	42.1	21.1	19.9
	293	20.5	8.7	23.5
	303	9.24	3.8	24.3
PhMe$_2$COOH	263	75.0	152	4.93
	273	33.8	54.6	6.18
	283	13.4	21.1	6.34
	293	7.0	8.7	8.08
	303	3.1	3.8	8.14

[a] M^{-2} s^{-1}. The uncertainties in these measured rated constants are better than ±10%. [b] M^{-1}. See ref 18. [c] M^{-1} s^{-1}.

The generalized rate expression for the formation of product can be expressed as eq 3 where m and n are the orders of reaction

$$dP/dt = k [ROOH]^m [NO_2]^n \qquad (3)$$

with respect to hydroperoxide and NO_2, respectively. The rate expression shown in eq 4 will be obeyed for experiments employing

$$dP/dt = k' [NO_2]^n \qquad (4)$$

a large excess of hydroperoxide; the observed rate constant k' will equal $k_3[ROOH]^m$. An approximate form of eq 4 that is amenable to solution on the stopped-flow data system is given by eq 5. For

$$\Delta P/\Delta t = k' [NO_2]_t^n \qquad (5)$$

eq 5, $[NO_2]_t$ is the mean concentration of NO_2 over time interval Δt and is found from the absorbance of the solution. The con-centration of product formed during this time interval, ΔP, is calculated from the NO_2 concentration via eq 1 and 2.

The kinetic order in NO_2, n, was determined by plotting ln $(\Delta P/\Delta t)$ vs. ln $[NO_2]_t$.[27] For the reactions of both CHP and TBH at all temperatures employed, n was found to be 2.0 ± 0.2 for at least the first 90% of the reaction amplitude. The observed rate constant, k', was taken to be the slope of the plot of $\Delta P/\Delta t$ vs. $[NO_2]_t^2$.

The order of reaction in hydroperoxide, m, was found by varying the concentration of hydroperoxide while still maintaining a large

---

(27) Van't Hoff, J. H. "Etudes de Dynamique Chimique"; Frederich Muller: Amsterdam, 1984; p 83.
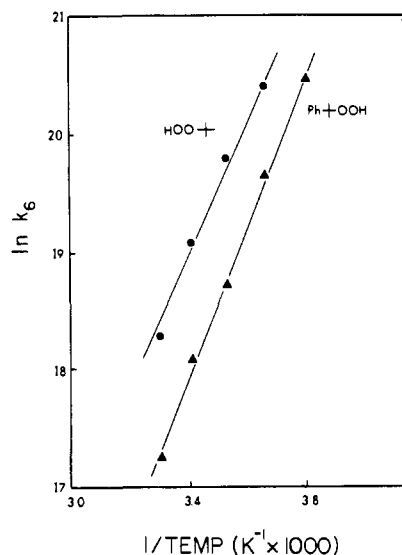
Figure 4. Arrhenius plot of rate constant k_6 for reaction of *tert*-butyl hydroperoxide (circles) and cumyl hydroperoxide (triangles) with NO_2/N_2O_4 in hexane. The best straight line (shown) was calculated with the data from 273 K and above for TBH and with data from 263 K and above for CHP.

excess. Figure 3 shows plots of ln k' vs. ln [TBH] for reactions carried out between 0 and +30 °C. The slopes of the lines at 30, 20, 10, and 0 °C are 1.12, 1.12, 1.17, and 0.96, respectively; we conclude that $m = 1$ under these conditions.[28] Thus, at the higher temperatures employed, the rate expression of eq 6 is followed.

$$\text{Rate} = k_6 \, [\text{ROOH}] \, [\text{NO}_2]^2 \qquad (6)$$

The rate constant k_6 for TBH at each of the temperatures where the order in hydroperoxide was 1 was determined from plots of k' vs. [TBH] and the values obtained are shown in Table III. An Arrhenius treatment of k_6 for the temperature range 0 to +30 °C gives an apparent negative activation energy, E_6, of –10.7 kcal/mol for reaction of TBH (Figure 4).

