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Preparation and Reactions of Unsymmetrically Labeled Hydroperoxides: Solvent Viscosity Dependent Oxygen Scrambling of Cumylperoxyl Free Radicals

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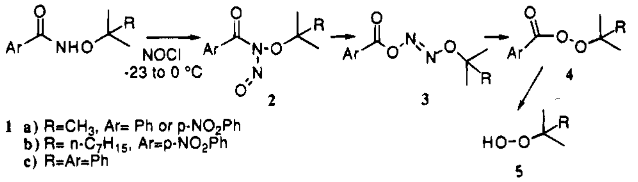
Hydroperoxides are the principal products formed in the free radical oxidation of organic compounds including items of commerce and biologically important molecules,[1] and they are also important oxidants in synthetically useful transformations such as the Sharpless epoxidation.[2] Mechanistic studies have provided a basic understanding of autoxidation and other synthetically useful oxidation processes involving hydroperoxides, but many questions remain unanswered.[3] One example of such an unresolved question concerns whether the proximal or terminal oxygen is transferred in the simplest reactions of hydroperoxides, *i.e.*, with phosphines and sulfides, as well as in the Sharpless epoxidation. While important information has been obtained utilizing labeled molecular oxygen or randomly labeled hydroperoxides,[1] unsymmetrically labeled hydroperoxides or peroxyl radicals have not been utilized in mechanistic studies, despite the fact that these compounds could provide decisive information about the chemistry of hydroperoxides and peroxyl free radicals. We report here the synthesis and study of two hydroperoxides labeled with ^{18}O exclusively at the terminal oxygen.

Koenig and his collaborators carried out a series of pioneering experiments[4] some 25 years ago in which hydroxamate esters were converted to peresters by reaction with nitrosyl chloride. The reaction proceeds *via* rearrangement of the *N*-nitrosohydroxamate ester, **2**, to an unsymmetrical hyponitrite, **3**, which decomposes to a mixture of products including the perester **4**. Experiments carried out on **1a** labeled with ^{18}O in the acyl oxygen established that perester **4a** is formed with essentially complete randomization of the ^{18}O label between the two benzoyloxy oxygens.



Perester **4a** reacts with methoxide to give methyl benzoate, which was analyzed for ^{18}O content, but the other product of the reaction, *tert*-butyl hydroperoxide, was not purified.[5]

We have now carried out the transformation **1** → **4** with R = CH_3, *n*-C_7H_{15}, and Ph, and we have isolated and purified the hydroperoxides formed by hydrolysis of the peresters **4b** and **4c**. The hydroxamate esters **1b** and **1c** were reacted with nitrosyl chloride in methylene chloride at temperatures <0 °C. ^1H NMR analysis of the reaction mixture indicated that the formation of an intermediate **2** was followed by its conversion to a new species **3** at temperatures between −20 and 0 °C.[6] Replacement of the methylene chloride with Nujol in solutions of **3** at 0 °C followed by overnight warming to room temperature gave the perester **4**. Perester **4b** was purified by chromatography, but the cumyl derivative **4c** proved to be unstable on silica. Hydrolysis of purified **4b** or crude **4c** with lithium hydroxide in aqueous THF gave the hydroperoxides **5b** and **5c**, which were purified by chromatography on silica. The overall yield for the sequence from hydroxamate esters **1** to purified hydroperoxides **5** ranged from 20% to 30%.

Isotopic oxygen was introduced into the hydroperoxide at the stage of the starting hydroxamate ester or from nitrosyl chloride. When the hydroxamate ester **1b** was reacted with $N^{18}OCl$ generated *in situ*,[7] the hydroperoxide product isolated, **5b**, gave an $M + NH_4^+$ ion by chemical ionization mass spectrometry (reagent gas 1% ammonia in methane), indicating the presence of 26% label.[8] A fragment ion of **5b** generated under these conditions of analysis, $MH^+ - H_2O$, was observed without evidence of any isotope label. The hydroxamate ester **1c** labeled with 66% ^{18}O in the carbonyl oxygen[9] gave cumyl hydroperoxide **5c**. Analysis of **5c** with CIMS (reagent gas 1% ammonia in methane) gave an $M + NH_4^+$ ion, indicating the presence of 33% label. The position of the label in the terminal position was demonstrated by analysis with methane as reagent gas. Neither $MH^+ - H_2O$ nor $MH^+ - CH_3OH$ fragment ions showed evidence of label. These data indicate that label is present only in the terminal oxygen of the hydroperoxides, consistent with the synthetic approach and the expected fragmentation by loss of the terminal oxygen from the MH^+ ion.

