

# Peroxide Synthesis from Alkyl Halides, Alcohols and Alkenes

Thomas A. Foglia\* and Leonard S. Silbert

USDA, ARS, Eastern Regional Research Center, Philadelphia, Pennsylvania 19118

New and improved methods of peroxide synthesis have been developed along with advances in peroxide analyses. Hydroperoxides were obtained by one of three methods: i) perhydrolysis of alkyl mercury tetrafluoroborates (RHgBF<sub>4</sub>); ii) perhydrolysis of alkyl trifluoromethanesulfonates (triflates, ROSO<sub>2</sub>CF<sub>3</sub>); and iii) photooxygenation of unsaturated fatty esters (methyl oleate) with sensitizer in a phase transfer catalysis (PTC) system. Dialkyl peroxides also were prepared by three methods: hydroperoxidation of the mercury and triflate intermediates and an innovation of the reaction of superoxide anion with alkyl halides in a PTC system. Chromatographic—gas-liquid chromatography (GLC) and high-performance liquid chromatography (HPLC)—methods were examined in detail for compositional analysis of hydroperoxides and dialkyl peroxides in reaction mixtures and for purity determinations. Dialkyl peroxides were further analyzed by an improved rapid iodometric method by using strong non-oxidizing acid (HClO<sub>4</sub>) and iron catalysis.

**KEY WORDS:** HPLC, hydroperoxides, organomercurials, oxygenation, peroxides, superoxide, triflates.

Current methods for the preparation of primary and secondary alkyl hydroperoxides and their subsequent conversion to dialkyl peroxide derivatives are limited in scope. In general, the more commonly employed precursors to peroxy compounds include alkyl halides, alkenes or alcohols (1-5). Typically, alkyl hydroperoxides have been obtained either by the oxygenation of metal alkyls to alkylperoxy metal compounds which hydrolyze to alkyl hydroperoxides (3) or from the photooxygenation of alkenes to yield allylic hydroperoxides (6). Alternative to alkyl halides (*i.e.*, bromides), which react slowly and often give low yields, if any, the perhydrolysis of alkyl methanesulfonates (mesylates) in alkaline alcoholic solution has become an important route to alkyl hydroperoxides (7-9) because mesylates are readily obtained from their alcohol antecedents by reaction with methanesulfonic acid anhydride. In a similar reaction, dialkyl peroxides can be prepared from alkyl mesylates by using alkyl hydroperoxide as the nucleophile (4,10). An alternate method for preparing dialkyl peroxides is the reaction of alkyl halides with alkali metal superoxides (11,12). Because peroxy compounds of numerous structural types have become increasingly important biologically and industrially and because lipid peroxides are of nutritional concern, improved methods of preparation and analysis are needed to provide peroxy compounds in high yields and purity. To address this problem, we have recently developed and reported several new or modified approaches in peroxide synthesis with model compounds. We herein present an overview of our work which should provide a basis for application to more complex organic structures.

## METHODS

**Gas-liquid chromatography.** The instrument was a Hewlett-Packard (Avondale, PA) Model 5830A gas chromatograph equipped with a capillary inlet system and a flame-ionization detector (200°C). The quartz capillary columns were 12 m × 0.2 mm coated with 0.33 μm methyl silicone fluid (HP-101) and a 4 m × 0.2 mm coated with 0.33 μm 5% crosslinked phenyl methyl silicone fluid (HP-5). Initial column temperature for the 12-m column was 50°C for hexyl hydroperoxide and 80°C for octyl hydroperoxide (injector port, 150°C) and 60°C for dodecyl hydroperoxide (injector port, 160°C). Alkyl *t*-butyl peroxides up to *t*-butyl dodecyl peroxide and alkyl triflates were analyzed on the 12-m column; *t*-butyl tetradecyl peroxide and dioctyl peroxide were analyzed on the 4-m column. All components in reaction mixtures were resolved by temperature programming at 2°C/min to a final temperature of 150°C, and the important components were identified by comparison with available standards. For differentiation of dialkyl ethers from dialkyl peroxides, the former were prepared by the alcohol alkylation method of Barluenga *et al.* (13).

