Peroxides and peroxide-forming compounds

By Donald E. Clark

Inorganic and organic peroxides, because of their exceptional reactivity and oxidative potential are widely used in research laboratories. This review is intended to serve as a guide to the hazards and safety issues 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 the characteristic structure of organic and inorganic peroxide molecules, and is the basis for their reactivity and tendency for spontaneous decomposition. 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. As a class, peroxides are exceptionally prone to violent decomposition that can be initiated by heat, mechanical shock, or friction, especially in the presence of certain catalysts and promoters.

The hazards of inorganic and organic peroxides and peroxide-forming chemicals have been long recognized so that most relevant information is now found in text books on organic chemistry and laboratory safety. A comprehensive three-volume series on the chemistry of organic peroxides includes a chapter on safety issues associated with these materials.[1,2,3,4]

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Bretherick[5] included a discussion of organic peroxide[5] in a chapter on highly reactive and unstable compounds and used "oxygen balance" to predict the stability of individual compounds and to assess the hazard potential of an oxidative reaction. Jackson et al.[6] addressed the use of peroxidizable chemicals in the research laboratory and published recommendations for maximum storage time for common peroxide-forming laboratory solvents. Several solvents, (e.g., diethyl ether) 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.[1,6] More recently, Kelly[7] reviewed the chemistry and safe handling of peroxide-forming chemicals and included procedures on detection and removal of peroxides from laboratory solvents. Safety awareness, prudent handling and proper storage are essential when working with these compounds.[1,2]

INORGANIC PEROXIDES AND PEROXYACIDS

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.[1]

Hydrogen peroxide alone is not explosive and has a long shelf life if it is handled properly and is not contaminated. However, concentrated hydrogen peroxide (>30%), in contact with ordinary combustible materials (e.g., fabric, oil, wood, or some resins) poses significant fire or explosion hazards. Peroxides of alkali metals are not particularly shock sensitive, but can decompose slowly in the presence of moisture and may react violently with a variety of substances, including water. Thus, the standard iodide test for peroxides must not be used with these water-reactive compounds.[1]

Inorganic peroxides are used as oxidizing agents for digestion of organic samples and in the synthesis of organic peroxides. They react violently with reducing agents and with several classes of organic compounds to generate organic peroxide and hydroperoxide products.[4] Dry Caro's reagent (monopersulfuric acid — K_2O_2 + con. H_2SO_4) reacts readily with carbonyl compounds (in the synthesis of organic peroxides) and can react explosively with aldehydes and alcohols.[3,4,5] Similar characteristics are associated with other inorganic peroxides and persalts. Peroxides may form on the surface of finely divided alkali metals and their amides and readily form superoxides, and ozonides such as KO_3.[8]

Inorganic per-compounds (e.g., sodium peroxide, sodium perborate, and sodium persulfate) may react with inorganic cobalt and copper compounds, iron or iron compounds, metal oxide salts, and acids or bases resulting in rapid, uncontrolled decomposition reactions. Persulfates (e.g., peroxy sulfate) are highly reactive and may ignite when in contact with metals.[2,4,8]

Perhalogen compounds (e.g., peroxy chloride) are extremely shock sensitive

and should be avoided unless absolutely necessary. They can react with acids (especially organic acids) to produce near-anhydrous perchloric acid. Perhalogen compounds of alkali metal and alkali earth elements are explosive, but are less sensitive than heavy metal perchlorates and organic perchlorates. 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 in contact with organic compounds or with a strong dehydrating acid (such as in a drying train that includes a sulfuric acid bubble counter) is possible.[9,10] Perchlorate hazards are multiplied by increased temperature, dryness and/or perchlorate content. Abuse of any one or more of these parameters accounts for nearly all perchlorate related incidents.

Perhalogen acids (e.g., hot perchloric acid) are widely used as potent oxidizing agents. Cold 70% perchloric acid is 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. The maximum concentration of perchloric acid commercially available is an aqueous solution of 70% $HClO_4$. However, perchloric acid solutions can become highly concentrated from evaporation (e.g., spill or heated digestion procedure) and anhydrous perchloric acid is capable of spontaneous explosion. Highly concentrated perchloric should be disposed of within 10 days or if any discoloration develops. Anhydrous perchloric is explosive in contact with wood, paper, carbon, and organic solvents. 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 dangerous organic or metallic (copper and copper alloys) perchlorates.[9] Aqueous perchloric acid solutions are not combustible.

