PEROXIDES

AND

PEROXIDE FORMING

COMPOUNDS

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Inorganic and organic peroxide, because of their exceptional reactivity and oxidative capacity are widely used in research laboratories. This review is intended to provide information and a guide to the hazards and safety concerns associated with the laboratory use, handling and storage of inorganic and organic peroxy-compounds and peroxide-forming compounds.

The relatively weak oxygen-oxygen linkage (bond-dissociation energy of 20 to 50 kcal mole^{-1}) is characteristic of organic and inorganic peroxide molecules. Essentially all of the features of peroxide reactivity are associated with the tendency for spontaneous change to form more stable products. The unusual weakness of the -O-O- bond is probably a consequence of the molecular and electronic structure of peroxide molecules and of the relatively high electronegative character of the oxygen atoms (30). As a class, peroxides are exceptionally prone to violent decomposition initiated by several mechanisms including heat, mechanical shock or friction. Organic peroxides are exceptionally susceptible to accelerated decomposition in the presence of certain catalysts and promoters. Knowledge, prudent handling and storage are essential when working with these compounds.

Several solvents commonly used in the laboratory can form explosive reaction products through a relatively slow oxidation process in the presence of atmospheric oxygen. The risk of explosion can be greatly reduced by following storage and handling practices that are compatible with the properties of these materials (23).

Information on the hazards of peroxides and peroxide forming chemicals is scattered in the literature. Most of the data prior to 1952 were summarized in a German-language publication by Criegee (21).   A comprehensive three-volume series on the chemistry of organic peroxides includes a chapter that addresses safety issues associated with these materials (26). Jackson et al (6) addressed the use of peroxidizable chemicals in the research laboratory (structure and examples, handling and operational procedures and detection of peroxides). His study included recommendations for maximum storage time for common peroxide forming laboratory solvents (6). More recently, Kelly (7) reviewed the chemistry and safe handling of peroxide forming chemicals and included detailed procedures on detection and removal of peroxides from laboratory solvents. Armour (34) provides detailed information on handling, spill cleanup and disposal of hazardous laboratory chemicals including the classes of per compounds addressed here.

INORGANIC PEROXIDES AND PEROXYACIDS

Inorganic peroxy compounds are potent oxidizers that pose fire or explosion hazards when in contact with ordinary combustible materials. Inorganic peroxides react with organic compounds to generate organic peroxide and hydroperoxide products and react violently with reducing agents (6). Sodium peroxide, hydrogen peroxide, sodium perborate, and sodium persulfate are present in many labs.

The O-O bond of hydrogen peroxide is covalent. In solution, persalts of alkali metals (M_2O_2) are ionized to the monopositive alkali metal ion M+, and the dinegative peroxide ion $(O_2)^{+2}$. Metallic peroxides are considered to be salts of hydrogen peroxide and react with water to produce H_2O_2 (18).

Hydrogen peroxide and perchloric acid are commonly found in research laboratories. Hydrogen peroxide alone is not explosive and has a long shelf life if not contaminated and if handled properly. However, concentrated hydrogen peroxide (>30%) may cause ignition if in contact with fabric, oil, wood, and some resins. Hydrogen peroxide may undergo violent decomposition in the presence of traces of certain catalytic metals (e.g. Fe, Cu, and Cr) or their salts. Dry Caro's reagent (monopersulfuric acid ---- K_2O_2 + con. H_2SO_4) reacts readily with carbonyl compounds and is used in the synthesis of organic peroxides (31). Caro's reagent can react explosively with aldehydes and alcohols (9, 15).

Similar hazards are associated with inorganic peroxides and persalts. Persulfates are highly reactive and may ignite when in contact with metals. Perhalogen compounds are extremely shock sensitive and should be avoided unless absolutely necessary. Perhalogen compounds can react with acids (especially organic acids) to produce near-anhydrous perchloric acid, an extremely hazardous compound.

Peracids are potent oxidizing agents, and react exothermically with easily oxidized substances. The reaction of perchloric acid with cellulose materials such as paper, cotton or wood can produce flammable or explosive products. Combustion may be accelerated by the presence of the peracid if the heat of reaction is sufficient to ignite other

materials. Readily oxidizable organic compounds such as alcohols, ketones, aldehydes, ketones, ethers, and dialkyl sulfoxides can react violently with concentrated perchloric acid. (25). Digestion of organic material in boiling perchloric acid must be conducted is a chemical fume hood that is specifically designed for that purpose. Perchloric acid fume hoods include a special wash-down feature to prevent buildup of explosive metallic peroxides.

Perchloric acid solutions are not combustible. However, anhydrous perchloric acid is unstable and is subject to explosive decomposition at ordinary temperatures or in contact with many organic substances. The maximum concentration of perchloric acid commercially available is an aqueous solution of 70% $HClO_4$. Cold 70% perchloric acid a strong acid but is not a strong oxidizing agent. The oxidizing power of perchloric acid increases with temperature and hot, concentrated solutions can be very dangerous. Perchloric acid solutions exceeding 70% may result from evaporation (e.g., spill or heated digestion procedure).

Furr included a review of the properties, hazards and use of perchlorates, including perchloric acid in the 4th edition of the CRC Handbook of Laboratory Safety (25). He stated that "The most detailed available account of the chemistry of perchloric acid and a reference highly recommended to everyone who will be working with perchlorates is given by J.S. Schumacher in the American Chemical Society Monograph Series 146, *Perchlorates, Their Properties, Manufacture, and Uses*" Procedures for dismantling an exhaust ventilation system suspected of perchlorate contamination are included in the CRC Handbook (25).

Perhalogen compounds of alkali metal and alkali earth elements are explosive, but are less sensitive than heavy metal perchlorates and organic perchlorate salts (13). Ammonium periodate is especially sensitive to friction. Perchlorates (e.g. magnesium perchlorate [$Mg(ClO_4)_2$] marketed as "Anhydrone") should not be used as a drying agent if contact with organic compounds or a strong dehydrating acid (such as in a drying train that has a bubble counter containing sulfuric acid) is possible (9, 25).

Peroxides, in contact with inorganic cobalt and copper compounds, iron or iron compounds, acetone, metal oxide salt, and acids or bases can react with rapid, uncontrolled decomposition of peroxides leading to fires and explosions (3). Peroxides may form on the surface of finely divided alkali metals and their amides and readily form superoxides, and ozonides such as KO_3 (3). Peroxides of alkali metals are not particularly shock sensitive, but can decompose slowly in presence of moisture and react violently in contact with water and many other substances. Therefore, the standard iodide test for peroxides must not be used with these compounds (3).

