Marginalia

THE STORY OF O

Roald Hoffmann

Everything in oxygen chemistry seemed more or less in place: Up there, in the stratosphere, there were oxygen atoms, \( \text{O}_2 \) molecules and ozone, \( \text{O}_3 \), as well as ions derived from these and a bit of active OH, all in a dance of creation and destruction.

Meanwhile, within our bodies, normal \( \text{O}_2 \) served us well. There was even a place, under enzyme supervision, for the somewhat nasty relatives hydrogen peroxide (\( \text{H}_2\text{O}_2 \) and its deprotonated form, \( \text{O}_2^{2-} \)) and superoxide (\( \text{O}_2^- \) and its protonated alter ego, \( \text{HOO}^- \)), whose chemistry may generate the harmful hydroxyl radical \( \cdot \text{OH} \). Of course, there’s also water everywhere. And here and there singlet dioxygen, a more reactive and excited state of normal diatomic oxygen.

A nice, neatly compartmentalized world: ozone for atmospheric chemists, but not biologists, who had plenty of more complicated molecules to worry about.

So they thought.

This complacent state has now changed—dramatically so—with a series of remarkable discoveries. There is new evidence for the occurrence of ozone in living cells. Hydrogen peroxide is being made by molecules thought incapable of doing so. Even a metastable laboratory curiosity, the unusual \( \text{HOOOH} \) molecule (which sounds like a holter; call it dihydrogen trioxide), may be in living systems. Meanwhile, we are still puzzling out the state of oxygen in high-temperature superconductors. And the menagerie of alternative forms of elemental oxygen continues to expand—there are strong theoretical arguments for the existence of a cyclic ozone isomer, and there may even be ways of stabilizing it.

A Diradical

Oxygen is the most abundant element in the crust of the Earth. It is mostly tied up in carbonates and phosphates, and in a wider range of silicates, from clays to zeolites to quartz.

Under ambient conditions, diatomic oxygen is the stable form of the element. \( \text{O}_2 \) is a strange molecule, for all its ubiquity. Its problem (no, our problem as we try to think about it) is that oxygen’s two least strongly held electrons, responsible for most of its chemistry, have available to them two orbitals. One electron goes into each orbital, so the ground state of \( \text{O}_2 \) has two unpaired electrons.

From here on I will refer to this ground state simply as \( \text{O}_2 \). The first excited state of \( \text{O}_2 \), usually simply called singlet oxygen or \( \text{O}_2^* \), lies 95 kilojoules per mole above the ground state. Singlet oxygen is an energetic, still more reactive form of oxygen that is relatively easy to make, either chemically or with light.

Normal ground state \( \text{O}_2 \) is not an inert molecule. A single unpaired electron on oxygen (as in \( \cdot \text{OH} \)) or on an organic fragment (as in methyl, \( \cdot \text{CH}_3 \)) makes such a “radical” very reactive. Radicals rip hydrogens from previously stable molecules; they also start polymerization chains. With its two unpaired electrons, \( \text{O}_2 \) is a “diradical.” It enters many organic and inorganic reactions—as we’ll soon see, this changed the course of evolution.

But compared to other diradicals, \( \text{O}_2 \) is surprisingly unreactive. “Otherwise California would be burning permanently, and not just from time to time all the time,” as a La Jolla-based colleague remarked in the midst of the recent fires. Many organic molecules have large barriers to reaction with \( \text{O}_2 \). The reasons for \( \text{O}_2 \)’s attenuated reactivity are still being debated, but there is no ambiguity about the destructive nature of singlet oxygen and the \( \cdot \text{OH} \) and \( \cdot \text{OOH} \) radicals. Or of the metastable allotrope of oxygen, ozone. These attach, with alacrity, nearly anything organic.

A Subversive Element

Diatomic \( \text{O}_2 \) apparently was not abundant early on in the history of the Earth, based in part on the age of oxidized iron deposits. So life, evolving as it did to utilize oxygen atoms in almost every molecule of consequence, got those atoms from carbon dioxide and carbonates. But the energy—and the electron donors and acceptors needed to run reduction-oxidation chemistry—came from elsewhere, likely first from reactions in the absence of light, such as \( \text{H}_2 \) reacting with \( \text{CO}_2 \). Later, with

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light but still without free $\text{O}_2$, the energy and electron sources may have been bacterial photosynthesis, described by the schematic equation

$$2\text{H}_2\text{X} + \text{CO}_2 \rightarrow [\text{CH}_2\text{O}] + 2\text{X} + \text{H}_2\text{O}$$

About two billion years ago, oxygen-releasing photosynthesis spread widely among biota, introducing vast amounts of $\text{O}_2$ into the atmosphere. One might look at the $2\text{X}$ in the generic equation above as just a waste product. But nature is opportunistic. The leavings of one organism, even if dangerous, provide food for another. Or (for $2\text{X}=\text{O}_2$) a breathable gas.

Yes, oxygen drove many of the early prokaryotes into anoxic niches, where they survive perfectly well to this day. Other survivors, prokaryotic and eukaryotic, evolved $\text{O}_2$ detoxification strategies. These schemes included enzymes such as superoxide dismutase, classes of molecules such as luciferins, and some isoprenoids. With these and other molecular constables, aerobic organisms created an intracellular balance (perhaps upset as we age): Some oxygen-containing radicals were kept dangerous, even as aerobes evolved the biochemistry to control them.