Further evidence identifying the position of the isotope label was provided by ^{13}C NMR analysis of the product hydroperoxides. In general, isotopic substitution with ^{18}O induces an upfield shift in the ^{13}C NMR spectra of directly-attached carbons.[10a] For the α-carbon of hydroperoxides substituted with ^{18}O, the magnitude of this shift is on the order of 0.04 ppm.

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(1) (a) For an early discussion of peroxide reaction mechanisms, see: Davies, A. G. *The Chemistry of Organic Peroxides;* Butterworths: London, 1957. See also: (b) Porter, N. A. Alkyl Hydroperoxides. In *Organic Peroxides;* Ando, W., Ed.; John Wiley & Son, Ltd.: Chichester England, 1992; pp 101. (c) Hiatt, R. R. In *Organic Peroxides;* Swern, D., Ed.; John Wiley & Son: New York, 1973; Vol. 2, pp 1. (d) Howard, J. A. In *Advances in Free Radical Chemistry;* Williams, G. H., Ed.; Academic Press: New York, 1972; Vol. IV, pp 49. (e) Ingold, K. U. *Acc. Chem. Res.* **1969**, *2*, 1. (f) Porter, N. A. *Acc. Chem. Res.* **1986**, *19*, 262.

(2) (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. (b) Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949.

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(4) (a) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1966**, *88*, 4518. (b) Koenig, T.; Deinzer, M. *J. Am. Chem. Soc.* **1968**, *90*, 7014. (c) Koenig, T.; Deinzer, M.; Hoobler, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 938. (d) Koenig, T.; Hoobler, J. A.; Mabey, W. R. *J. Am. Chem. Soc.* **1972**, *94*, 2514. (e) Koenig, T.; Hoobler, J. A. *Tetrahedron Lett.* **1972**, 1803. (f) Koenig, T. *Tetrahedron Lett.* **1973**, 3487.

(5) Analysis of the methyl benzoate resulting from reaction of perester **4a** with methoxide indicated that labeled carbonyl oxygen of the hydroxamate was scrambled into the ether-type oxygen of **4a**, presumably at the radical pair stage. Solutions of the methoxide reaction containing hydroperoxide were reconverted to the perester by reaction with *p*-nitrobenzoyl chloride to establish that the hydroperoxide was indeed labeled.

(6) The nitrosation and rearrangement sequence can be followed by ^1H NMR analysis of the *gem*-dimethyl singlet (referenced to TMS): **1b**, δ = 1.33 ppm; **2b**, δ = 1.21 ppm; **3b**, δ = 1.43 ppm; **4b**, δ = 1.34 ppm; **1c**, δ = 1.68 ppm; **2c**, δ = 1.66 ppm; **3c**, δ = 1.81 ppm; **4c**, δ = 1.74 ppm.

(7) $N^{18}OCl$ can be prepared *in situ* by bubbling HCl(g) into a two-phase reaction solution consisting of aqueous $NaN^{18}O_2$ and **1** in dichloromethane. Aqueous $NaN^{18}O_2$ is prepared *via* an exchange reaction of $NaNO_2$ and $H_2{}^{18}O$. $N^{18}OCl$ can also be prepared as a dichloromethane solution by addition of aqueous $NaN^{18}O_2$ to $HCl{\cdot}H_2{}^{18}O$ (prepared by saturation of $H_2{}^{18}O$ with HCl(g)) and distillation of the $N^{18}OCl$ generated (bp −5 °C) into dichloromethane at −78 °C. For NOCl preparation, see: Morton, J. R.; Wilcox, H. W. *Inorg. Synth.* **1953**, *4*, 48. For $NaN^{18}O_2$ preparation, see: (a) Rajendran. G.; Van Etten, R. L. *Inorg. Chem.* **1986**, *25*, 876. (b) Anbar, M.; Halmann, M.; Pinchas, S. *J. Chem. Soc.* **1960**, 1242.