These same observations were made in a less extensive set of experiments with CHP. At 20 °C the observed rate constant k' is linearly related to the concentration of hydroperoxide up to the highest concentration studied (0.05 M) and m equals 1.0. Values of k_6 determined at a single hydroperoxide concentration of 0.023 M are given in Table III for the temperature range –10 to +30 °C.[28] The Arrhenius plot of these data gives an apparent negative activation energy for the reaction of CHP of –12.4 kcal/mol (Figure 4).

Discussion

The results we have obtained for the reaction of NO_2/N_2O_4 with organic hydroperoxides in solution can be accounted for by the mechanism shown in Scheme I. Cumyl hydroperoxide has been selected as the specific substrate for this illustration since, as we will see below, this substrate yields more mechanistic insights than does *tert*-butyl hydroperoxide.

We have chosen to formulate the initial reaction as a nitrosation of the hydroperoxide by N_2O_4 (Scheme I, step a). Dinitrogen tetraoxide is formally a mixed anhydride of nitrous and nitric acids, $O=N—O—NO_2$. The anhydride of nitrous acid, N_2O_3, is a powerful nitrosating agent for a variety of compounds including alcohols.[29] The anhydride of nitric acid, N_2O_5, is a potent nitrating agent, giving nitrates from alcohols[30] and pernitrates from hydroperoxides,[31] for example. As a mixed anhydride, N_2O_4 has

Scheme I

Table IV. Acetophenone Yields from Reaction of Cumyl Hydroperoxide with NO_2/N_2O_4 in a Variety of Solvents

solvent	% PhCOMe[a]	solvent	% PhCOMe[a]
CCl_4	20.8 ± 1.2	C_6H_{14}	12.2 ± 0.4
CCl_4[b]	14.0 ± 1.8	c-C_6H_{12}	5.5 ± 0.1
$CHCl_3$	19.4 ± 2.1	$C_{10}H_{22}$	9.6 ± 0.5
CH_2Cl_2	21.2 ± 1.6	$C_{12}H_{26}$	10.7 ± 0.1
C_5H_{12}	12.4 ± 0.6		

[a] Based on reacted hydroperoxide; range for replicate experiments at 26 ± 1 °C. [b] Reverse addition protocol.

the potential to act either as a nitrosating or a nitrating agent. Probably because of the superiority of nitrate as a leading group, nitrosation appears to be the preferred reaction as evidenced by the formation of nitroso compounds from alcohols,[32] thiols,[3,29] and secondary amines.[33]

The nitrosation of a hydroperoxide yields a pernitrite, ROONO. Alkyl pernitrites have never been observed in solution, but they have been postulated as intermediates in the trapping of peroxy radicals by NO in the solid state[34] and in the nitrosation of hydroperoxides by NOCl in solution.[35] Since we observe similar product distributions from the reaction of TBH with either N_2O_4 or with NOCl (see Table II), it is reasonable to conclude that a common intermediate is produced in both systems.

We suggest that the primary mode for the decomposition of alkyl peroxynitrites in solution is via O–O bond homolysis to give an alkoxyl/NO_2 caged radical pair (Scheme I, step b). Cage recombination leads to the major product, an alkyl nitrate (Scheme I, step c). This pathway appears to account for about 74–85% of the reaction with TBH and about 58% of the reaction with CHP.

The remainder of the products would appear to arise from the dissociation of the radical pair to give free alkoxy radicals (Scheme I, step e). As is often the case with alkoxy radicals, products resulting from both H-abstraction (Scheme I, step f) and β-scission (Scheme I, step h) reactions are observed.[36] As we show in step g, part or all of the alcohol formed by H-abstraction may be

(28) At temperatures below 0 °C (TBH) and –10 °C (CHP) the kinetic order in hydroperoxide falls below unity and the ln k' vs. ln [ROOH] plots show signs of leveling off at the higher concentrations studied. Since eq 6 is not obeyed at these lower temperatures (Discussion), the data are not employed here.

(29) Williams, D. L. H. *Adv. Phys. Org. Chem.* **1983**, *19*, 381.