Organic alcohols, aldehydes, ketones, ethers, and dialkyl sulfoxides can react violently with concentrated perchloric acid, especially at elevated temperatures. Furr[9] included a review

of the properties, hazards and use of perchlorates, including perchloric acid in the CRC Handbook of Laboratory Safety. 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.[9] Publication of an updated version of Schilt's *Perchloric Acid and Perchlorates* is pending.[11]

Dilute hydrogen peroxide solutions (i.e., 3%) are contact irritants and higher concentrations can cause severe chemical burns. Peroxide chemical burns should be washed gently but thoroughly and may require medical attention.[5,10] 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 and is very corrosive and can cause severe burns to skin, eyes and mucous membranes at higher concentrations (especially when hot). Perchloric acid has not been found to be carcinogenic or to cause reproductive, or developmental toxicity in humans.[12]

ORGANIC PEROXIDES AND OTHER PER-COMPOUNDS

Organic peroxides are characterized by the bivalent -O-O- structure and are considered to be structural derivatives of hydrogen peroxide with one or both of the hydrogen atoms replaced by an organic moiety. Because of the weak peroxide bond, organic peroxides are predisposed to spontaneous decomposition. They are exceptionally labile to catalysts and promoters that accelerate decomposition.[1]

As a class, organic peroxides are among the most hazardous substances handled in the lab. Most are highly flammable and extremely sensitive to shock, heat, spark, friction, impact, and ultraviolet light. They readily react with strong oxidizing and reducing

agents. Each peroxide compound is characterized by a specific, condition-dependent rate of decomposition. A change in critical parameters (e.g., increased temperature) can promote rapid increase in the decomposition rate, culminating in a violent explosion.[1] The potential energy of organic peroxides is low compared to conventional explosives, but high enough to be very hazardous.

The acute toxicity of organic peroxides is relatively low (i.e., peracetic acid: oral LD_{50}, rat; 1540 mg/kg; dermal LD_{50}, rabbit 1410 mg/kg). However, most are highly irritating to skin, eyes, and mucous membranes and peracetic acid may be a weak carcinogen in mice. There are no data to suggest that exposure to peracetic acid produces carcinogenic, reproductive or developmental toxicity in humans. Other organic peracids (e.g., perbenzoic acid and m-chloroperbenzoic acid) are less toxic, less volatile and less hazardous to handle than peracetic acid.[12] Exposure to peroxides and associated materials, including vapors and aerosols, should be minimized. Aliphatic peroxyacids have a sharp, unpleasant odor, the intensity of which decreases with increasing molecular weight.[1,4] Liquid peroxides may penetrate rubber gloves upon extended exposure.[5]

ORGANIC PEROXIDES: SYNTHESIS AND USE

The synthesis of organic peroxides frequently begins with hydrogen peroxide. Hydroperoxides can be prepared by reaction of alkyl halides, esters of sulfuric or sulfonic acids, or alcohols with hydrogen peroxide in alkaline solution. Peroxy groups may be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of a catalyst such as cuprous chloride. Hydroperoxides and acylperoxides are prepared from amyl halides or anhydrides, and from amides of the imidazolide type. Diacyl peroxides are synthesized by treatment of carboxylic acids with hydrogen peroxide in the presence of dicyclohexylcarboiimide. Mixed alkyl-acylperoxides (peresters) can be made

from acyl halides and hydroperoxides.[13]

Organic peroxides are widely used as a source of free radicals to initiate a number of addition and polymerization reactions.[1,13] The chain reaction can be initiated by ultraviolet light, by the presence of a radical source, and/or by the peroxide itself. 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 organic synthesis. Other classes of organic peroxides include acylperoxides, polyperoxides, peroxyesters, alkylidene peroxides, percarboxylic acids, and cyclic peroxides. These compounds, because of their inherent instability and propensity for decomposition that increases with concentration, are generally not sold in high purity. Reactivity and instability decrease with increasing molecular weight. Some of the most common low molecular weight peroxides include *tert*-butyl peroxide, *tert*-butyl hydroperoxide, peracetic acid, benzoyl peroxide, and isopropylbenzene (cumene) hydroperoxide).

