two PAS-domain helix-loop-helix transcription factors BMAL1 and CLOCK stimulate transcription of the genes encoding the two cryptochromes CRY1 and CRY2 and the two period proteins PER1 and PER2. When CRY and PER proteins accumulate to a critical threshold, they act as transcriptional repressors of their own genes, supposedly by attenuating the activity of CLOCK-BMAL1 heterodimers. As a consequence, the concentrations of CRYs and PERs decrease, and once they fall below the threshold level required for autorepression, a new daily cycle of *Cry* and *Per* gene expression ensues. *Bmal1* and to a lesser extent *Clock* are also transcribed in a circadian manner, and this cyclic transcription is governed by the orphan nuclear receptor REV-ERBα (see the figure). In *Cry1*- and *Cry2*-deficient mice, *Wee1* is expressed constitutively at high levels in the regenerating liver. In cotransfection experiments, the *Wee1* gene promoter is activated by BMAL1/CLOCK and repressed by CRY proteins. On the basis of these observations, the authors argue that circadian transcription of *Wee1* may be controlled directly by the circadian oscillator. As expected, the constant and high expression of WEE1 in *Cry1*- and *Cry2*-deficient mice results in a sustained inhibition of CDC2 activity, thereby slowing down cycles of mitotic division. Nonetheless, at the end of the delayed regeneration process in *Cry1*- and *Cry2*-deficient mice, the reconstituted liver mass is the same as that attained in wild-type mice. Hence, although the circadian gating of mitotic division speeds up hepatic regeneration, it is not a sine qua non.

Circadian regulation of proliferation has been suggested for other cell types including tongue epithelium and intestinal crypt cells (*7, 8*). Moreover, a possible connection between cellular proliferation and circadian clock activity has been unveiled by work on *Per2*-deficient mice. In fact, these mice are prone to develop salivary gland hyperplasias and spontaneous and γ-radiation–induced lymphomas (*9*). Several epidemiological studies lend support to the hypothesis that perturbations of the circadian timing system may also promote tumorigenesis in humans. For example, breast cancer incidence is augmented in women performing rotating night-shift work over prolonged periods of time (*10*). Obviously, circadian timing affects many other aspects of physiology besides control of proliferation, including endocrine function, metabolism, and liver detoxification. I suspect that identification of the mechanisms through which the circadian clock acts as a tumor suppressor will turn out to be a formidable challenge.

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## CHEMISTRY

# A View of Unusual Peroxides

### Alexander Greer

Chemical processes involving oxygen can lead to unstable peroxide molecules such as three-membered ring dioxiranes (see the first figure). Indirect evidence points to the existence of many dioxiranes, but few have been characterized structurally. On page 259 of this issue, Ho *et al.* (*1*) report the structure of a novel peroxide, phosphadioxirane **1**, which contains a phosphorus atom in the dioxirane ring.

Until the 1970s, it was commonly believed that cyclic dioxirane structures, such as dimethyldioxirane **2**, could not exist. Today, reactions of dioxiranes with organic substrates are well established (*2–4*). The organic group $CR_2$ (where R may be any hydrocarbon substituent, such as methyl) can also be replaced by other chemical groups to yield $XO_2$, where X may for example be $R_3P$, RN, $R_2Si$, $R_2S$, or $R_2Se$ (*5*). The stability of these heteroatom-containing dioxiranes varies widely, allowing new kinds of peroxide structure and reactivity to be explored.

Many studies have been concerned with how peroxides form when oxygen reacts with organic and biological materials. Less commonly articulated is the fact that $^1O_2$ can add to organic and biological substrates faster at low temperature than at high temperature. The phenomenon, known as entropy control, can be of practical use because peroxides decompose at high temperatures.

The best tool for identifying unstable peroxides is the spectroscopic characterization of the reactive intermediates. However, such studies remain highly challenging. The presence or possible interconversion with ring-open species $(X^+\text{-}O\text{-}O^-)$ can complicate the characterization. The study of Ho *et al.* (*1*) stands as a rare success story in detecting a heteroatom-substituted dioxirane, wherein phosphadioxirane was deduced from low-temperature $^{17}O$ nuclear magnetic resonance (NMR) analysis.

