A new peroxide fragmentation: efficient chemical generation of $^{1}\text{O}_2$ in organic media

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A new peroxide fragmentation: efficient chemical generation of $^{1}\text{O}_2$ in organic media

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Abstract

Monoactivated derivatives of 1,1-dihydroperoxides undergo an unprecedented base-promoted fragmentation to efficiently generate singlet oxygen ($^{1}\text{O}_2$) in anhydrous organic solvents.

Singlet molecular oxygen ($^{1}\text{O}_2$), an important oxidant in chemistry, biology, and medicine, is most commonly generated via photosensitized excitation of ground state ($^{3}\text{O}_2$) dioxygen. However, many of these “dark” oxygenations have significant limitations. Due to the short half-life of $^{1}\text{O}_2$ in aqueous media, methods based upon reaction of $\text{H}_2\text{O}_2$ with hypohalites, alkaline earth metals, transition metals, lanthanides, or metalloenzymes must typically employ biphasic or emulsion conditions for preparative oxidations. Thermal generation of $^{1}\text{O}_2$ from phosphite ozonides, silyl hydrotrioxides, or arene endoperoxides can be conducted in organic solvents but requires preparation of unstable precursors. We report an efficient and convenient generation of $^{1}\text{O}_2$ in organic solvents via an unprecedented fragmentation of derivatives of 1,1-dihydroperoxides (Scheme 1).
Our discovery stemmed from earlier research on “reductive” ozonolysis, in which the presence of amine N-oxides was found to promote direct ozonolytic conversion of alkenes to aldehydes and ketones. The proposed mechanism, involving formation and fragmentation of a zwitterionic peroxy/oxyammonium acetal, also predicted stoichiometric generation of $^1$O$_2$ (Scheme 1). However, this prediction could not be easily tested within an ozonolysis reaction. In search of more accessible precursors for the putative fragmentation, we discovered that readily available derivatives of 1,1-dihydroperoxides will generate $^1$O$_2$ under preparatively useful conditions.

The precursor 1,1-dihydroperoxides are readily available and possess surprising kinetic stability. The dihydroperoxides of 4-$t$-butylcyclohexanone and 4-phenyl-2-butanone, 1b and 2b respectively, were prepared in high yield by Re$_2$O$_7$-catalyzed reaction of the ketones with aq. H$_2$O$_2$ (Scheme 2). Monoperesters (1c, 1e, 2c) and a monopercarbonate (1d) were prepared by acylation or carboxylation of the dihydroperoxides. The monoesters were stable for several days at room temperature or weeks at $-20\, ^\circ$C. In contrast, monopercarbonate 1d could be isolated and purified but undergoes slow ring-expansion to 4-$t$-butylcaprolactone even at room temperature.

Addition of KOtBu to a THF solution of 1c resulted in immediate bubbling, accompanied by disappearance of starting material and formation (TLC) of 4-$t$-butylcyclohexanone. Encouraged by this observation, we repeated the reaction in the presence of 1O$_2$ trapping reagents (Table 1 and Figure 1). Addition of KOtBu to a THF solution of 1c and terpinene (3) resulted in formation of ketone 1a (TLC) and endoperoxide 3-O$_2$. A similar result was obtained with percarbonate 1d. An increased yield of 1O$_2$ from 1c was observed at lower temperature, in acetonitrile (MeCN), or in the presence of diphenylisobenzofuran (DPBF, 4), a more reactive trap which was completely consumed whether present in 0.5 or 0.75 equivalents relative to the monoperoxyester. Efficient 1O$_2$ generation was also observed from reaction of monoperoester 1c with Cs$_2$CO$_3$, but not K$_2$CO$_3$ or KOAc. This disparity drew our attention to the potential importance of ion pairing, and we turned to nBu$_4$NF (TBAF) as a convenient base which would afford a highly dissociated peroxyanion. Gratifyingly, treatment of 1c with TBAF led to extremely rapid reaction and a 39% yield of 1O$_2$ (as 3-O$_2$).

The unprecedented fragmentation described above could involve a Grob-like fragmentation, or, alternatively, decomposition of an unstable peroxetane derived from 4-$exo$ ter attack of the peroxyanion on the activated peroxide (Scheme 4). Regardless of pathway, the fragmentation clearly requires both a highly dissociated peroxyanion and a peroxide activated towards heterolytic O-O scission. For example, the monoperoesters do not generate oxygen in

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the absence of base, while we found the 1,1-dihydroperoxides to be unaffected by the bases employed in these studies.\textsuperscript{26} The efficiency of $^1\text{O}_2$ production from the new fragmentation compares very favorably with known oxygen-generating systems.\textsuperscript{3,6,7,8}

In conclusion, we have developed a new heterolytic fragmentation that allows efficient and rapid generation of $^1\text{O}_2$ in nondeuterated organic solvents from readily available precursors. The clean regeneration of the parent ketone suggests an avenue for possible development of solid-supported or phase-separable reagents while the efficiency and rate of $^1\text{O}_2$ production points to potential application as a power source for chemical oxygen/iodine lasers.\textsuperscript{30}

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

### Acknowledgments

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### References

5. The half-life of $^1\text{O}_2$ ranges from 1–2 usec in $\text{H}_2\text{O}$ to 60 usec in $\text{CH}_3\text{CN}$ to nearly msec in perhalogenated solvents. See ref. 1a, and Wilkinson F, Helman WP, Ross AB. J Phys Chem Ref Data 1995;24:663.
16. Dihydroperoxide 1b is not detonated by a hammer blow and melts without decomposition at 78–80 °C. However, even though no hazards were experienced in the course of this work, any preparative work with peroxides should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions. See Supporting Information for references related to safe handling of peroxides.