(8) GC/CIMS analysis was carried out on Hewlett-Packard 5988A mass spectrometer, SPB-1 column, 15 m × 0.32 mm i.d., source temperature 150 °C, source pressure 1.1 atm. For **5b**, $CH_4/NH_3(g)$, $m/z = 192$ ($M + NH_4^+$), 157 ($MH^+ - H_2O$). For **5c**, $CH_4/NH_3(g)$, $m/z = 170$ ($M + NH_4^+$); $CH_4(g)$, $m/z = 135$ ($MH^+ - H_2O$), 121 ($MH^+ - CH_3OH$).

(9) ^{18}O-labeled benzoyl chloride is prepared in two steps from benzotrichloride and $H_2{}^{18}O$. Ponticorvo, L.; Rittenberg, D. *J. Am. Chem. Soc.* **1954**, *76*, 1705.

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Both of the hydroperoxides prepared *via* the hydroxamate ester pathway gave carbon spectra showing only the signal expected for hydroperoxides with α-carbons bearing only adjacent ^{16}O.[10b]

Important reactions of hydroperoxides were examined with the labeled compounds **5b** and **5c**. The reaction of triphenylphosphine and dimethyl sulfide with **5b** containing 26% ^{18}O label in the terminal oxygen gave triphenylphosphine oxide and dimethyl sulfoxide that analyzed for 26% ^{18}O content. The alcohol formed in these reactions, 2-methyl-2-nonanol, **6b**, showed no presence of label above background. Reductions of **5b** with bisulfite and iodide also gave unlabeled alcohol **6b**. Similar results were obtained in the reaction of labeled cumyl hydroperoxide with triphenylphosphine. While the suggestion has been made that phosphine, sulfide, bisulfite, and iodide reductions of hydroperoxides occur by transfer of the terminal oxygen,[11] we are aware of no previous unambiguous experiments supporting this proposal. The data reported above are unequivocal; *the terminal oxygen is transferred in these reactions.*

Sharpless epoxidation[12] of (*E*)-hex-2-en-1-ol and (*E*)-hex-3-en-1-ol utilizing **5b** (26% ^{18}O) as the oxidizing equivalent also demonstrated essentially complete transfer of the terminal oxygen. Thus, the epoxide product from the allylic alcohol contained (26%) label while the homoallylic alcohol gave epoxy alcohol containing 23–24% label under standard conditions. Epoxidation of the same unsaturated alcohols with **5b** and VO(acac)$_2$ gave epoxides with 22–23% label. Analysis of the alcohol byproduct **6b** formed in all of these epoxidation reactions showed no evidence of ^{18}O label above normal isotope background levels.

Reaction of 0.01 M labeled cumyl hydroperoxide (49% ^{18}O in the terminal oxygen) with AIBN initiator at 80 °C in hydrocarbon solvents[13] under an atmosphere of $^{16}O^{16}O$ led to substantial decomposition of the hydroperoxide with the formation of acetophenone, cumyl alcohol, and dicumyl peroxide. During the course of this decomposition, internal scrambling of the ^{18}O label from the terminal to the proximal position of **5c** occurred, as did external exchange with the atmosphere. After reaction of **5c** (49% labeled) for 10 h in heptadecane, for example, 51% decomposition had occurred and the hydroperoxide reisolated from this mixture by HPLC was a mixture consisting of 20% $H^{18}O^{16}OC(CH_3)_2Ph$ (no exchange), 14% $H^{16}O^{18}OC(CH_3)_2Ph$ (internal exchange), and 66% $H^{16}O^{16}OC(CH_3)_2Ph$ (external exchange).

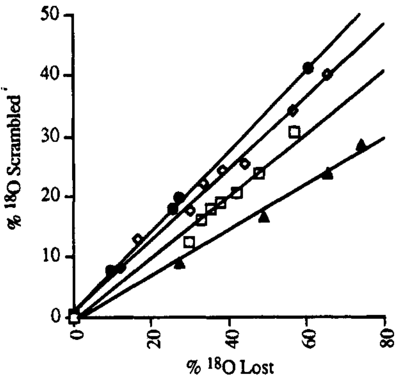

Figure 1. Solvent viscosity dependence on internal scrambling vs atmospheric exchange: ●, tetracosane; ◇, heptadecane; □, dodecane; ▲, heptane.

