Working with organic peroxides in the academic lab

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Working with organic peroxides in the academic lab

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The author has no formal training in chemical safety; the following guide is based upon two decades of experience with organic peroxides. Suggestions or corrections are welcomed at pdussault1@unl.edu.

ABSTRACT: The following is a brief introduction to peroxide safety from the viewpoint of a synthetic chemist. Topics include classes of peroxides and hydroperoxides, reactivity of organic peroxides, hazard identification, hazard minimization, reaction monitoring, and hazards of peroxidizable solvents.

KEYWORDS: peroxide, hydroperoxide, hydroperoxyacetal, ozonide, perester, dihydroperoxide, monoperoxyacetal, active oxygen, peroxide strips, TLC indicator, self-accelerating decomposition, radical, exothermicity, transition metals.

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1. Introduction: Some common peroxide classes are illustrated in Figure 1.\textsuperscript{1,2,3} Although characteristics can vary dramatically by class and even within classes, the following are general to many peroxides: 1) reactions, including decompositions, are often highly exothermic; and, 2) reactions often proceed with a low activation barrier. As a result, experimenters must always be aware of the potential for self-accelerating and exothermic processes. A review describing hazards of commercially available peroxides and peroxide-containing compositions towards detonation/deflagration/fire is dated but still informative\textsuperscript{4}

Figure 1. Common classes of organic peroxides

<table>
<thead>
<tr>
<th>Class (graphical)</th>
<th>R\textsuperscript{1}O\textsuperscript{-}O\textsuperscript{-}H \kern-0.5em</th>
<th>R\textsuperscript{-}O\textsuperscript{-}O\textsuperscript{-}R \kern-0.5em</th>
<th>O\textsuperscript{-}O\textsuperscript{-}OH \kern-0.5em</th>
<th>O\textsuperscript{-}O</th>
<th>Functional group</th>
<th>Commercial example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkyl hydroperoxide</td>
<td>(t\text{-}BuOOH)</td>
<td>(t\text{-}BuOO\text{f}Bu)</td>
<td>(\text{peracetic acid})</td>
<td>(\text{peracid})</td>
<td>(\text{ozonide})</td>
<td>(\text{Gem or 1,1-dihydroperoxide})</td>
</tr>
<tr>
<td>Cyclic peroxide, \text{~endoperoxide}</td>
<td>(\text{peresters})</td>
<td>(\text{bisacyl peroxide})</td>
<td>(\text{hydroperoxyacetal})</td>
<td>(\text{bisperoxyacetal})</td>
<td>(\text{benzoyl peroxide})</td>
<td>(\text{1,1-dihydroperoxy cyclohexane})</td>
</tr>
</tbody>
</table>

2. Why are peroxides so reactive? The O-O bond, which has a bond dissociation energy of 35-40 kcal/mol, is much weaker than the O-H (>105), C-O (80-85), and C=O pi (80-85) bonds. As a result, reactions and decompositions are often easily initiated and highly exothermic. This unique combination raises serious concerns about self-accelerating decompositions, in which exposure to heat, light, or small amounts of an initiator produces a spiraling cycle culminating in fires or explosions. Peroxides have been described as presenting greater handling risk than commercial explosives.\textsuperscript{5}
3. Determination of reactivity and minimization of hazard.

a. Calculate active oxygen content. “Active” oxygen (AO) content refers to the mass fraction of the active, or peroxide, oxygen. For example, H₂O₂ and water have 47% and 0% AO, respectively. Low AO does not guarantee safety (more on this below) but can often provide an early warning of danger. For example, MeOOH (33% A.O.) can spontaneously detonate, while octyl hydroperoxide (11% A.O.) is easily handled in small amounts. A rough guideline: Try to work with organic peroxides in which the nonperoxidic portion of the molecule has at least six carbons (or the equivalent mass). We make exceptions to this only for molecules whose behavior is well established, for example w t-butyl hydroperoxide.