**HPLC.** The solvent delivery system consisted of a Beckman (San Ramo, CA) Model 110A solvent delivery module equipped with an Altex 210 loop injector with either a 20-μL or 100-μL sample loop and a Waters Differential Refractometer Model R401 detector (Waters Associates, Milford, MA). The HPLC columns used were a 4.6 mm i.d. × 25 cm stainless steel column prepacked with 5-μm silica (Zorbax SIL, Dupont Co., Wilmington, DE) or 5-μm ODS (Altex Ultrasphere, Deerfield, IL) for analytical HPLC. Semipreparative isolation of 1-alkyl hydroperoxides was made on a Dynamax (Rainin Instrument Co., Woburn, MA) prepacked 8-μm silica column, 10 mm i.d. × 25 cm. The integrator/recorder was a Hewlett-Packard Model 3396A. Hydroperoxides were eluted isocratically from the silica columns with 98% hexane/2% isopropanol (v/v) at a flow rate of 1 mL/min (analytical) or 3 mL/min (semipreparative HPLC).

Dialkylperoxides were analyzed isocratically on the ODS column with 70% acetone/30% acetonitrile (v/v) at a flow rate of 1 mL/min.

**Syntheses: peroxy compounds from alkyl halides.** Alkyl bromides, which are readily available intermediates, have been revitalized in peroxide synthesis by two reactions, one for hydroperoxides and the other for dialkyl peroxides. The peroxy mercuration-demercuration of alkenes has been reported for obtaining secondary alkyl peroxides bearing β-functional substituents (14). Several mercury salts have been employed, namely Hg(OAc)<sub>2</sub>, Hg(NO<sub>3</sub>)<sub>2</sub> and Hg(C<sub>10</sub>H<sub>4</sub>)<sub>2</sub>, all of which have limitations in reactions, yields, and scope. This reaction apparently has no utility for hydroperoxide preparations, or at least it had not been studied toward that aim. A new highly reactive organomercurial RHgBF<sub>4</sub>, alkyl mercuric tetrafluoroborate, 1 has been reported for the preparation of alcohols, ethers and amines (13,15,16) but has not previously received attention as an intermediate in peroxide synthesis. To apply this reagent to primary hydroperoxide formation (17),

TABLE 1

% Yield of Peroxides (R<sub>1</sub>OOR<sub>2</sub>) from Alkyl Halides, Alcohols and Alkenes<sup>a</sup>

Entry no.	Carbon no. R <sub>1</sub> + R <sub>2</sub>	Peroxide Structure <sup>b</sup>	Hydroperoxide method			Dialkyl peroxide method	
			RHgBF <sub>4</sub> <sup>c</sup>	Triflate <sup>d</sup>	(O <sub>2</sub> ) <sup>e</sup>	KO <sub>2</sub> <sup>c</sup>	Triflate <sup>f</sup>
1	6	C <sub>6</sub> H <sub>13</sub> OOH	70 <sup>g,h</sup>	71 <sup>h</sup>			
2	8	C <sub>8</sub> H <sub>17</sub> OOH	72 <sup>g,h</sup>	72 <sup>h,i</sup>			
3	8	C <sub>5</sub> H <sub>11</sub> CHC <sub>2</sub> H <sub>5</sub> <sup>j</sup>   OOH	54 <sup>h,j</sup>				
4	8	C <sub>5</sub> H <sub>11</sub> CHCH=CH <sub>2</sub> <sup>k</sup>   OOH			57 <sup>h</sup>		
5	10	C <sub>10</sub> H <sub>21</sub> OOH		70 <sup>h</sup>			
6	12	C <sub>12</sub> H <sub>23</sub> OOH	77 <sup>h</sup>	72 <sup>i</sup>			
7	12	C <sub>8</sub> H <sub>17</sub> OOCBu- <i>t</i>					84 <sup>h</sup>
8	14	C <sub>8</sub> H <sub>17</sub> OOC <sub>4</sub> H <sub>9</sub>				42 <sup>h</sup>	
9	14	C <sub>14</sub> H <sub>29</sub> OOH	80 <sup>i</sup>	60 <sup>i</sup>			
10	16	C <sub>16</sub> H <sub>33</sub> OOH		58 <sup>i</sup>			
11	16	C <sub>8</sub> H <sub>17</sub> OOC <sub>8</sub> H <sub>17</sub>				68 <sup>h,i</sup>	70 <sup>h</sup>
12	18	C <sub>7</sub> H <sub>15</sub> CHCH=CH(CH <sub>2</sub> ) <sub>7</sub> COOCH <sub>3</sub> <sup>l</sup>   OOH			77 <sup>i</sup>		
13	18	C <sub>14</sub> H <sub>29</sub> OOCBu- <i>t</i>					72 <sup>h</sup>
14	24	C <sub>12</sub> H <sub>23</sub> OOC <sub>12</sub> H <sub>23</sub>				83 <sup>i</sup>	
15	32	C <sub>16</sub> H <sub>33</sub> OOC <sub>16</sub> H <sub>33</sub>				75 <sup>i</sup>	