Although aqueous hydrogen peroxide solutions of less than 50% are contact irritants, contact with solutions of higher hydrogen peroxide concentration can cause a severe chemical burn (9, 15). Peroxide chemical burns should be washed gently but thoroughly and given competent medical attention (1). The acute toxicity of perchloric acid is moderate [oral LD_{50} (rat) 1100 mg/kg; oral LD_{50} (dog) 400 mg/kg]. It is a potent irritant at low concentrations. Higher concentrations are very corrosive and can cause severe burns to skin, eyes and mucous membranes. Perchloric has not been found to be carcinogenic or cause reproductive or developmental toxicity in humans (15).

ORGANIC PEROXIDES

Organic peroxides contain the bivalent -O-O- structure and are considered to be structural derivatives of hydrogen peroxide where one or both of the hydrogen atoms is replaced by an organic moiety (16, 21, 23). Alkyl- or aryl hydroperoxides (R-O-O-H) and dialkyl peroxides (R-O-O-R_1) are the most common types of organic peroxides used in the laboratory. Other classes of peroxides include acylperoxides, polyperoxides, peroxyesters, alkylidene peroxides, percarboxylic acids, and cyclic peroxides (15, 21).

As a class, organic peroxides are among the most hazardous substances commonly handled in the lab. Most are highly flammable and extremely sensitive to shock, heat, spark, friction, impact and light and readily react with strong oxidizing and reducing agents. Each peroxide compound is characterized by a specific, condition-dependent rate of decomposition. A change in conditions (e.g., increased temperature) can cause the rate of decomposition to auto-accelerate, culminating in a violent explosion. Most organic peroxides (especially lower MW compounds) are unstable at or near room temperature and must be kept under refrigeration during shipping and storage. Storage temperature of peroxides should not exceed 80° F (27°C) since shelf life is usually inversely related to storage temperature (15). (This may not be true for all peroxide solutions. See "Storage" below) The hazards associated with specific peroxides used in organic synthesis are addressed in the three-volume set "*Organic Peroxides*" (26).

Heat, mechanical shock, friction, shaking or contamination can initiate explosive decomposition of many organic peroxides. Within a structural series of the peroxy compounds, sensitivity and instability increase as active oxygen

content and oxygen balance increase (3). Peroxide sensitivity may also be related to its heat of decomposition, activation energy and reaction kinetics. Some peroxides that are usually regarded as being relatively innocuous may become highly hazardous under certain conditions. Combination of hydrogen peroxide (>30%) and many organic compounds are potentially detonable (21). The potential energy of organic peroxides is low compared with that of conventional explosives, but high enough to be very hazardous. Hence, safety in dealing with organic peroxides depends on knowledgeable handling and storage.

Although physical properties may differ, the reactivity and toxicity of other percarboxylic acids are similar but less than those of peracetic acid. As a rule, longer-chain peroxycarboxylic acids are not shock sensitive, but may detonate when heated. Peroxyformic and peroxyacetic acids are particularly explosive when relatively pure (21). Violent exothermic reactions may result when peracids contact ethers, metal chloride solutions, olefins, and some alcohols and ketones. The reaction of these substances, as well as carboxylic anhydrides, with peracids can produce shock-sensitive peroxide derivatives. "Run-away" peroxide decomposition may result from contact between peracids and some metal ions (e.g., iron, copper, cobalt, chromium, and manganese) (13).

Peracetic acid is probably the most toxic (chronic and acute) of the percarboxylic acids. The acute toxicity of peracetic acid is relatively low [oral LD_{50} (rat) 1540 mg/kg; dermal LD_{50} (rabbit) 1410 mg/kg]. It is highly irritating to skin, eyes and mucous membranes and may be weak carcinogen in mice. There is no such evidence to suggest carcinogenic, reproductive or developmental toxicity in humans. Other peracids (e.g., perbenzoic acid and m-chloroperbenzoic acid) are less toxic, less volatile and less hazardous to handle than peracetic acid (13). Although the toxicity and irritation hazards of the organic peroxides are moderate, it is prudent to minimize exposure to peroxides and associated materials, including vapors and aerosols. Aliphatic peroxyacids have a sharp, unpleasant odor, the intensity of which decreases with increasing chain length (21).
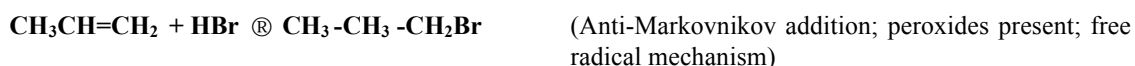
GUIDELINES FOR HANDLING ORGANIC PEROXIDES (9, 14, 19, 23)

❖ Use only the minimum quantity required.
❖ Wear nitrile gloves, eye protection and body protection such as a lab coat or apron.
❖ Conduct procedures inside a chemical fume hood or from behind a protective shield.
❖ Do not return unused peroxides to the container.
❖ Clean up liquid spills up immediately. Keep spills of solid peroxides wet with an appropriate inert solvent (e.g. water or aliphatic hydrocarbon). Cover the spill with a wet (water) mixture (1:1:1, by weight) of sodium carbonate, "kitty litter" or vermiculite, and sand. Dispose promptly as hazardous waste. See Armour (35) for recommended procedures for specific compounds.
❖ Reduce the sensitivity of peroxides to heat and shock by dilution with inert solvents (e.g. aliphatic hydrocarbons).
❖ Avoid using solutions of peroxides in volatile solvents. Solvent evaporation should be controlled to avoid dangerous concentration of the peroxide.
❖ Do not allow peroxides to contact iron or compounds of iron, cobalt, or copper, metal oxide salts, acids or bases, or acetone.
❖ Do not use metal spatulas to handle peroxides.
❖ Do not allow open flames, other sources of heat or sparks, friction, grinding or forms of impact near peroxides.
❖ Do not use glass containers with screw-cap lids or glass stoppers. Use polyethylene containers, screw caps or stoppers.
❖ Protect from heat and light.
❖ Store peroxides at the lowest possible temperature consistent with their solubility and freezing point. *CAUTION: Do not store liquid or solutions of peroxides at a temperature below that at which the peroxide freezes or precipitates. Peroxides in this form are extremely shock and heat-sensitive. Refrigerated storage of peroxides or other flammable chemicals must be ONLY in "Lab-Safe" or explosion-proof units.*

ORGANIC PEROXIDES IN CHEMICAL SYNTHESIS

Organic peroxides are widely used to generate free radicals for polymerization and similar reactions (23). For the substrate R-H, the chain reaction can be initiated by ultraviolet light, by the presence a radical source, and by the peroxide itself. Oxygen adds to the R moiety to generate the peroxide radical R-O-O[*]. The chain is propagated

as the peroxide radical abstracts a hydrogen atom from R-H (15). The catalytic potential of organic peroxides and the free radicals they generate, can change the course of a planned reaction, for example (11, 27):

CH₃CH=CH₂ + HBr ® CH₃ -CHBr - CH₃   (Markovnikov addition; peroxides not present)

CH₃CH=CH₂ + HBr ® CH₃ -CH₃ -CH₂Br   (Anti-Markovnikov addition; peroxides present; free radical mechanism)

The reversal of the orientation of the addition reaction is known as the "peroxide effect." The premise of free-radical mechanism is supported by the fact that very low levels of peroxide can alter the orientation of the reaction, and conversely, very small amounts of peroxide-inhibitor can prevent it (24). Thus, reagent purity can be extremely important for avoiding undesired results.