<table>
<thead>
<tr>
<th>AO</th>
<th>Comments (provided as approximate guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>Usually safe. Normal precautions unless very large scale</td>
</tr>
<tr>
<td>5-10%</td>
<td>Use caution in the following situations: multigram scale; known issues with the substrate or similar molecules; reaction will be heated; or presence of redox-active transition metals capable of decomposing this class of peroxide.</td>
</tr>
<tr>
<td>10-15%</td>
<td>Be cautious even on small scales. On multigram scale, consider use of shields. Cumene hydroperoxide offers an instructive example.</td>
</tr>
<tr>
<td>&gt;15%</td>
<td>Assume the material could detonate or deflagrate without warning. For example, 2-methoxyprop-2-yl hydroperoxide (AO ~15%), a reagent developed in our lab and used by others without event, has nonetheless been observed to deflagrate on a scale of 10-20 mmol.</td>
</tr>
</tbody>
</table>

What is known about this class of peroxide? Has this or a similar molecule been reported to explode or undergo violent decomposition? The experimental descriptions ("explosiv" or "Hoch explosiv") within Houben-Weyl: Methoden der Organische Chemie are useful. Structure is also important. tert-Butyl hydroperoxide (18% active oxygen) is generally stable on moderate scale unless "provoked" (see below) while triacetone triperoxide (A.O. ~ 20%) is an easily detonated (friction, heat, spark, shock) high explosive. The CAMEO Chemicals database, supported by the US National Oceanographic and Atmospheric Administration (NOAA), includes a substantial grouping of safety sheets for organic peroxides. For a discussion of methods for testing and handling peroxides, see the following reference.

b. Minimizing Danger During Reactions
Minimize scale: Reactions of peroxides are often associated with substantial exothermicity. For example, a formal 2-electron, 2-proton reduction of $\text{H}_2\text{O}_2$ has an associated reaction enthalpy of approximately -75 kcal/mole. Particularly with low molecular weight peroxides (this includes concentrated solutions of $\text{H}_2\text{O}_2$!), minimize scale. An explosion on 1-2 mmol may simply make for a good story, but explosions on gram or multigram scales can cause major injuries. This point is valid even with some familiar peroxides. Benzoyl peroxide (AO < 7%), a familiar peroxide in both academic and industrial settings, undergoes autoignition at 80 °C and has been repeatedly observed to explode violently upon exposure to heat, friction, or flammable organics.3,4,13

Distance/Protection: An explosion at the end of a clamp, or better yet, behind a shield, is better than one in the hand.

Avoid provoking decomposition reactions:

• If you must heat peroxides, conduct an initial calorimetric survey (see "Working with isolated peroxides", below) and then take extra safety precautions (distance, shield).

• Do not expose hydroperoxides, dihydroperoxides, peracids, peresters, diacyl peroxides, or low molecular weight ozonides to transition metals, particularly Co, Fe, Mn, or Cu. (In general, unstrained dialkyl peroxides and related structures such as peroxyacetals are often less sensitive to metal-catalyzed decomposition reactions; however, caution is nonetheless called for, particular for reactions on large scales or involving high concentrations). Never allow a metal needle to contact concentrated solutions of $\text{H}_2\text{O}_2$ or tBuOOH. Instead, use a glass pipette to place a minimal amount of the reagent into a glass vial and syringe from this. A better alternative, especially on large scale, is to use Teflon needles and plastic syringes.14

• A number of peroxides can decompose violently in the presence of strong acids.15

• Fe(II) salts react with even hindered peroxides to generate reactive radicals. In the case of strained peroxides, even traces of ferrous iron can lead to exothermic decomposition.16

• Hydrogen peroxide or low molecular weight hydroperoxides (e.g., tBuOOH) should be washed out of reaction mixtures prior to concentration. $\text{H}_2\text{O}_2$ will generally wash out with water while alkyl hydroperoxides can be removed with moderate base or mild reducing agents.9 A final rinse with sulfite or bisulfite will remove most remaining hydroperoxides but will not attack dialkyl
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peroxides and will rarely attack ozonides. The removal of hydrogen peroxide or hydroperoxides can be monitored using peroxide indicator strips (see below).

• Reduction of dialkyl peroxides and related species (e.g., bispeoxyacetals) will require stronger reducing agents such as triphenyl phosphine or Zn/HOAc.17

c) Methods of monitoring reactions:

TLC: The formation or loss of peroxides is easily monitored using a TLC dip based upon $N,N'$-dimethyl-p-phenylenediamine.18 Unhindered ozonides, hydroperoxides, peracids, and hydroperoxyacetals give a dark magenta color upon dipping, while less reactive dialkyl or alkyl/silyl peroxides will generally show a color change only after heating.