<sup>a</sup>% Weight yield × % peroxide content × 10<sup>-2</sup> = % yield of peroxide.<sup>b</sup>All alkyl chains are primary except where indicated by structure.<sup>c</sup>Peroxides from alkyl bromides.<sup>d</sup>Peroxides from alcohols.<sup>e</sup>Peroxides from alkenes.<sup>f</sup>Peroxides from hydroperoxides and triflates.<sup>g</sup>Yields include 3-5% hydroperoxide isomers.<sup>h</sup>Composition based on GLC.<sup>i</sup>Composition based on HPLC.<sup>j</sup>Reaction carried out with 3-bromooctane; 15% peroxide isomers.<sup>k</sup>Reaction carried out with 1-octene.<sup>l</sup>Mixture of 8(11) methyl oleate hydroperoxide obtained from methyl oleate.

we have prepared 1 *in situ* by reaction of alkyl bromide with mercuric oxide in the presence of ethereal fluoroboric acid (Equation 1). Reaction of 1 with 85% hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) gives a primary hydroperoxide (Equation 2) within 3 hr and with 80-90% conversion of alkyl bromide to hydroperoxide 2 (Table 1, entry 1 and 2). A disadvantage of the method is a minor isomerization of primary alkyl mercuric tetrafluoroborate to isomeric peroxy compounds of about 3%. The reaction also works well with secondary alkyl bromides in the preparation of secondary alkyl hydroperoxides, but in these instances isomerization to hydroperoxide isomers is about 15% (Table 1, entry 3).

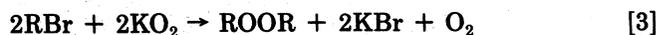


1



2

action of metal superoxides with alkyl halides (11,12) in the presence of crown ether. Superoxide anion, a unique anion radical, undergoes reactions that are classified as either nucleophilic, radical or redox. Its use as a nucleophile, however, is limited because of its reactivity with protic solvents and the limited solubility of metal superoxides in polar aprotic solvents. The reactions of superoxide anion with alkyl halides were studied with potassium superoxide (KO<sub>2</sub>) as the source of superoxide anion. The major product formed in this reaction was the symmetrical dialkyl peroxide, together with lesser amounts of the alcohol derived from the alkyl halide (Equation 3) (Table 1, entry 11, 14, 15). Our modification improved the reaction by replacing the crown ether by a phase transfer catalyst (PTC) to solubilize the inorganic KO<sub>2</sub> in organic solvents (18), thus dramatically increasing the rate and yield of reactions products (Table 1).