19. Monoester 1c is not detonated by a hammer blow and melts without decomposition at 37 °C. It is stable for less than a day at 60 °C.

20. Percarbonates of tertiary hydroperoxides and monoperesters of 1,1-dihydroperoxides are both known to undergo Criegee rearrangement: Villenave JJ, Filliatre C, Maillard B, Jaouhari R. Bull Soc Chim Belg 1982;91:301. Velluz L, Amiard G, Martel J, Warnant J. Compt Rend 1957;244:1937. We are uncertain as to the basis for the increased stability of 1c vs. 1d.

21. Reported yields are based upon either isolation or quantitative GC/MS of oxidation products relative to an internal standard; see Supporting Information for details. In general, the ketone byproduct (1a or 2a) was recovered in good yield from the decomposition reactions.

22. Due to the facility of self-sensitized oxidation, the use of DPBF for quantitative experiments should include control reactions or take care to exclude light and oxygen. See: Owakowsa M. J Chem Soc, Faraday Trans 1 1984;80:2119.


25. Although 4-exo/5-endo displacements by peroxyanions to form dioxetanes have been observed (Kopecky, K., Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J-Y. Can. J. Chem. 1975, 53, 1103), the corresponding closure to peroxetanes is unknown. The intermediacy of peroxetanes could in principle be established by the relative fractions of $^{18}$O/$^{16}$O formed upon decomposition of dihydroperoxides derived from mixtures of H$^{18}$O$^{18}$OH and H$^{16}$O$^{16}$OH. We thank one of the referees for this suggestion.


Figure 1.
Trapping substrates and products
Scheme 1.
Fragmentation of peroxyacetals
Scheme 2.
Preparation of peroxide substrates

\( \text{a} \) ref 17 (b) Ac2O, DMAP (c) EtOC(O)Cl, pyr (d) BzCl, pyr
Scheme 3.
Generation of $^1$O$_2$ from 1,1-dihydroperoxide

\[
\text{HO}_2 \text{OOH} \quad \text{i-Pr} \quad \text{TsCl (1.0 equiv)} \quad \text{KOTBu (2.4 equiv)} \quad \text{THF, 0 °C} \quad \text{i-Pr} \quad \text{O}_2
\]

\[
\text{1b} \quad \text{(1.0 equiv)} \quad \text{3} \quad \text{(0.5 equiv)} \quad \text{3-O}_2 \quad \text{(21%, based upon 1b)}
\]
Scheme 4.
Potential mechanisms
Table 1

Generation of $^{1}$O$_2$ from 1c and 1d$^a$

<table>
<thead>
<tr>
<th>reagents</th>
<th>base</th>
<th>solv</th>
<th>time (h)</th>
<th>temp (°C)</th>
<th>prod</th>
<th>yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>3</td>
<td>KOtBu$^c$</td>
<td>THF</td>
<td>1</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>KOtBu$^c$</td>
<td>THF</td>
<td>2</td>
<td>−78</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>KOtBu</td>
<td>MeCN</td>
<td>0.5</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>4</td>
<td>KOtBu</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>4-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>4</td>
<td>KOtBu</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>4-O$_2$</td>
</tr>
<tr>
<td>1d</td>
<td>3</td>
<td>KOtBu$^c$</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>K$_2$CO$_3$</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>Cs$_2$CO$_3$</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>KOAc</td>
<td>MeCN</td>
<td>1</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>TBAF</td>
<td>MeCN</td>
<td>0.2</td>
<td>0</td>
<td>3-O$_2$</td>
</tr>
</tbody>
</table>

$^a$Trapping agents shown in Figure 1.

$^b$3-O$_2$ or 4-O$_2$ vs 1c or 1d.

$^c$Base added to substrates.

$^d$Isoalted yield.

$^e$0.75 equiv of 4.
Table 2

Protocols for preparative oxidation

<table>
<thead>
<tr>
<th>perester (equiv)</th>
<th>trap</th>
<th>promoter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>t (h)</th>
<th>temp (°C)</th>
<th>products (yield)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c (3)</td>
<td>4</td>
<td>TBAF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5</td>
<td>0</td>
<td>4-O&lt;sub&gt;2&lt;/sub&gt; (91%)</td>
</tr>
<tr>
<td>1c (2)</td>
<td>7</td>
<td>TBAF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>1c (4)</td>
<td>3</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>3-O&lt;sub&gt;2&lt;/sub&gt; (69%)</td>
</tr>
<tr>
<td>1c (1.5)</td>
<td>4</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>4-O&lt;sub&gt;2&lt;/sub&gt; (94%)</td>
</tr>
<tr>
<td>1c (8)</td>
<td>5</td>
<td>CsF, TMA</td>
<td>1</td>
<td>rt</td>
<td>5-O&lt;sub&gt;2&lt;/sub&gt; (81%)</td>
</tr>
<tr>
<td>1c (6)</td>
<td>6</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>6-O&lt;sub&gt;2&lt;/sub&gt; (76%)</td>
</tr>
<tr>
<td>1e (8)</td>
<td>7</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>7-O&lt;sub&gt;2&lt;/sub&gt;9-O&lt;sub&gt;2&lt;/sub&gt;8 (91%, 58:28:14)</td>
</tr>
<tr>
<td>1e (3)</td>
<td>3</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>3-O&lt;sub&gt;2&lt;/sub&gt; (62%)</td>
</tr>
<tr>
<td>2c (3)</td>
<td>3</td>
<td>CsF, TMA</td>
<td>0.5</td>
<td>rt</td>
<td>3-O&lt;sub&gt;2&lt;/sub&gt; (66%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Promoter present in 2.4 equiv relative to monoperester.

<sup>b</sup>Based upon conversion of trap to product.

<sup>c</sup>THF as solvent.