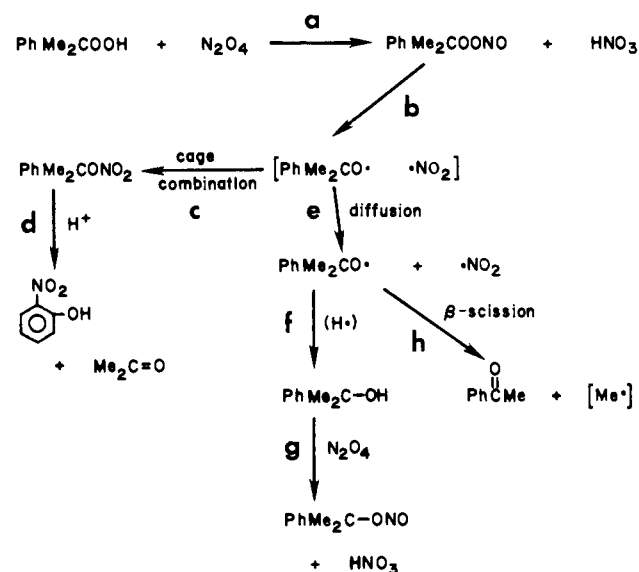(30) Bachman, G. B.; Connon, N. W. *J. Org. Chem.* **1969**, *34*, 4121.

(31) Duynstee, E. F. J.; Housmans, J. G. H. M.; Vieugels, J.; Voskuil, W. *Tetrahedron Lett.* **1973**, 2275.

(32) The normal reaction of N_2O_4 with alcohols gives nitrosation: Yoffe, A. D.; Gray, P. *J. Chem. Soc.* **1951**, 1412. N_2O_4 is able to nitrate alcohols but only at low temperatures and with strong base to deprotonate the alcohol; see, for example, ref 33 and: Taube, H.; Anbar, M. J. *J. Am. Chem. Soc.* **1955**, *77*, 2993.
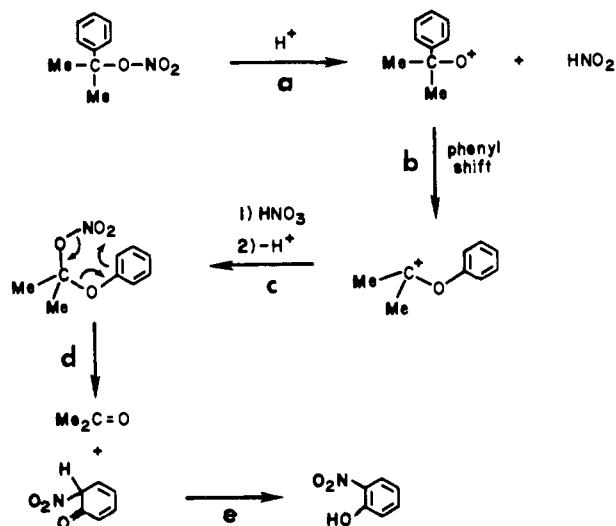
(33) White, E. H.; Feldman, W. R. *J. Am. Chem. Soc.* **1957**, *79*, 5832.

(34) Janzen, E. G.; Meyer, J. L., Jr.; Ayers, C. L. *J. Phys. Chem.* **1967**, *71*, 3108.

(35) Barton, D. H. R.; Hesse, R. H.; Pechet, M. M.; Smith, L. C. *J. Chem. Soc., Chem. Commun.* **1977**, 754.

(36) Huyser, E. S. *Adv. Free Radical Chem.* **1965**, 1, 77.

Scheme II

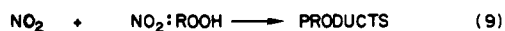further nitrosated by N_2O_4 to give the alkyl nitrite products.

A significant fraction of the alkoxyl radicals appear to give β-scission products. Thus, acetone is a product from TBH, while CHP gives acetophenone in the presence of base. In this regard, the chemistry of CHP is particularly diagnostic. In the β-scission reaction a methyl group is lost to give acetophenone (Scheme I, step h); methyl radicals are known to be much better leaving groups than are phenyl radicals.[37] If we take the yield of carbonyl product divided by the yields of alcohol plus nitrite as being equal to the ratio of β scission to H abstraction, we find this ratio to be about 0.7 in all experiments with THP (except protocol D, where the ratio is 0.2). (See Table II.) This is comparable to literature values for β scission/H abstraction reported by Walling and Padwa[38] and Sakurai and Hosomi.[39]