The hazards and consequences of fires and explosions during the laboratory synthesis and use of organic peroxides in the laboratory are widely recognized. There is no way to assure, with any degree of certainty that accidental explosions will not occur when working with such dangerous materials. Spontaneous or induced decomposition may culminate in a variety of ways, ranging from moderate gassing to spontaneous ignition or explosion. The heat released from spontaneous decomposition of an energy-rich compound causes a rise in the surrounding temperature. The temperature will rise until thermal balance is established or until the material heats to decomposition (3, 23).

All chemical reactions involve energy changes, usually as heat released during exothermic reactions. Destructive results occur when a reaction releases energy in a quantity or a rate too great to be dissipated by the immediate environment of the reacting system. The failure to recognize the effects of physiochemical factors associated with reaction kinetics is often the root-cause of many unexpected violent chemical reactions. The most important of these factors are those governing reaction rate by controlling concentration and temperature rise as the reaction proceeds (12)

Temperature control is critical in high-energy reactions. The Arrhenius equation shows that the reaction rate will increase exponentially with increase in temperature. That the reaction rate will double or triple with each 10^0 C temperature increase is a useful "Rule of Thumb." Thus, appropriate temperature control and heat dissipation is essential for avoiding the out-of-control acceleration of exothermic reactions (normal, polymerization, or decomposition). Fail-safe devices to protect against events such as utility failure should be incorporated into procedures that are unfamiliar or unattended.

Although relative uncommon, laboratory situations can approach adiabatic conditions when a strongly exothermic reaction is driven by an unusually well insulated heating system (e.g., flask completely surrounded by a thick heating mantle with a top jacket) or with unusually high heat capacity and inertia (e.g., deep-well oil bath) (12). Any impediment to ready dissipation of heat flow will increase the internal temperature. Under adiabatic conditions, spontaneously unstable materials must always self-heat to destruction (3, 23).

The most effective means for minimizing the consequences of an accident is to limit quantities to a practical minimum. Even gram-scale explosions can be very serious. Prudence requires stringent precautions and down scaling (concentration, quantity, volume), especially working with a new or unfamiliar organic peroxide or procedure. Lab personnel should be familiar with the ignition and combustion potential of the materials they use. It is essential for laboratory personnel to pay close attention to details. Once ignited, the burning of peroxides cannot be controlled. The area should be evacuated if any appreciable quantity of peroxide ignites.

Reactant concentration is critical in reactions involving peroxides and other highly reactive chemicals. It follows, from the Law of Mass Action, that the concentration of each reactant has direct influence on reaction velocity and the rate of heat release. Thus, it especially important to minimize reactant concentrations, especially in previously untried reactions. Unless there are compelling reasons to do otherwise, peroxide concentration should be limited to 10% (or less with vigorous reactants). Peroxide concentration is rarely as high as 1% in the reaction mixture of polymerization and other free-radical reactions. For most reactions, catalyst concentration should be much less (23). Dire consequences can result from the intentional or accidental increase in reactant or catalyst concentration to an otherwise safe procedure (12).

The peroxide should be added slowly and cautiously to the reaction medium. This should be completed prior to heating and with good agitation. It is essential to conduct all such operations in a properly functioning chemical

fume hood. All sources of accidental ignition must be excluded from areas where peroxides are used.

It may be hazardous to make concentrated stock solutions of organic peroxide monomers. Addition of peroxide to the hot monomer is extremely dangerous. A violent reaction (e.g., fire or explosion) can result from inadvertent mixing of promoters (frequently used with peroxides in polymerization systems) with full-strength peroxide (23).

Organic peroxides are very sensitive to contamination (especially heavy-metal compounds, metal oxide salts, alkaline materials including amines, strong acids, and many varieties of dust and dirt). This can initiate rapid, uncontrolled decomposition of peroxides and possible fire or explosion (2, 23). The consequences of accidental contamination from returning withdrawn material to the storage container can be disastrous. Once withdrawn, peroxides must never be returned to its storage container.

Vessels containing hazardous or suspicious materials should not be handled directly. Remote handling (e.g., tongs), personnel protective equipment (e.g., gloves, face and eye protection, etc) and explosion-proof barricades (including the fume hood sash) should be used to minimize close contact with reactants, reaction mixture and products. It is useful to be mindful of the inverse square law when designing laboratory work with hazardous materials. The blast effect from small charges attenuates very rapidly in the open. The safest available peroxide composition that will do the job should be selected for each use. The use of paste or water-wet benzoyl peroxide, for example, can nearly eliminate risk from mechanical shock and friction (12).

SAFETY CONSIDERATIONS FOR CHEMICAL REACTIONS INVOLVING PEROXIDES (12)
- ❖ Adequate temperature control and heat dissipation mechanism for liquid and vapor phases;
- ❖ Correct proportion and concentration of catalyst and reactants;
- ❖ Purity of components (absence of catalytic impurities);
- ❖ Appropriate solvent(s);
- ❖ Viscosity of the reaction medium;
- ❖ Control of rates of reactant combination;
- ❖ Allow for induction period;
- ❖ Agitation (mechanism, degree)
- ❖ Control of reaction atmosphere;
- ❖ Pressure release and control;
- ❖ Shielding from actinic radiation;
- ❖ Avoid conditions that might cause ignition, decomposition, etc. of unstable materials;
- ❖ Shielding and personal protective equipment.

STORAGE OF ORGANIC PEROXIDES

Store peroxides in isolation and separated from the work area and from organic materials. Information on appropriate material and design criteria for peroxide storage is available (23, 25, 28). Decomposition of stored reagents can lead to excessive loss of activity, self-heating and runaway decomposition. Contaminated, partially decomposed, off-strength or surplus organic peroxides should disposed of or destroyed under stringently controlled conditions.

Published data on the decomposition kinetics of organic peroxides at storage temperatures are sparse. Some crystalline peroxides can be stored for years at room temperature with little evidence of decomposition. On the other hand, many peroxides must be prepared at low temperatures and are very unstable at room temperature (23).