Peroxide test strips: These colorimetric indicators, available from a number of vendors, are designed to quantitate $\text{H}_2\text{O}_2$ in aqueous media but can also employed for reasonably accurate determination of the concentration of $\text{H}_2\text{O}_2$ or alkyl hydroperoxides in ethereal solvents or alcohols.19 For low-boiling solvents, place a drop or two of the sample to be tested on the indicating pad, and blow (exhale) across the pad to remove solvent and supply necessary moisture. See http://www.sigmaaldrich.com/chemistry/solvents/learning-center/peroxide-formation.html

d. Working with isolated peroxides. Even unstable peroxides are sometimes tractable when in solution; the solvent provides a thermal buffer protecting against rapid temperature rise. Working with isolated peroxides requires additional care, particularly, if the structure or active oxygen content (above) predicts hazard.

Acquire thermal data using a scanning calorimeter (DSC/TGA). Pay attention to the onset of decomposition and the amount of heat released. See the references below for some examples,20 and for the temperature-dependent half-lives of some common classes of peroxides.21

Crystalline peroxides. Crystalline peroxides can be extremely dangerous. If you unexpectedly isolate crystals of a peroxide, particularly one of low molecular weight, put the sample behind a shield and try to get it back into solution. If you must work with a family of crystalline
peroxides, test a small amount for shock sensitivity: place 10-15 mg on some weighing paper, fold up the paper and place it on a concrete floor or step, and then tap it with a hammer. In our experience, an obvious reaction (pop, or flame) is sign of a highly shock-sensitive peroxide. Do not subject crystalline peroxides to friction (spatula, screw top of a vial) or expose to any metal implements (use a porcelain or Teflon spatula). Avoid mixtures of low molecular ketones, acids, and hydrogen peroxide, which can readily produce crystalline 1,2,4,5-tetraoxanes, 1,2,4,5,7,8-hexaoxan ones, and polymeric peroxides.

4. Toxicity of peroxides

Hydroperoxides are relatively irritating.\textsuperscript{11} It is especially critical to avoid breathing high vapor concentrations of low molecular weight hydroperoxides (this includes odorless H\textsubscript{2}O\textsubscript{2}!!) and to avoid contamination of the eye. Some classes of peroxides have significant exposure risks. For example, peracetic acid, a common industrial and sanitizing chemical, is a GHS category 1 hazard for skin corrosion and category 1A for eye damage.\textsuperscript{22} The recommended limit for prolonged peracetic acid exposure (10 min to 8 h) is only 0.17 ppm.\textsuperscript{23}

5. Peroxide-forming solvents:

The autoxidation of ethers and other readily oxidized materials is a significant, but easily preventable, hazard. Many organics can undergo free radical oxidation. The rate-limiting abstraction of a hydrogen atom by a peroxyl radical is most favorable for substrates where the derived carbon radical is allylic or benzylic (cumene, ethyl benzene) or else substituted by an alkoxide or amide (THF, ether). The references provided do a good job of identifying common materials most susceptible to peroxide formation.\textsuperscript{8,24,25,26}

Even if autoxidation does occur, the resulting solutions are rarely dangerous to handle unless the peroxides crystallize out, as is the case with diisopropyl ether. However, once the solutions are heated or concentrated, the higher boiling hydroperoxide can accumulate to dangerous levels. Under these conditions, extremely violent explosions occur without warning. In an incident from my own department, an attempt to distill 4L of old tetrahydrofuran (THF) under air and in the absence of any effective reducing agent, resulted in an explosion so violent that a portion of the apparatus was propelled through a tempered glass sash.
Testing: See peroxide test trips, above. If the stock solvent (for example, ether or THF) shows any significant blue coloration, you should consider either: purifying the solvent from a still that will decompose peroxides (for example Na/benzophenone under N2 or Ar) or disposing of the solvent.

Prevention: Date ethereal solvents upon opening. If a significant period of time has elapsed since the can or bottle was first opened (my university recommends six months) the solvent should be checked before use. Avoid storage of peroxidizable solvents in clear bottles. Avoid having a headspace of air; if you must store ethereal solvents under a significant headspace, consider blanketing with some nitrogen or argon.

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22 https://cameochemicals.noaa.gov/chemical/5112 (accessed 2 March 2016)