As an additional probe of the β-scission/H-abstraction ratio, we have measured the yields of acetophenone from the reaction of cumyl hydroperoxide with N_2O_4 in a series of solvents with widely varying H-donating abilities; a solvent of increased H-donating ability would be expected to favor H-abstraction and thus give lower yields of acetophenone.[36] The results are shown in Table IV. These data show a modest suppression of the acetophenone yield by these H-donor solvents, with cyclohexane being the most effective. Cyclohexane has a rate constant for reaction with alkoxy radicals (2×10^6 M^{-1} s^{-1})[40] that is approximately 2 orders of magnitude lower than the rate constant for the reaction of alkoxyl radicals with hydroperoxides (3×10^8 M^{-1} s^{-1}).[41] Thus, with a hydroperoxide concentration of 0.1 M and a cyclohexane concentration of about 9 M, the rates for H abstraction from the two donors should be about equal. For the other donors, which are significantly less reactive toward alkoxyl radicals than is cyclohexane, the primary donor would be the hydroperoxide. (Decane and dodecane, which probably have reactivities similar to cyclohexane, may show slightly increased yields of β scission as a result of increased viscosity stabilizing the caged radical pair.)

In the absence of base, the cumyl nitrate was observed to rearrange to acetone and o-nitrophenol (>80%). Acetone could not arise by β scission of a cumyloxy radical;[37] instead, we suggest that acetone arises from the rearrangement of a cationic oxygen intermediate formed by acid-catalyzed decomposition of the nitrate as illustrated in Scheme II (steps a and b). The migratory aptitude of a phenyl group to a cationic center far exceeds that of a methyl group.[42] For example, the acid-catalyzed rearrangement of CHP

gives acetone with no acetophenone. Scheme II also suggests a route to o-nitrophenol that would account for its high yield. Trapping of the carbocation by nitric acid followed by loss of a proton gives the nitrate ester of a hemiketal (step c). An intramolecular shift of the nitro group, analgous to a Claisen rearrangement, gives acetone and the ortho-substituted phenol (steps d and e).

Kinetics. Three possible reaction schemes can give the rate expression shown in eq 6. One is termolecular (eq 7), a second

$$2NO_2 + ROOH \longrightarrow PRODUCTS \qquad (7)$$

$$NO_2 + ROOH \rightleftharpoons NO_2{:}ROOH \qquad (8)$$

$$NO_2 + NO_2{:}ROOH \longrightarrow PRODUCTS \qquad (9)$$

$$2NO_2 \rightleftharpoons N_2O_4 \qquad (10)$$

$$N_2O_4 + ROOH \longrightarrow PRODUCTS \qquad (11)$$

involves a reversible preassociation of NO_2 with hydroperoxide to form an intermediate that then reacts with a second molecule of NO_2 (eqs 8 and 9), and the third involves reaction by the dimer, N_2O_4 (eq 10 and 11). The observed negative activation energies imply the involvement of an exothermic, reversible reaction as the initial kinetic event. Clearly the mechanism shown in eq 7 does not involve such an equilibrium, and this mechanism can therefore be immediately ruled out. Although we have no data that conclusively rules out eq 8 and 9, there is no literature precedent for a complex of NO_2 such as is formed in eq 8.

As we have discussed above, we believe that the mechanism depicted by eq 10 and 11 provides the best rationalization of our data. If so, the apparent activation energy for the reaction would be the enthalpy of eq 10 plus the activation energy of eq 11. Taking the literature value for the enthalpy of eq 10 (-14.6 kcal/mol)[18] and subtracting this enthalpy from the apparent activation energies found for TBH and CHP gives E_{11} equal to 3.9 and 2.2 kcal/mol, respectively. These E_a values lead to activation entropies for eq 11 of -27 eu and -39 eu for TBH and CHP, respectively. A highly ordered, cyclic transition state such as structure I could account both for the low activation energy and the large negative entropy of activation.[43]

I
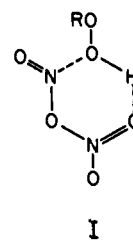
The rate constants k_6 in Table III apply to eq 6, which describes the overall rate expression found by monitoring NO_2 in stopped-flow experiments. Rate constants for the reaction of N_2O_4 with hydroperoxide, eq 11, are equal to k_6 divided by K_{10}. The rate constants k_{11} calculated in this way are tabulated in Table III. When the NO_2/N_2O_4 equilibrium has been taken into account, the rate of eq 11 increases with temperature in a manner consistent with the low activation energy estimated above. It should be appreciated that the calculation of k_{11} values in this manner will underestimate the true rate constants for reaction of $ONONO_2$ with hydroperoxide since equilibrium constant K_{10}

(37) Karasch, M. S.; Fono, A.; Nudenberg, W. *J. Org. Chem.* **1951**, *16*, 105.