The potential for violent decomposition is inversely related to molecular weight. Lower molecular weight peroxides are extremely shock-sensitive and can easily deflagrate or detonate. They are especially unstable when dry, and should be stored only under wet (water or inert hydrocarbon) conditions. Benzoyl peroxide can explode spontaneously and dry acetyl peroxide is very unstable and violently explosive. Detonation can be initiated by friction generated by unscrewing a lid in contact with the dry peroxide. Labs should maintain the minimum practical supply on hand and one-day supply in the work area. The condition of the containers should be confirmed at regular intervals (15).

Although cooling is generally extends shelf life, there are situations in which cooling may cause increased impact sensitivity. This can occur when the cooling of a liquid composition causes separation of liquid phases or precipitation of peroxide crystals. In either case, one of the separated phases is very likely to be more impact-

sensitive than the original solution. For example at 0° C, crystals of acetyl peroxide (extremely impact-sensitive) can precipitate from a 25% solution in dimethyl phthalate. Users of new or incompletely studied peroxy compounds (especially liquids and solutions) should be alert to the possibility of enhanced hazards on cooling. The appearance of a new phase is a very strong indicator of increased impact sensitivity (23).

The consequences of storage at elevated temperature are highly scale-dependent. Container size is the primary determinant of the rate of decomposition without self-acceleration. Unless the self-decomposition rate is known to be low, experimental peroxide compositions should be handled and stored in small vessels (23). The self-accelerating decomposition test (SADT) is designed to deal with the scale-dependence phenomenon (17). The SADT (also called the "Temperature of No Return" or "Ignition Temperature") is the temperature at which a heat-sensitive compound can auto-ignite with rapid and violent decomposition. The SADT is used internationally to estimate safe storage and transportation conditions for unstable chemicals. The SADT can be a very useful characteristic of peroxides and is often included in the MSDS (2).

Although dilution of peroxide solutions decreases the potential for violent decomposition, the rate of auto-decomposition often increases. At elevated temperatures, the decomposition of organic peroxides (dilute solutions in inert solvents) usually follows first-order kinetics. The half-life of a peroxide in dilute solution (50^oC) range from about 100 hr for many of diacyl peroxides to many hundreds of hours for peroxyesters, hydroperoxides, and dialkyl peroxides. The half-life is short (minutes) for dilute diacyl peroxide solutions at about 100^oC and for most other peroxides at much higher temperatures ($130-250^oC$). Activation energies range from about 30 kcal/g-mole for diacyl peroxides to about 35 to 40 kcal/g-mole for hydroperoxides and dialkyl peroxides. The relationship between decomposition at elevated temperatures and relative storage stability is minimal. This indicates that different reaction pathways are condition-dependent (23).

Because of enhanced contact, liquid compositions tend to be more susceptible to contamination than solids. However, small quantities of liquid catalysts or promoters can lead to intense local temperature rise in solid peroxides. Limited diffusion and lack of convection may lead to an intense hot spot that can initiate a violent, self-propagating reaction (23).

Stabilizers are usually not necessary with solid organic peroxides. However, there are a few instances in which the rate of decomposition can be reduced by inclusion of materials that complex or adsorb heavy-metal ions in the composition. For example, additives (e.g. dipicolinic acid and sodium pyrophosphate) that function as "anti-catalysts" can greatly reduce the decomposition rate of aqueous peroxy acid solutions. This is analogous to the stabilization of hydrogen peroxide solutions. Free-radical-trapping materials can reduce the decomposition rate when a chain reaction mechanism is followed. This may be of limited practical use if the chain scavenger also depletes the free radicals necessary for the reaction (23).

AUTOXIDATION OF ORGANIC SOLVENTS

A number of commonly used organic solvents can undergo autoxidation to produce unstable and dangerous hydroperoxide and peroxides products. "Autoxidation" generally refers to the slow reaction between organic chemicals and elemental oxygen under mild conditions. Although ethers are generally recognized as dangerous peroxide formers, other organic structures (e.g. acetals, certain allylic alkenes, chloro- and fluoroalkenes, dienes, aldehydes, amides, lactams, ureas, some alkylarenes, ketones, vinyl monomers, and some alcohols) are capable of spontaneous autoxidation to form of highly unstable hydroperoxides, and monomer- and polymeric peroxides. Organic functional groups likely to form peroxides are shown in Figure 1. Not all compounds containing these groups form peroxides. However, the presence of any of these groups in a compound should be taken as a warning that hazardous concentrations of unstable peroxides might be present (6).

Molecular structure is a major factor in determining the rate of autoxidation and shelf life within a class of peroxide forming chemical (3). The auto-peroxidation potential of a compound is greatly influenced by adjacent and nearby functional groups. These relationships were first reported by Jackson et al (6) and subsequently refined by other authors (3, 15, 16, 22). Peroxide-forming compounds invariably contain an autooxidizable hydrogen atom that is activated by adjacent structural components and/or actinic radiation (not necessarily continuous). These compounds react with atmospheric oxygen under ambient conditions to initially form a hydroperoxide (3). Initially, the autocatalytic reaction proceeds very slowly, then the rate gradually increases to a maximum velocity.

Activated hydrogen atoms are often on a:

❖ Methylene group adjacent to an ethereal oxygen atom ($-O-CH_2-$, e.g. diethyl ether, THF, dioxane,

diglyme).

- ❖ Methylene group adjacent to a vinyl group or benzene ring (C=C-CH$_2$- or Ph-CH$_2$-, e.g. allyl or benzyl compounds).
- ❖ CH group adjacent to two ethereal oxygen atoms (-O-CH-O-, e.g. acetals or methylenedioxy compounds).
- ❖ CH group adjacent to two methylene groups (-CH$_2$-CH-CH$_2$-, e.g. isopropyl compounds and decahydro-naphthalenes).
- ❖ CH group between a benzene ring and a methylene group (-CH$_2$-CH-Ph, e.g. cumene and tetrahydro-naphthalenes).
- ❖ A vinyl group (-C=CH$_2$, e.g. vinyl compounds, dienes, styrenes or other monomers) (3).

Chemical structures that include more than one of these groups are at particular risk of peroxidation. For example, vinyl groups are increasingly susceptible to peroxidation when they are further activated by the addition of an attached halogen atom, a phenyl or carbonyl moiety, or another unsaturated structure, (7). Within a class of peroxide-forming chemicals, the peroxidation potential is usually inversely related to the molecular weight of the compound. Compounds with ten or more carbon atoms at a peroxidizable site are considered low-risk systems (3, 6, 22).