Scheme 1

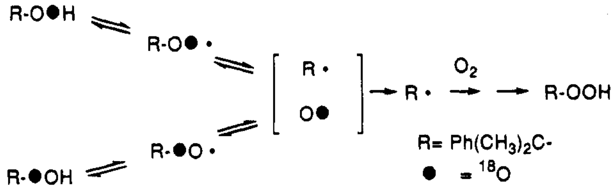

Figure 1 shows the percentage of terminal oxygen label that is scrambled into the proximal position of the hydroperoxide compared to the percentage of oxygen label that is lost from the hydroperoxide to the atmosphere. During the AIBN-initiated decomposition of **5c** the scrambling of label due to internal exchange compared to that of atmospheric exchange was dependent upon solvent viscosity. For example, at 60% loss of label from the starting hydroperoxide, internal scrambling amounted to 41%, 38%, 31%, and 22% for the C_{24}, C_{17}, C_{12}, and C_7 solvents, respectively.

The mechanism shown in Scheme 1 accounts for the viscosity dependent exchange behavior observed during the free radical decomposition of cumyl hydroperoxide.[14] Internal return of the cumyl radical–oxygen reactive pair gives the peroxyl radical with label scrambled between the terminal and proximal oxygens. Competing with this internal exchange is diffusive escape of the cumyl radical from the pair followed by its reaction with atmospheric oxygen. The labeled hydroperoxide allows detection for the first time of what amounts to a cage effect of 20–35% in the decomposition of cumyl peroxyl radicals.[15]

The availability of labeled hydroperoxides promises to provide a new window for observation of a wide range of important reactions of peroxides and peroxyl radicals. Attempts to broaden the scope of the synthetic approach are in progress and will be reported in due course.

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(10) (a) For a general discussion of the ^{18}O isotope effect on ^{13}C NMR spectra, see: Risley, J. M.; Van Etten, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 4609. (b) For **5c**, *C*(CH$_3$)$_2$OOH, δ 84.1 ppm. The chemical shift of the corresponding carbon in $^{18}O_2$-labeled cumyl hydroperoxide is shifted upfield by 0.03–0.04 ppm.

(11) See, for example: ref 1a, pp 129–136. See also: Edwards, J. O. In *Peroxide Reaction Mechanisms*; Edwards, J. O., Ed.; Wiley Interscience: New York, 1962; pp 67.

(12) (a) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823. (b) Sharpless, K. B.; Finn, M. G. in *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1985; Vol. 5, p 247.

(13) In some experiments, AIBN initiator was added in 0.08 equiv aliquots in 1–2 h intervals. In other experiments, 0.1 equiv of the initiator was added at the start of the reaction only. In the latter experiments, substantial decomposition occurred during the first 2 h but the reaction slowed considerably after this time. The data presented in Figure 1 are from both types of experiments.

(14) Peroxyl radical fragmentation has been observed by exchange of oxygen with the atmosphere in several experiments, but internal exchange is not detected by these experiments. (a) Howard, J. A.; Chenier, J. H. B.; Yamada, T. *Can. J. Chem.* **1982**, *60*, 2566. (b) Howard, J. A.; Bennett, J. E.; Brunton, G. *Can. J. Chem.* **1981**, *59*, 2253. (c) Beckwith, A. L.; Davies, A. G.; Davison, I. G.; Macoll, A.; Mruzek, M. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 815. (d) Chan, H. W. S.; Levett, G.; Matthew, J. A. *Chem. Phys. Lipids* **1979**, *24*, 245.

(15) The rate of the reaction of radicals and oxygen is at or near the diffusion limit. Cage coupling of chiral allyl radical–oxygen reactive pairs with retention of configuration has been suggested recently. Porter, N. A.; Mills, K. A.; Caldwell, S. E.; Dubay, G. R. *J. Am. Chem. Soc.* **1994**, *116*, 6697.