(38) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1593.

(39) Sakurai, H.; Hosomi, A. *J. Am. Chem. Soc.* **1967**, *89*, 458.

(40) Howard, J. A.; Scaiano, J. C., unpublished results.

(41) Paul, H.; Small, R. D., Jr.; Scaiano, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 4520.

(42) Hedaya, E.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1661.

(43) A somewhat analogous transition state has been postulated for the nitrosation of alcohols by nitrosyl chloride in a participating solvent. Dalco, A.; Bruylants, A. *Tetrahedron Lett.* **1975**, 377. Napoleone, V.; Schelly, Z. A. *J. Phys. Chem.* **1980**, *84*, 17.

relates to the total dimer concentration, N_2O_4.[18]   To our knowledge, there is no work in the literature that would enable us to calculate the relative contributions of the $ONONO_2$ and O_2NNO_2 isomers to the total dimer pool.

The kinetics discussed above are for dilute solutions of hydroperoxide. At the higher concentrations studied, and especially at low temperature, the order of reaction in hydroperoxide falls below unity. This phenomenon is quite common[44] in hydroperoxide chemistry in nonpolar solvents and is attributed to the formation of hydroperoxide dimers. We have chosen not to attempt to correct for dimer formation by using the thermodynamic parameters provided for TBH by Walling and Heaton for example.[45]   Rather, we have limited our analysis of rate data to the lower hydroperoxide concentrations and higher temperatures used; i.e., the linear portions of plots such as those in Figure 4.

Summary, Conclusions, and Toxicological Implications

We have shown that N_2O_4 readily nitrosates organic hydroperoxides in solution, giving pernitrite esters that ultimately rearrange to give alkyl nitrates as major products. Nitrates are susceptible to acid-catalyzed decomposition to nitrous acid; the potential for damage by nitrous acid in a biological system is well-known.[46]   In addition, a significant fraction of the initially formed pernitrite (ca. 20–30%) appears to decompose to form alkoxyl free radicals. Alkoxyl radicals initiate lipid autoxidation and cause biological damage.[47]

Is the reaction of NO_2/N_2O_4 with lipid peroxides important in the lung for environmental levels of NO_2? There is extensive evidence that NO_2 initiates the autoxidation of unsaturated fatty acids in the lung, forming hydroperoxides.[48]   In addition, the lung contains high levels of lipoxygenase and prostaglandin systems, leading to lipid hydroperoxides. The relative rates of attack by NO_2/N_2O_4 on hydroperoxides and olefins can be estimated from our data. Taking the rate constant for nitrosation of hydroperoxides by N_2O_4 as about $10^4 \ M^{-1} \ s^{-1}$ and the rate of addition of NO_2 to an olefin to be about $10^{-1} \ M^{-1} \ s^{-1}$,[49] we obtain a rate constant ratio k_{ROOH}/k_{olef} of 10^5. A 10 ppm level of NO_2 in the gas phase would give a ratio of N_2O_4/NO_2 in solution of about 10^{-3}. Thus, for *equal* concentrations of ROOH and olefin, the ratio of reaction of NO_2/N_2O_4 with these two species equals $(k_{ROOH}/k_{olef})([N_2O_4]/[NO_2]) = 10^5 \times 10^{-3} = 100$; that is, the hydroperoxide is the favored target. If the concentration of ROOH were 1% of the olefin concentration, a ratio that is possible under conditions of high oxidative stress,[50] significant portion of the NO_2/N_2O_4 would react with the hydroperoxide by the mechanism we have outlined.

(44) The self-association of hydroperoxides is one of their most characteristic physical propertites. See, for example: Richardson, W. H. In "The Chemistry of Funtional Groups, Peroxides"; Patai, S., Ed.; Wiley: New York, 1983, p 128.