Peroxidation is generally peculiar to the liquid state. Minimal hazard is usually associated with solid, vapor or gaseous potential peroxide formers. However, the peroxidation reaction can proceed on the surface of finely divided solids. (1). Compressed gases (e.g., butadiene, tetrafluoroethylene, vinylacetylene, and vinyl chloride) are relatively resistant to autoxidation. However, the difficulty of completely eliminating residual oxygen from the receiving vessel increases the hazard when the material is transferred to a secondary container. Addition of an appropriate inhibitor to the receiving container prior to transfer can reduce the hazard. The peroxidation potential may be greatly increased if these gases condense inside the cylinder or secondary vessel. Processes involving these gases should be thoroughly evaluated to determine the likelihood of forming a liquid phase (7, 13).

The peroxidation process can be initiated by ultraviolet light (photoperoxidation), by the presence of a free radical source, by the peroxide itself (15), or by impurities such as acetaldehyde (7). Exposure of susceptible compounds to oxygen always enhances peroxide formation. However, the effects of heat, light and contaminants are variable and unpredictable. The effect of light exposure on susceptible alcohols can be potentiated by intentional or incidental contamination of peroxidizable alcohols with ketones. It is likely that similar interactions may occur with other compounds (1).

The autoxidation reaction proceeds by a free-radical chain mechanism with peroxidation of a carbon atom adjacent to an oxygen atom producing the peroxy radical, R-O-O[*] (Figure 2). Organic free radicals are often formed in solution upon heating (in some cases, merely dissolving) a compound having weak covalent bonds (4). Resonance or similar mechanism can stabilize the intermediate free radical. The chain reaction continues when the peroxy radical abstracts a hydrogen atom from R-H. Like other free-radical reactions the autoxidation process is self-propagating. Thus, a single initiating event may lead to self-sustaining reaction with the rate of the peroxide formation increasing with time (22).

Peroxidation reactions usually include an induction period that precedes a relatively rapid accumulation of the corresponding hydroperoxide. In some cases, hydroperoxide concentration may reach 5-15%. The hydroperoxide concentration may stabilize or decrease as the hydroperoxide decomposes to form byproducts (e.g. alcohols and water) which interfere with the free radical chain reaction and/or peroxidation. The byproduct content may continue to increase, but the peroxide content remains stabile. This scenario does not apply when peroxides crystallize and precipitate from the solution. In those cases, the peroxy compound remains undiluted by solvent or byproducts and constitutes a serious hazard (1).

The hydroperoxide is likely to be highly unstable and usually undergoes further addition, rearrangement or disproportionation leading to dialkyl, polymeric, cyclic, and other unstable higher peroxide products (3, 7, 13). This is an important safety consideration because these products are more difficult to detect and remove than simple hydroperoxides (6, 13). The instability of these products becomes increasingly dangerous with heating and/or concentration (3, 7). This hazard can be reduced by rigidly following storage and handling techniques that are accurately matched to the properties of the materials concerned (3). *The Chemistry of the Ether Linkage* (22) includes useful information on ethers and an "Appendix on Safety Measures."

Most alkyl monohydroperoxides are liquids. The lower members are soluble in water and are explosive (21). Oxidation of p-dioxane produces very dangerous levels (more than 30% of total peroxide) of diperoxide products.

Autoxidation of isopropyl ether forms a variety of higher M.W. peroxides, including cyclic peroxides of acetone, which may be particularly explosive (3, 7).

The degree of peroxide accumulation is determined by the equilibrium established between peroxide formation and degradation, further reaction, and concentration of the peroxide. The equilibrium varies with compound and conditions (1). The structure-induced stability of the peroxide products varies greatly.   For example, α-phenylpropionyl peroxide is so unstable that it cannot be isolated under ambient conditions, whereas t-butyl hydroperoxide is stable for weeks when stored at ambient temperature and in the dark (4).

USE AND STORAGE OF PEROXIDE-FORMING COMPOUNDS

The opportunistic peroxidation of susceptible solvents or solutions is a function of atmospheric oxygen, light and storage time. Ultraviolet light, including sunlight, promotes both autoxidation and depletion of the inhibitor. But the reaction cannot proceed in the absence of oxygen or oxidizers. The rate of peroxidation increases significantly when stored under conditions that do not exclude oxygen and actinic radiation (6). Since autoxidation is structure dependent, shelf life (before significant peroxidation occurs) and resulting products vary widely between compounds and storage conditions.

Laboratory chemicals known to form peroxides have been categorized into three groups based on their susceptibility to peroxide formation (Table 1). (NOTE: Certain monomers included in Table 1 are not generally available in laboratory quantities). The recommended maximum shelf life for each group is conditioned on the premise that the compounds are stored in opaque containers under an inert (oxygen-free) atmosphere, and are based upon time after opening the container. Susceptible solvents are normally supplied with an antioxidant or free-radical scavenger. These additives can slow, but not prevent peroxidation (19). Therefore, it is critical to include procedures to guard against unanticipated results.

The chemicals in Group A can form explosive peroxide levels even in an unopened container, and some will separate from solution. Isopropyl ether is particularly dangerous: the presence of two tertiary carbon atoms makes it readily peroxidizable to a hydroperoxide. The hydroperoxide then polymerizes to form a product that readily precipitates from the ether solution as an explosive crystalline solid (9, 13).

Group B compounds can form explosive levels of peroxides, but usually become hazardous only if the peroxides are concentrated by evaporation, distillation, etc. The common laboratory solvents (e.g., diethyl ether, THF, cyclohexene, the glycol ethers, and isopropanol) become increasingly hazardous when evaporation concentrates peroxide to increasingly dangerous levels. Most of these solvents are also volatile, such that repeated opening of a container may allow enough evaporation to concentrate peroxides to an explosive level. These solvents should never be distilled or concentrated to dryness or near dryness unless the absence of peroxides is assured (3, 5, 9, 12).

 Group C includes examples of vinyl monomers that are usually not particularly hazardous. However, their decomposition may initiate the explosive polymerization (Trommsdorf effect) of the bulk monomer (6). It is important to add a suitable polymerization inhibitor prior to distillation or concentrating any of these compounds (3, 9). Kelly (7) included an additional list of about 125 compounds with structural potential for undergoing peroxidation. However, they have not been clearly characterized and are not included here.

The autoxidation reaction proceeds slowly (relative to other types of chemical reactions) so that extended storage provides time for accumulation of unstable products. Peroxidation of susceptible solvents or solutions typically occurs when containers are not fully sealed and blanketed with inert gas. A breach of the container seal may allow sufficient oxygen to eliminate the inhibitor then initiate and support the autoxidation process. Temperature and barometric pressure fluctuations facilitate infiltration of atmospheric oxygen into the containers. Initial peroxide buildup is usually slow because the exchange of air (containing only 20% oxygen) is gradual (1). Air should always be flushed out of the free space with an inert gas (usually nitrogen) before sealing. This is especially critical for the chemicals in Groups A and B, especially if the inhibitor has been removed (e.g. distillation) or depleted.