Reagent purity can be extremely important in reactions that intentionally or unknowingly involve peroxides. The catalytic potential of organic peroxides and the free radicals they generate can change the course of a planned reaction. For example, the addition of hydrogen halides to simple olefins, in the absence of peroxides, proceeds via an electrophilic mechanism, and the orientation is in accord with the Markovnikov Rule.[13] When peroxides are present, the reaction proceeds via a free-radical mechanism. The reorientation of the reaction is called the anti-Markovnikov addition (Figure 1).[13] 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, can be prevented by very small amounts of peroxide-inhibitor.[13] This can be critical in a reaction mixture if autoxidation of the solvent has produced small amounts of peroxide derivatives. Organic peroxides are very sensitive to contamination (especially heavy-metal compounds, metal oxide salts, alkaline materials including amines,

1. $CH_3CH=CH_2 + HBr \longrightarrow CH_3\text{-}CHBr\text{-}CH_3$

Markovnikov Addition (Peroxides not present)

2. $CH_3CH=CH_2 + HBr \longrightarrow CH_3\text{-}CH_2\text{-}CH_2Br$

Anti-Markovnikov Addition (Peroxides present)

Figure 1. Effect of the presence of peroxide on chemical reaction products.

strong acids, and many varieties of dust and dirt). The presence of these materials can initiate rapid, uncontrolled decomposition of peroxides and possible fire or explosion. The consequences of accidental contamination from returning withdrawn material to the storage container can be disastrous. Once withdrawn, the peroxide must never be returned to its storage container.[1]

Within a structural series of the peroxy compounds, sensitivity and instability increase as active oxygen content and oxygen balance increase. Oxygen balance is the difference between the oxygen content of a molecule or mixture, and that required for complete oxidation of oxidizable elements (i.e., CO_2, H_2O, etc). If the oxygen is deficient, oxygen balance is negative, and positive if in excess. Oxygen balance is expressed as a weight percentage with the appropriate sign.[5] The stability of a compound becomes increasingly doubtful as the oxygen content approaches that necessary to oxidize the other elements to their lowest valance state. Peroxide sensitivity may also be related to its heat of decomposition, activation energy, and reaction kinetics.[1,4,5]

In a laboratory reaction system, it is important to maintain the oxygen balance as low (negative) as possible in order to control the rate of energy release. This is aided by slow addition of oxidant to the reaction mixture and by controlling reaction conditions. Appropriate mixing and temperature controls are essential to prevent localization of the oxidant and development of "heat pockets," conditions that can lead to an uncontrollable reaction.

Violent exothermic reactions may result when peracids contact ethers, metal chloride solutions, olefins, some alcohols and ketones, and carboxylic anhydrides, with peracids to 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).[1,4,5] Hence, safety in dealing with organic peroxides depends on knowledgeable and prudent handling and storage.

The rate of peroxide-involved reactions increases exponentially with increase in temperature. Once initiated, the reaction temperature will continue to rise until thermal balance is established or until the material heats to decomposition. Destructive results occur when the reaction releases energy in a quantity or a rate too great to be dissipated by the immediate environment of the reacting system.[1,5,14] Any impediment to ready dissipation of heat flow will lead to dramatically increased internal temperature.

In certain conditions, a chemical reaction can approach adiabatic conditions when a strong 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 (e.g., deep-well oil bath). Under adiabatic conditions, spontaneously unstable materials will self-heat to destruction. Thus, appropriate temperature control and heat dissipation is essential for avoiding the out-of-control acceleration of the exothermic reactions (normal, polymerization, or decomposition). The reaction rate and heat and/or gas released that

may go unnoticed during small-scale experiments may lead to an explosive situation when conducted on a larger scale. It is especially important to include fail-safe devices to protect against events such as utility failure into procedures that are unfamiliar or unattended.[5]

Because even gram-scale explosions can be very serious, reactant quantities should be limited to a practical minimum. Stringent precautions and down scaling (concentration, quantity, volume) are especially critical when working with a new or unfamiliar organic peroxides or procedure. Once ignited, the burning of peroxides cannot be controlled. The area should be evacuated if any appreciable quantity of peroxide ignites.[1,5]

Reactant concentration is especially critical in reactions involving highly reactive chemicals, including peroxides. Peroxides should be added slowly and cautiously to the reaction medium. The addition should be completed prior to heating and with good agitation. Agitation should be friction-free and should never be provided by gases unless inert and free of oxygen or other reactive components (even in trace quantities).