A small number of dioxiranes—including compounds **1** and **2**—have been characterized spectroscopically, allowing their chemical structures to be established unambiguously (see the second figure). The structures of dioxaziridine **3** and dioxasilirane **4** have been assigned on the basis of low-temperature matrix isolation and infrared or electron spin resonance analysis, which provides strong but not unambiguous evidence. The evidence for cyclic forms of
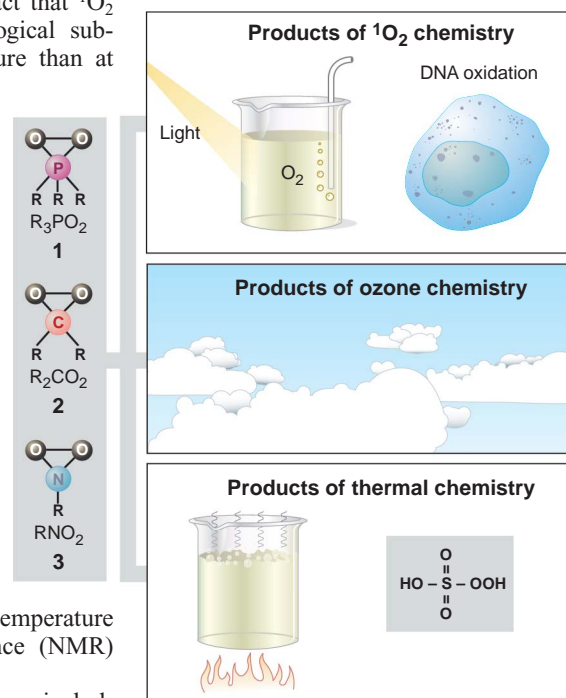


**Some sources of dioxiranes.**

The author is in the Department of Chemistry, Graduate School and University Center and City University of New York–Brooklyn College, Brooklyn, NY 11210, USA. E-mail: agreer@brooklyn.cuny.edu

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$R_2SeO_2$, $R_2TeO_2$, and $R_2SO_2$, for which only kinetic and computational data exist, is more tenuous. Computational studies predict that cyclic $O_3$ (ozone) and cyclic $SO_2$ can exist, but experimental evidence remains elusive. Many other cyclic peroxides have been proposed, but their structures and reactivities are yet to be characterized (5).

Chemists have invested much synthetic effort into devising new peroxides, in the hope that these compounds will enable the selective introduction of oxygen into alkanes and related organic species. To synthesize new peroxides, chemists can introduce architectural changes in the compound. Such changes may result in changed reactivity. Modification of the R group in heteroatom-containing dioxiranes provides an unlimited number of potential analogs.

For example, bulky side groups may be used to protect unstable compounds and help deduce structure. In 1973, Collman et al. showed that a transient intermediate in the reaction of iron(II) porphyrin with $^3O_2$ can be stabilized if the adduct is not permitted contact with another porphyrin (6). A similar "steric" strategy has been used by Sander et al. (7) on mesityldioxirane and by Ho et al. (1) on phosphadioxirane. They use bulky R groups that prohibit or slow contact with another substrate molecule once the dioxirane is formed. Electronic factors also play a role in dioxirane stability and reactivity.