Since peroxidation is accelerated by heat, light, oxygen or air, and elevated temperature, storage of peroxidizable chemicals in open, partially empty, or transparent containers greatly increases the risk of peroxide formation. Laboratory procedures (e.g. evaporation, distillation, spills) that increase peroxide concentration or allow extensive exposure to air or oxygen are particularly dangerous. The stability of potential peroxide-formers can be greatly enhanced by storage under an inert atmosphere (nitrogen or argon) or under vacuum (19). Peroxide

impurities in higher boiling point chemicals (e.g. long-chain alkyl ethers and the glycol ethers) usually undergo thermal decomposition at distillation temperatures. However, this may not be true in reduced-pressure procedures and dangerous peroxide levels may develop (6).

Peroxides are less volatile than the parent compound, therefore become concentrated upon evaporation of the parent solvent. It is prudent to test potential peroxide-formers immediately prior to distillation or evaporation. It can be extremely dangerous to distill or significantly concentrate any uninhibited solvent in Groups A or B unless known to be free of peroxidation products. At least 10% of the bottom residuals should be retained in distillation of peroxide-formers. The hazard can be reduced by addition of a nonvolatile organic compound (e.g. mineral oil) to the distillation flask. The mineral oil will remain in the distillation vessel and dilute the remaining peroxides. It is essential to always include a magnetic stirrer, boiling chips or an inert gas bleed to avoid a build-up of pressure. Air or other oxygen-containing mixtures should never be used for mixing during distillation (6).

Refrigeration can retard peroxidation of volatile organic peroxidizable compounds. However, peroxide accumulation may actually be enhanced by refrigeration if the rate of peroxide degradation is slowed more than the rate of peroxide formation. Peroxides may precipitate from solution if the solvent is cooled to near the freezing point and becomes very shock sensitive and extremely dangerous. In any case, only completely spark-proof refrigerators should be used to store ethers or other volatile peroxide formers. Some peroxidizable organometallic compounds (e.g., Grignard reagents) should not be refrigerated (9, 12). There is little or no evidence that refrigeration slows oxidation of diethyl ether. The vaporization of ether may lead to the formation of an explosive atmosphere, even at freezer-temperatures (9).

Despite the use of inhibitors, peroxide-induced explosions have occurred. Antioxidant inhibitors are usually depleted along with peroxides formation and subsequent degradation. Eventually, the inhibitor be depleted to a point that will allow peroxide-formation to proceed as though uninhibited. When this occurs, peroxides may accumulate in a material that has been stabilized for a long time. The presence of both peroxides and inhibitor should be assured if potential peroxide-formers are retained for extended time (5). If the inhibitor is exhausted, additional inhibitor must be added or the material must be treated as though uninhibited. Stabilized reagents should be used unless the antioxidant interferes with its use. *CAUTION:* Because distillation of the stabilized solvent will remove the stabilizer, the distillate must be stored with care and closely monitored for peroxide formation. Uninhibited peroxide formers should not be held over 24 hours (6, 16, 19).

Low levels of free-radical scavengers (e.g. 100ppm hydroquinone or diphenylanine; 2,6-di-tert-butyl-p-methylphenol (BHT); polyhydrophenols, aminophenols and arylamines) are added to inhibit the chain reaction of the peroxide forming solvent. One report indicated that diethyl ether containing 10ppm pyrogallol was stabilized for over 2 years (19). Phenolic compounds are often added to commercial vinyl monomers. However, phenolic inhibitors are ineffective if some oxygen is not present. Thus, solvents inhibited by these chemicals should not be stored under inert gas (6).

Formation of peroxides in diethyl ether is inhibited by the addition of iron wire to steel containers. However, iron or other metals will not inhibit peroxidation of isopropyl ether and are probably ineffective for other chemicals. In fact, iron may catalyze peroxidation in some solvents. Water can be used to dissolve oxidation products but will not prevent their formation in ethers. Other inhibitors of peroxide formation include Dowex-1 (ethyl ether); hydroquinone (tetrahydrofuran); 100 ppm 1-naphthol (isopropyl ether); and stannous chloride or ferrous sulfate for dioxane. Substituted stilbenequinones have been patented for stabilization of oxidative deterioration of ethers and other compounds (3, 19).

Because many peroxide formers are commonly used solvents, they are often purchased in relatively large volume. Peroxide-forming compounds should be purchased in limited quantities, used in order of receipt and never stockpiled. It is prudent practice to date all chemicals both when they are received and when they are opened. Peroxide-forming compounds should be clearly identified by additional labeling, and stored in tightly sealed containers (preferably in the container furnished by the supplier) away from light and heat. Periodic testing to detect peroxides should be performed and documented on each container (especially for compounds in Groups A and B, Table 1).

DETECTION OF PEROXIDES

Visual inspection of the container and contents of organic solvents in glass bottles can detect the presence of very high levels of peroxides. Visualization of the contents of a glass container can be accomplished by using a

non-hazardous light source (e.g. a flashlight).   The light source should provide back light or side light the bottle to avoid distortion. Visible indicators of peroxide presence include:

- ❖ Clear liquid containing suspended wisp-like structures,
- ❖ Precipitated crystal formation appearing as chips, ice-like structures, solid mass,
- ❖ Appearance of cloudiness,
- ❖ Gross contamination

The observation of any of these indicators warrants extreme caution. Additional testing or handling should be avoided. Only individuals with skill and experience in handling extremely hazardous materials should perform handling and disposal. . Do not move or disturb any container if there is any question regarding the presence of peroxides

A variety of quantitative, semi-quantitative, and qualitative methods to detect peroxides in organic and aqueous solutions have been developed. Kelly (7) included detailed procedures for four most commonly used semi-quantitative procedures. These include the iodine detection method (two qualitative variations), the qualitative ferrous thiocyanate method, and the use of semiquantitative redox dip strips. Procedures for quantitative analysis of organic peroxides are available (26).

HAZARDOUS LEVELS OF ORGANIC PEROXIDES

Kelly (7) reviewed the literature to determine the minimum hazardous concentration of peroxides in solution with organic solvents. Peroxide concentration of 100 ppm has been widely used as a control point, but lacks scientific justification and is probably based on the practical detection limit of the potassium iodide method. Kelly reported great disparity (range 50-10,000 ppm as hydrogen peroxide) between various references. There was little agreement between authors and none provided supporting data. The highest level (10,000 ppm) was found in a National Safety Council publication (16). However, the NSC publication included no supporting references for the latter statement or the NSC recommendation for administrative control value of 100 ppm.