The concentration of each reactant has direct influence on reaction rate and therefore, the rate of heat release. Peroxide concentration should rarely be as high as 1%, in a polymerization or other free-radical reaction. Unless there are compelling reasons to do otherwise, peroxide concentration should not exceed 10%, especially with vigorous reactants. Very hazardous situations can result from the intentional or accidental increase in reactant or catalyst concentration to an otherwise safe procedure. It is essential to conduct all such operations in a properly functioning laboratory chemical hood. All sources of accidental ignition must be excluded from areas where peroxides are used.[5,6]

Preparation of concentrated stock solutions of organic peroxide monomers may be extremely hazardous. A violent reaction can result from inadvertent mixing of promoters (frequently used with peroxides in polymerization systems) with full-strength peroxide. The addition of peroxide to the hot monomer is also extremely dangerous.[1]

Preplanning and attention to detail are essential when handling highly reactive materials. Manipulation of equipment during the reaction should be minimized. Appropriate protective devices (e.g., fume hood, barricade shield) should be in place. Equipment to provide full protection to eyes, face, hands, and body should be worn. Other potentially exposed persons should be notified whenever a hazardous procedure is initiated.[14] Specific safety guidelines for laboratory use of organic peroxides can be found in references 1 and 5.

STORAGE OF ORGANIC PEROXIDES AND PER-COMPOUNDS

Published data on the decomposition kinetics of organic peroxides at storage temperatures are sparse. However, the tendency of organic peroxides to undergo spontaneous decomposition and gassing is well recognized.[1,9]

Peroxides should be purchased in minimum practical quantities and storage time in inventory should be minimized. The quantity within the work area should be limited to a one-day supply. Peroxides should be stored in isolation and separated from the work area and from other organic chemicals and combustible materials. Specific information on appropriate material and design criteria for peroxide storage is available.[14] The condition of the containers should be confirmed at regular intervals.

Containers must be vented and kept upright to avoid escape of liquid through the vent. In most cases, peroxides should be stored in plastic containers to maintain structural integrity and to minimize the potential for detonation from shock or friction. In addition, plastic containers are mechanically weak and don't provide high confinement thus reducing the extent of pressure buildup before the container ruptures. Peroxides must never be housed in a container with screw cap or ground glass closure because detonation can be initiated by friction generated by opening a lid in contact with the dry peroxide.[1]

Organic peroxides are especially unstable when dry, and should be stored only under wet (water or non-reactive hydrocarbon) conditions. Most organic peroxides (especially lower MW compounds) are extremely unstable at or near room temperature and must be prepared, shipped and stored under refrigeration. Conversely, some crystalline peroxides can be stored for years at room temperature with little evidence of decomposition. There are also 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. Any evidence of layer separation or crystal formation is a very strong indicator of increased impact sensitivity.[1]

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, the storage vessel of experimental peroxide compositions should be as small as practical.[1]

The self-accelerating decomposition test (SADT) addresses the scale-dependence phenomenon. 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.[1,4,15]

Liquid compositions tend to be more susceptible to contamination than solids. However, the presence of 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. Although dilution of peroxide solutions decreases the potential for violent decomposition, the rate of auto-decomposition often increases.[1] Decomposition of stored reagents can lead to loss of activity, as well as self-heating and runaway reactions. Contaminated, partially decomposed, outdated, or surplus organic peroxides should be disposed or destroyed under stringently controlled conditions.[16]

Stabilizers are usually not necessary with solid or aqueous solutions of 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. Materials that trap free radical can reduce the reaction rate of a decomposition reaction that proceeds through a chain reaction mechanism. This may be of limited practical use if the chain scavenger also depletes the free radicals necessary for the reaction.[1]

PEROXIDATION OF ORGANIC SOLVENTS

Certain organic solvents slowly undergo autoxidation under very mild conditions (<100° C in the presence of a free radical initiator), to form unstable and dangerous products. Although ethers are generally recognized as peroxide formers, other organic structures are also capable of spontaneous autoxidation to generate highly unstable hydroperoxides, and monomer- and polymeric peroxides.[7] The reaction is catalyzed by light or some impurity and occurs when compounds are allowed access to atmospheric oxygen. Under certain circumstances oxygen attacks the C-H bond of certain hydrocarbons to form hy-

droperoxides (compounds containing the -OOH group).