Theoretical calculations have helped to predict the reactivity and other properties of dioxiranes (8). By allowing transition states on the potential energy surface to be probed in detail, such calculations can provide information that is inaccessible by ex-
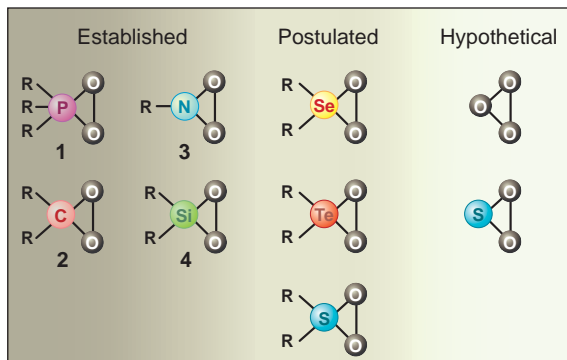


**Shades of confidence in the assignment of peroxide structure.**

periment. Calculated transition state geometries have, for example, shed light on the epoxidations of ethylenes by dioxiranes. Combined computational and experimental studies are particularly important for studying the reaction mechanism of new peroxides and their potential to serve as oxygen atom donors to other molecules.

A major goal of oxygen chemistry is the functionalization of molecules with controllable selectivity (9). Several groups have shown that dioxiranes of the $R_2CO_2$ type may be used to transfer an oxygen atom regio- and stereoselectively. Chiral dioxiranes have been remarkably successful in enhancing the selectivity in alkene and alkane oxidations. Singlet oxygen, hydroxyl radical, hydrogen peroxide, and molecular oxygen are themselves oxidizing agents. However, their chemistry can be unselective, because it is often governed by zwitterionic, (di)radical, or electron-transfer reactions. This lack of stereochemical control has limited the use of these oxygen sources in synthetic and industrial applications.

Dioxiranes of the $R_2CO_2$ type appear to be less prone to interact with substrates by electron transfer. Dioxiranes may not suffer the same problems as the other oxidants and may therefore be useful in applications.

The method used by Ho et al. for obtaining direct evidence for dioxirane intermediates (1) may also be used to study more complicated biological or inanimate systems. For example, recent evidence suggests that a dioxirane intermediate arises in a DNA base reaction with $^1O_2$ (10). It is as yet unclear to what extent three-membered ring peroxides occur in living material. Spectroscopic characterization is the best tool for identifying reactive intermediates such as dioxiranes. Indirect methods can probe in vivo activity more easily, but they often cannot discriminate between different oxidizing agents.

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ATMOSPHERIC SCIENCE

# Ozone and Climate Change

**David J. Karoly**

Many studies into the possible causes of recent climate change have tried to separate natural climate variability from human influences, such as increasing greenhouse gases. In 2001, the Intergovernmental Panel on Climate Change concluded that "most of the observed (global) warming over the last 50 years is likely to have been due to the increase in greenhouse gas concentrations" (1). Less attention has been paid to the possible impact of human-induced ozone depletion in the stratosphere on climate in the lower atmosphere.

The author is in the School of Meteorology, University of Oklahoma, Norman, OK 73019, USA. E-mail: dkaroly@ou.edu

Over the past 40 years, climate has warmed over much of the Southern Hemisphere. The circumpolar westerly winds have also increased in strength, as a result of increasing atmospheric pressure at mid-latitudes and decreasing pressure and temperatures at high latitudes. These observed changes in Southern Hemisphere climate at high latitudes have a distinct seasonal structure, with largest amplitude in late spring and summer. Thompson and Solomon (2) have argued that they may be caused by stratospheric ozone depletion over Antarctica in spring.

On page 273 of this issue, Gillett and Thompson (3) report a modeling study of the seasonality, spatial structure, and am-

plitude of high-latitude climate change in the Southern Hemisphere. They show that the observed spring and summertime changes can indeed be explained as a response to Antarctic ozone depletion. It is the first modeling study to show quantitative agreement between observed climate change in the lower atmosphere and the climate response to ozone depletion in the stratosphere. Together with other research presented at a recent workshop (4), it helps to quantify the possible influence of the stratosphere on weather and climate.

Of course, trends in Southern Hemisphere climate at mid- and high latitudes are also observed in winter. It is difficult to argue that ozone depletion in spring could be their cause. Climate models forced with increasing atmospheric greenhouse gas concentrations also show an increase in the circumpolar westerly winds in the Southern Hemisphere and an increase in the southern annular mode (SAM), with increased pres-