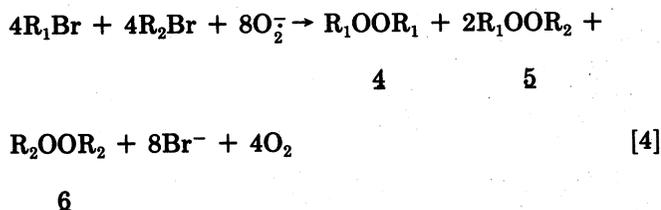


3

Dialkyl peroxides are prepared in a single stage by re-

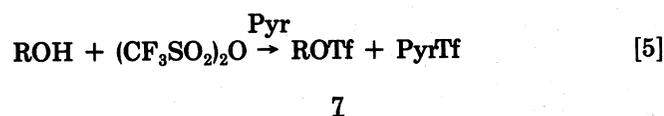
The yields of peroxides in this reaction were studied as functions of solvent polarity and of the type of PTC employed. Best yields were obtained with *N,N*-dimethylformamide as solvent and tetraethylammonium bromide as the PTC catalyst. Reaction pathways that account for the products of this reaction are in accordance with superoxide anion exhibiting both nucleophilic and radical redox reactions. Our PTC modification has not been studied with secondary alkyl bromides, but secondary peroxides have been reported in low yields (19–29%) for the 2-heptyl bromide and 2-octyl bromide reactions (12).

While the PTC reaction is effective for preparation of symmetrical primary dialkyl peroxides, mixed primary dialkyl peroxides are obtainable by admixing two different bromides. A difference in alkyl chain length by 4 or more carbon atoms enables easy separation of the three dialkyl peroxides, two symmetrical and one mixed (Equation 4).

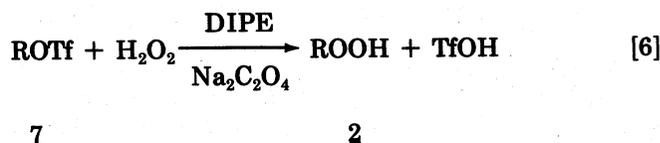


In the preparative example for 1-butyl 1-octyl peroxide (Table 1, entry 8), the products 4, 5 and 6 can be separated by distillation in the ratio 1:2:1.

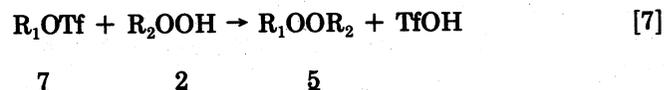
*Peroxy compounds from alcohols.* An alternative method studied for the preparation of alkyl hydroperoxides was the perhydrolysis of trifluoromethanesulfonate esters (triflates). The latter esters are  $10^4$  times more reactive than alkyl toluenesulfonates (19), which are similar to mesylates in nucleophilic displacement reactions. The triflate esters are prepared by reaction of an alcohol with trifluoromethanesulfonic acid anhydride ( $Tf_2O$ ) in the presence of pyridine (Equation 5).



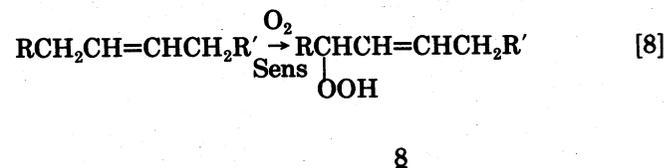
The reaction of ditriflates of 1,3-dihydroxy compounds with  $H_2O_2$  has been carried out previously yielding cyclic peroxides (20), but the reaction apparently has not been formerly studied with monohydric alkyls for hydroperoxides. Application of this reaction to alkanols uncovered parameters that were greatly different from those reported with the ditriflates that resulted in a new hydroperoxide synthesis (21). After forming the triflate 7 (Equation 5), the solution was filtered to remove the pyridinium triflate salt, solvent was removed *in vacuo*, and the alkyl triflate 7 was perhydrolyzed by  $H_2O_2$  (Equation 6) in diisopropyl ether (DIPE) solvent. In this reaction sodium oxalate, a mild base, was used to neutralize the triflic acid, which would otherwise catalyze decomposition of the hydroperoxide. Under these conditions, conversions of alkyl triflates 7 to alkyl hydroperoxides 2 (Equation 6) are 70–75% (Table 1), but the reaction is accompanied by some aldehyde and alkanol decomposition products.