The hydroperoxides can react further to produce alcohols, ketones, peroxides, and more complex products. These reactions are relatively unpredictable, so that the reaction has limited use in synthetic chemistry. As with other free radical reactions of C-H bonds, some are attacked more readily than others.[13] The Chemistry of the Ether Linkage[17] provides details of these reactions and includes an "Appendix on Safety Measures."

Molecular structure is the primary factor in determining the rate of autoxidation and shelf life within a class of chemicals.[5,6] Peroxide-forming compounds invariably contain an autooxidizable hydrogen atom that is activated by adjacent structural components.

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 tetrahydronaphthalenes);
- a vinyl group (-C=CH$_2$, e.g. vinyl compounds, dienes, styrenes or other monomers).[5]

Not all compounds containing these groups form peroxides. However, the presence of any of these groups in a compound provide (especially low molecular weight) a warning that hazardous concentrations of unstable peroxides might be present.[4,5] 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.[17]

Within a class of peroxide-forming chemicals, the peroxidation potential is usually inversely related to the molecular weight of the compound.[5,17] One source[18] states that compounds with ten or more carbon atoms at a peroxidizable site are considered low-risk systems, but does not provide supporting data. Kelly[7] listed over 125 compounds with structural potential for undergoing peroxidation.

Autoxidation can be initiated by ultraviolet light (photoperoxidation), by the presence of a free radical source, by the peroxide itself, or by impurities such as acetaldehyde. The reaction cannot proceed in the absence of oxygen or oxidizers. Exposure of susceptible compounds to oxygen always enhances peroxide formation, whereas the effects of heat, light and contaminants are variable and unpredictable. Ultraviolet light, including sunlight, promotes both autoxidation and depletion of (antioxidant) inhibitors.[1,17] Secondary alcohols (e.g., isopropanol, 2-butanol) are susceptible to slow peroxidation and the presence of a ketone (higher than acetone) greatly increases the rate and extent of photoperoxidation. It is likely that similar interactions may occur with other compounds.[5,17]

The autoxidation reaction proceeds by a free-radical chain mechanism that usually begins with the abstraction of an active hydrogen from R-H by the peroxy radical to produce an alkyl radical (R*). Oxygen adds to the R* radical to generate the peroxide radical R-O-O*. In almost all cases, the abstraction involves a univalent atom (e.g. hydrogen or halogen). The abstraction step determines what the chain reaction product will be.[13] For the substrate R-H, the chain reaction can be initiated by ultraviolet light, by the presence of a radical source, and/or by the peroxide itself. Like other free-radical reactions, the autoxidation process is self-propagating. Organic free radicals are often formed in solution upon heating (in some cases, merely dissolving) a compound having weak covalent bonds.[14] Thus,

a single initiating event may lead to self-sustaining reaction with the rate of the peroxide formation increasing with time.[1,13,17]

The relatively slow induction period is often followed by a more rapid accumulation of the corresponding hydroperoxide. In some cases, hydroperoxide concentration may reach 5–15% and may either stabilize or decrease as the hydroperoxide decomposes to form byproducts (e.g. alcohols and water) that interfere with the free radical chain reaction and/or peroxidation. The byproduct content may continue to increase while the peroxide content remains stabile. This scenario does not apply when the peroxy compounds crystallize and precipitate from the solution. In those cases, the precipitate remains undiluted by solvent or byproducts, and constitutes a serious hazard.[8]

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. The structure-dependent 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]

The hydroperoxide is likely to be highly reactive and usually undergoes further addition, rearrangement or disproportionation leading to dialkyl, polymeric, cyclic, and other unstable higher peroxide products. These products become increasingly dangerous with heating and/or concentration by evaporation.[5,7,17] This is an important safety consideration because detection and removal of the intermediates are more difficult than for simple hydroperoxides. Rigid adherence to storage and handling techniques that are matched to the properties of the materials is critical.[7,17]

Most alkyl monohydroperoxides are liquids. The lower members are soluble in water and are explosive.[4] Autoxidation of isopropyl ether forms a variety of higher M.W. peroxides,

including cyclic peroxides of acetone, which may be especially explosive when dry. Oxidation of p-dioxane produces very dangerous levels (more than 30% of total peroxide) of diperoxide products.[17]