The Material Safety Data Sheet for diethyl ether cautions against concentrating ether containing peroxide level above 100 ppm (10). Presumably, instability and hazard increase with concentration such that at some point, the solution spontaneously explodes. Kelly suggested that it is likely that the control concentration of 100ppm, in some cases may be overly conservative by at least an order of magnitude. This may apply to the chemicals listed in Table 1-B unless the unstable materials are concentrated as result of solvent evaporation (7).

Kelly (7) stated that "theoretically, explosion should be impossible for most solutions of <1% peroxides." However, to rationally establish a safe/hazard concentration is complicated by a number of factors. For example, some of the liquid may remain on the threads and cap when peroxidized liquids are dispensed from glass containers with screw-caps or with ground-glass stoppers. As the solvent evaporates, the peroxide can be concentrated to dangerous levels within in the threads of the cap. Thus, a volatile solvent containing relatively low peroxide contamination could explode because of peroxide concentration at the cap (3, 7).   Dilute solutions of most peroxidizable chemicals or solutions in solvents with low volatility (B.P. $\geq 300\,^{\circ}$C or V.P. <0.1 mm Hg at $20\,^{\circ}$C) usually do not pose a peroxide hazard and are not likely to concentrate. Thus, it is usually unnecessary to treat such solutions as peroxide hazards (3, 5).

Some of the peroxidation products of the chemicals in Group A (Table 1) are less structurally stable than those in Group B. Thus even peroxide concentrations of less than 100 ppm should be considered very hazardous. Unstabilized isopropyl ether can readily form highly unstable peroxides. Even low small concentrations produced through solvent evaporation are very dangerous and may explode on shaking (33).   The temperature and concentration at which explosion of peroxides of isopropyl ether becomes probable has never been authoritatively stated (20).

CLEANUP AND DISPOSAL OF PEROXIDES
AND PEROXIDE-FORMING CHEMICALS

Pure peroxides must be diluted prior to disposal and should never be disposed of directly.   Small quantities ($\leq$25 gm) of peroxides should be diluted with water to a concentration of 2% or less, then transferred to a plastic container containing an aqueous solution of a reducing agent such as ferrous sulfate or sodium bisulfite. The material can then be handled like any other hazardous chemical waste. However, it must not be commingled with other chemical waste.

Larger quantities of organic peroxide may require special handling. Handling, storage and disposal requirements are determined are determined by the physical and chemical characteristics of the particular chemical (13, 15). Procedures for cleanup and disposal of laboratory spills of per compounds are included in Armour's book (34).

Any container of peroxidizable chemicals that is old, deteriorated or of unknown age or history must not be moved or disturbed. Any peroxidizable chemical with visible discoloration, crystallization, or liquid stratification must be treated as potentially explosive.

❖ NEVER attempt to force open a rusted or stuck cap on a container of a peroxide-forming chemical.
❖ NEVER attempt to clean by scraping or rubbing glassware or other containers that may contain peroxides or peroxide-forming chemicals if an oily deposit or crusty residue is visible.
❖ Empty containers of ether or other peroxide-formers can be discarded in regular trash after triple rinsing with water and defacing or removal of the label.

Diacyl peroxides can be deactivated by reaction (inside a chemical fume hood) with an acidic iodine solution [0.22mole (10% excess) of sodium or potassium iodide in 70 ml glacial acetic acid per 0.01 mole of diacyl peroxide]. Add the peroxide slowly, with gentle stirring at room temperature. As the reaction proceeds, the release of iodine will cause the solution to darken. This process should be completed in about 30 minutes.   For destruction of dialkyl peroxides, add 1 ml of 36% HCl; heat the solution to 90 - 100° over a steam bath for 30 min., then hold at that temperature for 5 hours (13, 15).

Absorb spilled peroxides on vermiculate as soon as possible. If appropriate facilities are available, the vermiculate-peroxide mixture can be incinerated directly or may be slurried by stirring with a suitable solvent. The slurry can be treated with an acidic ferrous sulfate solution (60gm ferrous sulfate + 6 ml con sulfuric acid + 110 ml water). Never flush organic peroxides down the drain (13, 15).

SAFETY GUIDELINES FOR PEROXIDE-FORMING COMPOUNDS

❖ Protect from heat and light. Store peroxide formers only in air-tight containers in a cool, dry and dark location.
❖ Do not allow open flames, other sources of heat or sparks, friction, grinding or forms of impact near peroxides
❖ Store peroxides at the lowest possible temperature consistent with their solubility and freezing point. *CAUTION: Do not store liquid or solutions of peroxides at a temperature below that at which the peroxide freezes or precipitates. Peroxides in this form are extremely shock and heat-sensitive. Refrigerated storage of peroxides or other flammable chemicals must be ONLY in "Lab-Safe" or explosion-proof units.*
❖ Do not use glass containers with screw-cap lids or glass stoppers for extended storage. Use polyethylene containers, screw caps or stoppers.
❖ Maintain the minimal practical inventory of peroxide-forming chemicals.
❖ Do not retain or store redistilled or otherwise unstabilized peroxide formers.
❖ Dispose of peroxide-forming chemicals prior to the time of expected peroxide formation.
❖ Test suspect materials for peroxides and discard as necessary.
❖ Label potential peroxide-formers should to show the date received, date opened and disposal date.

SUMMARY

Peroxides and peroxide-forming organic solvents are commonly found in chemistry laboratories. There are often far more peroxide-forming organic compounds in the normal laboratory than commonly expected. Ethers are of greatest concern due to their omnipresence in laboratories and ease at which they form peroxides. Nevertheless, instructors, stockroom attendants and researchers alike must consider the hazards associated with other potential peroxide-forming organic compounds.

The use of peroxide-forming organic compounds should be carefully evaluated. Their use in teaching or research should be avoided or minimized whenever possible. If use is unavoidable, appropriate testing and decontamination is important. The safe use of these materials require a chemical fume hood and personal protective equipment such as properly selected gloves, clothing, eyewear, and face shields. Operations that include heating, distillation, or evaporation of these substances warrant extra precautions. These procedures must always be conducted within a chemical fume. The hood sash should be positioned as low as possible and explosion shielding may be necessary.

Chemical reactions involving peroxides can be conducted safely by experienced personnel following good laboratory techniques and prudent practices. Initial or unfamiliar reactions should be limited to minimal quantities

(< 1 gm). Review of the properties of analogous materials can provide valuable guidance in determining risk. Hazard always increases (pattern not necessarily predictable) with increased active-oxygen content. Virtually all organic peroxides become less prone to violent reaction if diluted (23). A large excess of aqueous sodium hydroxide can be used to hydrolyze and deactivate a reaction mixture (23).