With the availability of hydroperoxide, the triflate reaction can be applied to the formation of dialkyl peroxides 5 in similar fashion (20,21). The advantage of this method is that it provides a route to preparing unsymmetrical dialkyl peroxides (Equation 7) (Table 1, entry 7).



*Peroxy compounds from alkenes.* The addition of singlet oxygen to alkenes to give allylic hydroperoxides has been extensively studied (6). Singlet oxygen, a transient excited state of oxygen, can be generated either chemically or photochemically by energy transfer from triplet sensitizers. We have studied the reaction of singlet oxygen with 1-alkenes and methyl oleate in solution (T.A. Foglia, unpublished results). Singlet oxygen that was generated photochemically by use of a photosensitizer reacted with the double bond of the alkene, *e.g.*, methyl oleate, to yield allylic hydroperoxides 8 (Equation 8) (Table 1, entry 4 and 12).



The rate of formation and yields of hydroperoxides were studied as functions of the photosensitizer used. The incorporation of a phase transfer catalyst (PTC) to solubilize the photosensitizer enhanced the efficiency of this photochemical reaction. For example, yields of methyl oleate hydroperoxides approached 80% when rose bengal was used as the photosensitizer in the presence of tetraethylammonium chloride as the PTC in methylene chloride solvent.

*Analyses of products: chromatography.* Definitive methods of analyses for peroxide compositions have long been needed to monitor peroxide formation, decomposition and purity. Formation of hydroperoxides is often accompanied by several coproducts, namely aldehyde from primary hydroperoxide, ketone from secondary hydroperoxide, alcohol, dialkyl ether and dialkyl peroxide. Chromatographic methods are most promising for component separation, but peroxides exceeding about 5 carbon atoms in chainlength have not been studied in detail (5). We have found capillary gas chromatography (GLC) to be effective for the compositional analysis of hydroperoxides of 8 carbon atoms or less (Table 1, footnote e) on a 12-m column and up to 12 carbon atoms on a 4-m column. Because of the general thermal instability of hydroperoxides, GLC was ineffective for the compositional analysis of hydroperoxides beyond 12 carbon atoms in chainlength. On the other hand, high-performance liquid chromatography (HPLC) has been found to be an

effective method for the analyses of both alkyl and dialkyl peroxides regardless of chainlength or structure. In our studies with analytical normal-phase HPLC, hydroperoxide is resolved from its alcohol antecedent, whereas the combination of aldehyde and dialkyl coproducts are rapidly eluted as low-retention-time components. In contrast, analytical reverse-phase HPLC resolves dialkyl ether and peroxide, leaving the remaining components only partially resolved. Moreover, pure hydroperoxides may be isolated semipreparatively by application of preparative normal-phase HPLC-refractive index detector combination (T.A. Foglia, L. Silbert and P. Vail, unpublished data). These HPLC techniques together thus provide essentially quantitative analyses that cannot be obtained easily by other methods.

**Iodometry.** The most difficult among peroxide classes to determine iodometrically are the dialkyl peroxides. The method most commonly used for dialkyl peroxides employs conc. HCl/acetic acid/iodide ion, 1 hr at 120°C with complete elimination of air in a specially designed flask and is associated with a titration correction factor of about 20% (22). We have devised a greatly improved method for dialkyl peroxide determination by modification of the Wheeler method (23) in standard iodine flasks with perchloric acid as a strong non-oxidizing acid, and iron as a catalyst. Thermal input (25°-100°C) depends on the peroxide structure (24). The method provides quantitation within 20 min. The following peroxide order of increasing stability and decreasing reactivity has been found for the structures: di-*n*-alkyl; *t*-butyl-*n*-alkyl; dicumyl; di-*t*-butyl.

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