Peroxidation is generally peculiar to the liquid state. Minimal hazard is usually associated with potential peroxide formers in the solid or vapor phase. However, the peroxidation reaction can proceed on the surface of finely divided solids.[9] 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 risk. Processes involving these gases should be thoroughly evaluated to determine the likelihood of forming a liquid phase.[7,8]

USE AND STORAGE OF PEROXIDE-FORMING SOLVENTS

Jackson et al.[6] categorized laboratory chemicals known to form peroxides into Groups A, B, and C (Table 1), on the basis of their susceptibility to peroxide formation. (Some monomers identified by Jackson are no longer available in laboratory quantities.) Shelf life (before significant peroxidation occurs), and the resulting products vary widely between compounds and storage conditions. The recommended maximum shelf life for each group is based upon time after opening the container, and is conditioned on the premise that the compounds are stored in opaque containers under an inert (oxygen-free) atmosphere. Containers of susceptible solvents are normally supplied with an antioxidant or free-radical scavenger. These inhibitors can slow, but not prevent peroxidation. Therefore, when using these peroxide-forming reagents, it is critical to include procedures to guard against unanticipated results.[6,17]

Group A includes the chemicals most likely to form dangerous levels of autoxidation products. These chemi-

cals can form explosive peroxide levels even in an unopened container, without concentration, and some will separate from solution. Even low initial concentrations of autoxidation products in a solution can be concentrated to dangerous levels by solvent evaporation and may explode upon shaking.[5,6] Isopropyl ether is particularly dangerous: the presence of two tertiary carbon atoms in the molecule enhance the tendency to oxidize to the corresponding hydroperoxide. The hydroperoxide then polymerizes to form a product that precipitates from the ether solution as an explosive crystalline solid.[1,6] The temperature and concentration at which explosion of peroxides of isopropyl ether becomes probable has never been authoritatively stated.[1]

Group B includes widely used laboratory solvents (e.g., diethyl ether, THF, cyclohexene, the glycol ethers, and isopropanol) that can form explosive levels of peroxides. The autoxidation products are less volatile than the parent compound, and therefore become extremely hazardous when evaporation concentrates the unstable autoxidation products to increasingly dangerous levels. Most of the solvents in Group B are also volatile so that repeated opening of a container may allow enough evaporation (and exposure to atmospheric oxygen) to concentrate peroxides to a dangerous level. 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.[1,5,8]

Group C includes examples of vinyl monomers that are usually not particularly hazardous. However, they can form peroxides that can initiate explosive polymerization (Trommsdorf effect) of the bulk monomer. It is important to add a suitable polymerization inhibitor prior to distilling or otherwise concentrating any of these compounds.[5,9]

Although the autoxidation reaction is a relatively slow process (months to years in some cases), extended storage provides time for accumulation of un-

Table 1. Potential Peroxide-Forming Chemicals[6]

GROUP 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

GROUP 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	

GROUP 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[a]	Chlorotrifluoroethylene	Vinyl acetylene
Chlorobutadiene	Styrene	Vinyl chloride
Chloroprene[a]	Tetrafluoroethylene	Vinyl pyridine
Vinyl acetate	Vinyldiene chloride	

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

stable products. Storage of peroxidizable chemicals in open, partially empty, or transparent containers greatly increases the risk of peroxide formation. Peroxidation is accelerated by heat, light, oxygen or air, and elevated temperature. Fluctuations of temperature and barometric pressure 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. A breach of the container seal may allow sufficient oxygen to eliminate the inhibitor then initiate and enhance the autoxidation process. 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, particularly if the inhibitor has been removed (e.g. distillation) or depleted.[1,5]

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. If the solvent is held near it's freezing point, peroxidation products may precipitate from solution and become very shock sensitive and dangerous. Some peroxidizable organometallic compounds (e.g., Grignard reagents) should not be refrigerated, and 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 temperature.[1,5,14] In any case, only completely spark-proof refrigerators should be used to store ethers or other volatile peroxide formers.