(45) Walling, C.; Heaton, L. *J. Am. Chem. Soc.* **1965,** *87,* 48.

(46) Menzel, D. B. In "Free Radicals in Biology"; Pryor, W. A., Ed.; Academic Press: New York, 1976; Vol. II, p 181.

(47) Pryor, W. A. In "Free Radicals in Biology"; Pryor, W. A., Ed.; Academic Press: New York, 1976; Vol. I, p 1.

(48) Thomas, H. V.; Mueller, P, K.; Lyman, R. L. *Science (Washington, D. C.)* **1968,** *159,* 532.

(49) Sprung, J. L.; Akimoto, H.; Pitts, J. N. *J. Am. Chem. Soc.* **1971,** *93,* 4358.

(50) To our knowledge, there have been no direct measurements of levels of hydroperoxides in lung materials exposed in vivo to NO_2. We calculate the level of conjugated diene found in ref 48 to be about 5% of the total lung lipid isolated. Hydroperoxides will be lower than this value due to decomposition and reduction by peroxidases.

Stereochemistry of the Wittig Reaction. Effect of Nucleophilic Groups in the Phosphonium Ylide[1]

Bruce E. Maryanoff,* Allen B. Reitz, and Barbara A. Duhl-Emswiler

Contribution from the Chemical Research Department, McNeil Pharmaceutical, Spring House, Pennsylvania 19477. Received May 11, 1984

Abstract: Anionic, nucleophilic groups in the side chain of triphenylphosphonium ylides cause a shift in stereochemistry of the alkene products toward the *E* isomer in reactions with aldehydes. The effect is frequently stronger with aromatic aldehydes than with aliphatic aldehydes. Substituents investigated include oxido, carboxylate, amino, and amido groups. The enhancement of *E* stereoselectivity is highly dependent upon the distance of the anionic group from the phosphorus atom. Also, in the case of oxido ylides, the effect is sensitive to the cation involved. Deuterium-labeling and ^{31}P NMR studies were performed to evaluate possible mechanistic interpretations. An intramolecular Schlosser-type mechanism (as proposed in ref 8a,b) is not chiefly responsible for the anomalous *E* stereoselectivity. It is suggested that the metalloanionic group facilitates oxaphosphetane interconversion via reaction reversal, and it may also perturb the original carbon–carbon bond-forming process.

The Wittig reaction has played a prominent role in synthetic chemistry for several decades, yet a clear mechanistic understanding of its stereochemistry has failed to emerge.[2,3]   Non-

stabilized triphenylphosphorus ylides generally react with aldehydes to afford mainly *Z* alkenes, by a process suggested to involve betaine and/or oxaphosphetane intermediates.[2-4]   The stereochemistry of such reactions can be affected by solvent, cation,

(1) Presented in part at (a) the 185th National Meeting of the American Chemical Society, Seattle, WA, March 1983 ("Abstracts of Papers"; American Chemical Society: Washington, DC, 1983; ORGN-28) and (b) the International Conference on Phosphorus Chemistry, Nice, France, September 1983 (see: Maryanoff, B. E.; Duhl-Emswiler, B. A.; Reitz, A. B. *Phosphorus Sulfur* **1983,** *18,* 187).

(2) For reviews of the Wittig reaction see: (a) Schlosser, M. *Top. Stereochem.* **1970,** *5,* 1. (b) Gosney, I.; Rowley, A. G. In "Organophosphorus Reagents in Organic Synthesis"; J. I. G. Cadogan, Ed.; Academic Press: New York, 1979; pp 17–153.

(3) For some recent mechanistic proposals see: (a) Thacker, J. D.; Whangbo, M.-H.; Bordner, J. *J. Chem. Soc., Chem. Commun.* **1979,** 1072. (b) Bestmann, H. J. *Pure Appl. Chem.* **1979,** *51,* 515. (c) Bestmann, H. J. *Ibid.* **1980,** *52,* 771. (d) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981,** *103,* 2823. (e) Schlosser, M.; Schaub, B. *Ibid.* **1982,** *104,* 5821. (f) Olah, G. A.; Krishnamurthy, V. V. *Ibid.* **1982,** *104,* 3987.

(4) Schlosser, M.; Christmann, K. F. *Justus Liebigs Ann. Chem.* **1967,** *708,* 1.