And organisms did evolve to use $\text{O}_2$. What was waste, now nourished. Yet oxygen does more than fuel cellular fires. The immune system is actively involved in making killing forms of oxygen, such as peroxide and ozone.

**Burning Water**

Part of the immune system is adaptive, an assortment of receptors that cover the surface of white blood cells. Some of these receptors are antibodies, which recognize and bind to pathogens. To actually destroy them, to disrupt bacterial membranes or initiate ingestion, immunologists thought that antibodies had to signal other parts of the system.

In the past three years, Scripps Research Institute chemists and biochemists have dramatically revised this picture. Richard Lerner, Albert Eschenmoser and Paul Wentworth, Jr., collaborating with several groups, first discovered that all antibodies could produce hydrogen peroxide. More recently, they have found that antibodies appear to catalyze the generation of ozone! The overall reaction (unbalanced, and obscuring many intermediate steps) is

$$\text{H}_2\text{O} + ^1\text{O}_2 \rightarrow \text{H}_2\text{O}_3 \rightarrow \text{O}_3 + \text{H}_2\text{O}_2 + \text{O}_2$$

This reaction includes many of oxygen's protean molecular manifestations: Aside from the familiar water, hydrogen peroxide, excited singlet and
normal ground state oxygen, it contains the unusual HOOOH molecule. Dihydrogen-trioxide was proposed more than 60 years ago, but direct proof for its existence has trickled in over the last 30 years. There is also a possible role for the HOO• radical, not shown in the equation, which in turn may be a masked •OH. All are reactive molecules, as shown by their short halflives in water: around 1 minute for ozone, 20 milliseconds for HOOOH and 1 microsecond for H₂O₂.

The narrative of discovery that details the unraveling dogma is fascinating. Initial observations of H₂O₂ production in the presence of antibodies were startling enough. But as the Scripps group thought about what they saw, so much H₂O₂ was being produced that it became an enigma where all the electrons come from. The problem was resolved when the researchers realized that two molecules of singlet oxygen could react with water to give HOOOH, which could then go on to form ozone and hydrogen peroxide. A simple experiment ran the process in ¹⁸O-labeled water and showed that the label wound up in the H₂O₂; this result immediately supported the hypothesis. Albert Eschenmoser says:

The situation is reminiscent of photosynthesis when it started to use water as an electron donor and then began to poison the environment. It is "burning water," in one case by excitation of a cofactor by light, and in the other case by singlet oxygen mediated by an antibody.

And where does the singlet oxygen, the energy source, come from? Certain white blood cells produce it when stimulated by infection. In the tight economy of the cell (Lavoisier, the banker, would have loved this), everything is utilized.

Recent work from the same imaginative collective has shown that atherosclerotic plaques also generate ozone. That ozone attacks cholesterol and the consequent oxidation products are all-around bad actors, implicated in cytotoxicity and mutagenesis.

This seemingly unorthodox chemistry has been with us (albeit unknowingly) for years. There is an old, potent oxidation system used to cleanse industrial quantities of soil and water contaminated with PCBs and worse, the peroxone process. In it, the samples are treated with a syn-

Figure 2. Shining bright, a single crystal of murine antibody demonstrates the formation of H₂O₂ in a photochemical color test. (Photograph courtesy of Paul Wentworth. Copyright 2000, National Academy of Sciences, U.S.A.)

Figure 3. In a, the as-yet unknown cyclic isomer of ozone. Panel b shows the two resonance structures for the known ozone molecule.

The Ring
So now we have oxygen chemistry in the atmosphere, in the cell, in a decontamination process. But have we exhausted all of oxygen’s secrets?

For a few intriguing small molecules you can draw a perfectly good Lewis structure. But they don’t exist. Beginning chemistry students, nicely unsullied by the burden of knowing the answer, often give us one—ask them for a Lewis structure of ozone, O₃, and they are as likely to write down the cyclic molecule in Figure 3a as the known form in Figure 3b, for which one has to draw two resonance structures. So what’s wrong with the ring in Figure 3a? Or four-, or five-,
Actually, there has been one observation of cyclic ozone on an annealed magnesium-oxide surface. The technique used to image the molecules, transmission electron diffraction, showed O₃ rings that appeared to be centered over underlying Mg ions.

Incidentally, the solid state is a fine place to look for oxygen in other weird forms. A mystery remains (one of many) about the chemical nature of oxygen in the cuprate superconductors. Oxygen doping is necessary for high-temperature superconductivity (high T_c) in systems such as La₂CuO₄. During the synthesis of this composite, the oxygen enters as O₂⁻ but it surely does not reach its equilibrium positions in the lattice in this form. To get at the problem in another way— all the signs are that the holes (missing electrons) in high T_c cuprates are partially on Cu²⁺, partially on (formal) O²⁻. But a hole, or one electron less, on O²⁻ makes it O. And this radical (here they are again!) will not sit still in the lattice. Large or small motions of the oxgens, static or dynamic formation of O₂⁻, O₂⁻⁻, O₂⁻⁻⁻ or even a bigger aggregate—what will it be?

Crazy Like a Fox

Would it surprise me to see cyclic ozone, or an as-yet unknown, metastable, oxygen-containing radical in a biological system? Two years ago I would have said, “You’re crazy.” After the beautiful and exciting Scripps work of the past two years, I’d rather leave the final word to Marie Anne Pierrette Paulze Lavoisier, who in a recent play about the element, puts it simply: “Imagine!”

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Bibliography