Laboratory procedures (e.g. evaporation, distillation, or spills) that increase peroxide concentration or allow extensive exposure to air or oxygen are particularly dangerous. At least 10% of the bottom residuals should be retained during distillation or evaporative concentration of any potential peroxide-former. The hazard can be reduced by addition of a nonvolatile organic liquid (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 prevent the localized concentration of heat and pressure. Air or other oxygen-containing mixtures should never be used for mixing during distillation of potential peroxide formers.[1,6]

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.[9]

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 generally added to inhibit the chain reaction of the peroxide forming solvent. Peroxidation of 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 as well. In fact, iron may catalyze peroxidation in some solvents. One report indicated that diethyl ether containing 10ppm pyrogallol was stabilized for over 2 years. 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 proposed for stabilization of oxidative deterioration of ethers and other compounds.[1,17] 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.[1,6,14]

Antioxidant inhibitors are usually depleted as peroxidation products are formed. The inhibitor will eventually 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 levels of both peroxides and inhibitor should be monitored, especially if potential peroxide-formers are retained for extended time. Inhibitor levels must be maintained or the material must be treated as though uninhibited. It is always prudent to use stabilized reagents unless the antioxidant interferes with its use. Because distillation will separate a stabilized solvent from 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.[1,7,16]

Peroxide-forming compounds should be purchased in limited quantities, used in order of receipt and never stockpiled. It is prudent 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 (Not with glass stoppers or screw caps), preferably in the container furnished by the supplier and 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).[6,16,17]

DETECTION OF PEROXIDES

Visual inspection of an organic solvent in a glass container can detect the presence of very high levels of peroxides. This can be accomplished by using back light or side light with a nonhazardous light source (e.g. a flashlight). 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. Any container of peroxidizable chemicals that is old, deteriorated or of unknown age or history must not be moved or disturbed (including additional testing). A container must not be moved or disturbed if there is any question regarding the presence of peroxides Only individuals with skill and experience in handling extremely hazardous materials should perform handling and disposal.[1,17]

A variety of quantitative, semiquantitative, and qualitative methods to detect peroxides in organic and aqueous solutions have been developed.[19] Kelly[7] included detailed procedures for the 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. Alkali metals and their amides may form peroxides on their surface. DO NOT apply the standard peroxide tests to such materials because they react strongly with water and oxygen.[1]

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 validation 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. However, the NSC publication included neither supporting references for the latter statement nor for the recommendation for administrative control value of 100 ppm.[7,18]

The Material Safety Data Sheet for diethyl ether cautions against concentrating ether containing peroxide levels above 100-ppm.[16] Presumably, the concentration of unstable oxidation products increases to a point at which the solution spontaneously explodes. Kelly suggested that it is likely that the control concentration of 100 ppm may, in some cases, be overly conservative by at least an order of magnitude. This may especially apply to the Group B chemicals listed in Table 1, unless the unstable materials are concentrated as result of solvent evaporation.[7]

Kelly[7] stated that "theoretically, explosion should be impossible for most solutions containing <1% peroxides." However, establishment of a safe concentration may be complicated by circumstances that allow the unstable material to be concentrated through some mechanism such as evaporation.

A dilute solution of most peroxidizable chemicals, or a solutions in a solvent with low volatility (B.P. $\geq 300°$ C or V.P. <0.1 mm Hg at $20°$ C) are not likely to concentrate and do not usually pose a peroxide hazard.[1,7]

CLEANUP AND DISPOSAL OF PEROXIDES AND PEROXIDE-FORMING CHEMICALS

Handling, storage, and disposal procedures are dictated by the physical and chemical characteristics of the particular material. Vessels containing hazardous or suspicious materials should not be handled directly. Remote handling (e.g., tongs), personal 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 or 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 practical peroxide composition should be selected for each use.[1]

- *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 materials.

Liquid peroxides do not readily ignite, but once ignited the burn rate increases as the fire progresses. Spontaneous combustion can occur upon contact of the peroxide with combustible materials. Solid organic peroxides ignite more readily and burn with increasing rate as the fire progresses. Contact with finely divided combustible material may produce an explosive mixture. Because of the extreme sensitivity of solid per-compounds to shock and friction, they might ignite from friction or upon contact with the oils on shoe soles. Therefore, workers must not be allowed to walk through a spill. Emergency responders and fire fighters should be aware of the special care required when organic peroxides are involved. Spills on clothing constitute a significant fire risk as well as severe dermal irritation or burn. Contaminated clothing should be changed immediately and thoroughly laundered (solvent or alkaline water washing) before storage or return to use.[20]

Pure peroxides must be diluted prior to disposal and should never be disposed of directly. In some cases small quantities (≤ 25 g) of peroxides can 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 co-mingled with other chemical waste. Larger quantities of organic peroxide may require special handling by well-trained personnel. Empty containers of peroxides or peroxide-formers can be discarded in regular trash after triple rinsing with water and defacing or removal of the label.[20]

Spilled peroxides should be absorbed 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 (60 g ferrous sulfate + 6 mL con sulfuric acid + 110 mL water). Never flush organic peroxides down the drain.[20]

Special transportation procedures are necessary because of the flammability and explosiveness of organic peroxides. Most organic peroxides can be shipped at ambient temperature, but some require refrigeration. (See *"Storage of Organic Peroxides and Per-Compounds"*). Failure of the refrigeration system can result in decomposition and fire.