Organic peroxide compositions should be treated with extreme caution until the hazard is determined. Laboratory-scale tests for mechanical and heat sensitivity of organic peroxides have been developed (23). The synthesis of organic peroxides frequently starts from hydrogen peroxide. Mixtures of concentrated hydrogen peroxide and organic substances are powerful and sensitive explosives within certain concentration ranges. This is extremely important in organic syntheses involving hydrogen peroxide (23).

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TABLE 1.   Peroxide-Forming Chemicals (9, 13, 15, 16, 19)

A.	Chemicals that form explosive levels of peroxides without concentration. Severe peroxide hazard after prolonged storage, especially after exposure to air. All have been responsible for fatalities. *Test for peroxide formation before using or discard after 3 months.*

Butadiene[a]   Isopropyl ether   Sodium amide

Chloroprene[a]   Potassium amide   Tetrafluoroethylene[a] Divinyl

acetylene   Potassium metal   Vinylidene chloride

B.	Peroxide hazards on concentration. *Test for peroxide formation before distillation or evaporation. Test for peroxide formation or discard after 1 year.*

Acetal   Dicyclopentadiene   2-Pentanol

Acetaldehyde   Diethylene glycol dimethyl ether (diglyme)   4-Penten-1-ol

Benzyl alcohol   Diethyl ether   1-Phenylethanol

2-Butanol Dioxanes   Ethylene glycol ether acetates (cellosolves)   2-Phenylethanol

Chlorofluoroethylene   Furan   Tetrahydrofuran

Cumene (isopropylbenzene)   4-Heptanol   Tetrahydronaphthalene

Cyclohexene   2-Hexanol   Vinyl ethers

2-Cyclohexen-1-ol   Methyl acetylene   Other   secondary   alcohols

Cyclopentene   3-Methyl-1-butanol

Decahydronaphthalene (decalin)   Methyl-isobutyl ketone

Diacetylene (butadiyne)   4-Methyl-2-pentanol

C.	Chemicals, which are hazardous due to, peroxide initiation of autopolymerization. The peroxide-forming potential increases for liquids of this group, especially for butadiene, chloroprene and tetrafluoroethylene, such that these materials should be considered as a peroxide hazard. *Test for peroxide formation or discard liquids after 6 months; discard gases after 1 year.*

Butadiene[b]   Chlorotrifluoroethylene   Vinyl acetylene

Chlorobutadiene   Styrene   Vinyl chloride

Chloroprene[b]   Tetrafluoroethylene[b]   Vinyl pyridine

                                   Vinyl acetate   Vinyldiene chloride

[a]When stored as a liquid monomer.   [b]Can form explosive levels of peroxides when stored as liquid. When stored as gas, peroxide accumulation may cause autopolymerization.

FIGURE 1. Peroxidizable Organic Moieties: Ordered From Most to Least Likely to From Dangerous Peroxides (3, 13, 15)
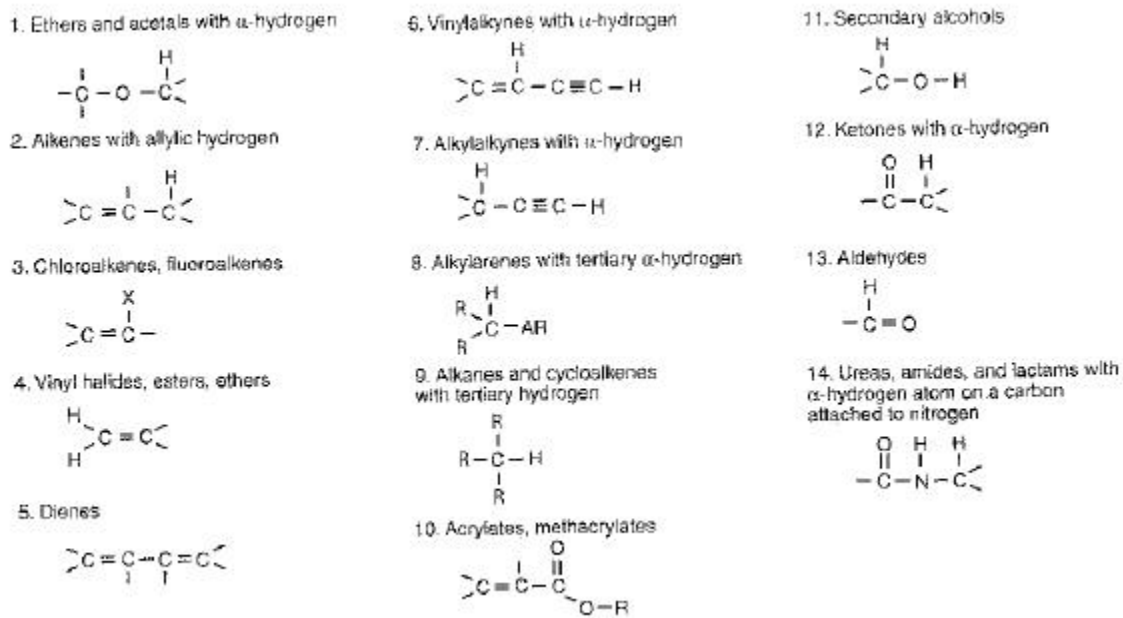
FIGURE 2. Oxidative Conversion of Isopropyl Ether to the Corresponding Hydroperoxide
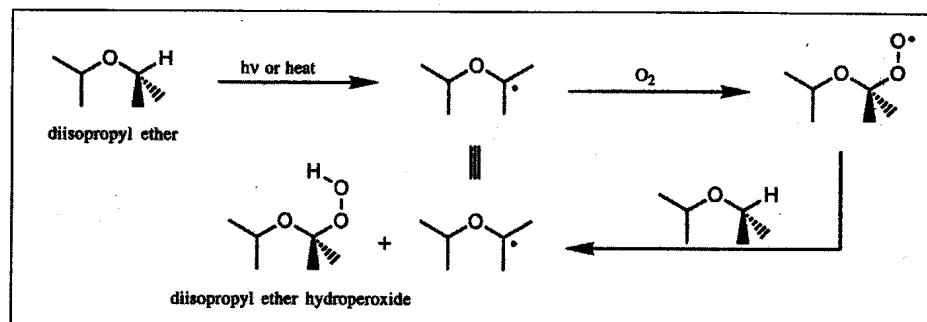
Heat or light generally initiates the free-radical process. The pathway to the hydroperoxide involves subsequent reaction of the ether radical with molecular oxygen to form the peroxy radical, which abstracts hydrogen from another ether molecule to form the hydroperoxide and consequently propagate the chain reaction (8, 15).