CONCLUSIONS

Peroxides and peroxide-forming organic solvents are commonly found in chemistry laboratories and lab personnel may not be aware of their presence or of the associated hazards. Ethers are of greatest concern due to their omnipresence in laboratories and the ease with which they form peroxides. Instructors, stockroom attendants and researchers alike must consider the hazards associated with other potential peroxide-forming organic compounds. The instability of peroxides slowly formed in organic compounds in the presence of oxygen is preventable by storage and handling techniques that are accurately matched to the properties of the material concerned.

The need to use peroxides and peroxide-forming organic compounds should be carefully evaluated and their use should be avoided or minimized whenever possible. If use is unavoidable, appropriate testing and decontamination of questionable reagents is essential. 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. Procedures that include heating, distillation, or evaporation of these substances warrant extra precautions. These procedures must always be conducted within a chemical fume with the hood sash positioned as low as possible. The need for explosion shielding should be seriously considered.

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 g). Review of the properties of analogous materials can provide valuable guidance in determining hazard of new or unfamiliar reagents or procedures. Although the pattern is not necessarily predictable, reactivity always increases with increased active-oxygen content of a molecule. Virtually all organic peroxides become less prone to violent reaction if diluted. The reaction mixture can be deactivated by addition of a large excess of aqueous sodium hydroxide. Mixtures of concentrated hydrogen peroxide and organic substances can react to produce powerful and sensitive explosives. This is extremely important in organic syntheses involving hydrogen peroxide.

The hazards and consequences of fires and explosions during the laboratory use of organic peroxides are widely recognized. There is no way to assure,

with any degree of certainty that accidental explosions will not occur when working with such reactive and potentially dangerous materials. Spontaneous or induced decomposition may culminate in a variety of ways, ranging from moderate gassing to spontaneous ignition or explosion. The failure to recognize the effect of physical and chemical factors associated with reaction kinetics is often the root-cause of unexpected violent chemical reactions. Reactant concentration and temperature control are critical the for control of reaction rate.[1]

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Appendix I. Safety Guidelines for Handling Organic Peroxides[17,22]

- Purchase and 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 behind a protective shield.
- Do not return unused peroxides to the container.
- Clean up liquid spills immediately. Dispose promptly as hazardous waste. See Armour[23] for recommended procedures for specific compounds.
- 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.
- Use plastic (not metal) spatulas to handle peroxides.
- Do not allow open flames, or other sources of heat, sparks, friction, grinding or forms of impact near peroxides.
- Do not use glass containers with screw-cap lids or glass stoppers. Use polyethylene containers with polyethylene screw caps or stoppers.
- Protect from heat and light.
- Store peroxides at the lowest possible temperature consistent with their solubility and freezing point.
- Long term storage (e.g., greater than one year) should be avoided.
- Refrigerated storage of peroxides or other flammable chemicals must be ONLY in "Lab-Safe" or explosion-proof units

Appendix II. Safety Checklist for Chemical Reactions Involving Peroxides

- ❏ temperature control and heat dissipation mechanism are appropriate for liquid and vapor phases;
- ❏ correct proportion and concentration of catalyst and reactants are used;
- ❏ purity of components (absence of catalytic impurities) is assured;
- ❏ the reaction solvent is appropriate for the reaction conditions;
- ❏ the viscosity of the reaction medium is appropriate;
- ❏ the rate of reactant combination is appropriate for the conditions
- ❏ an appropriate induction period is included;
- ❏ the procedure includes appropriate stirring or agitation (mechanism, degree)
- ❏ the reaction atmosphere is controlled;
- ❏ appropriate pressure release and controls are incorporated into the system;
- ❏ conditions that might cause ignition, decomposition, (e.g. actinic radiation) of unstable materials are avoided;
- ❏ shielding and personal protection devices are in place.