

The NO hat trick. Small amounts of NO stimulate mitochondrial biogenesis and boost the supply of oxygen and respiratory substrates to mitochondria. In contrast, high amounts of NO produced by iNOS block mitochondrial respiration, and can be cytotoxic. Cold exposure results in noradrenaline release by sympathetic nerves, which elevates intracellular calcium ions and cAMP (via β_3 -adrenergic receptors) in brown fat adipocytes. This increase induces NO production by eNOS, which activates cGMP production from soluble guanylate cyclase. Expression of the transcriptional coactivator PGC-1 is enhanced by cGMP, resulting in increased production of NRF-1 and mtTFA, which stimulate mitochondrial biogenesis. Vasodilation of blood vessels (due to the action of NO on vascular smooth muscle) results in an increased supply of oxygen and respiratory substrates to mitochondria. Inflammation enhances iNOS expression, resulting in elevated production of NO, which directly blocks mitochondrial respiration and energy production.

eNOS is itself a master regulator of mitochondrial number, and thus potentially of aerobic exercise, heat production, and obesity.

This surprising discovery has important implications for understanding energy metabolism and suggests therapeutic interventions for treating obesity. However, a number of questions remain to be answered about NO's ability to stimulate mitochondrial biogenesis. For example, does NO induce mitochondrial biogenesis in all tissues and does it interact with other biogenesis regulators? What is the mechanism of NO/cGMP action? Do iNOS and mtNOS behave in the same way as eNOS? Are the newly formed mitochondria different from their parents? NO can also regulate the proliferation and differentiation of various cell types, including the adipocytes of

brown fat (9). The relation between these activities and NO's ability to stimulate mitochondrial biogenesis requires further investigation. The evidence for in vivo regulation of mitochondrial biogenesis by NO, however, remains weak. Encouragingly, Momken and colleagues (10) recently reported a decrease in mitochondrial enzymes and oxidative phosphorylation in the aerobic skeletal muscles of mice deficient in eNOS. If NO indeed regulates mitochondrial number in human skeletal muscle, it might be possible to stimulate production of mitochondria in muscles with drugs or gene therapy, in order to increase sports performance, reduce obesity, or even reverse aging. On the downside, mitochondria can themselves contribute to cell death and aging, and NO regulates many other cellular processes (4, 5). But we now know that low levels of NO produced by

eNOS can stimulate aerobic metabolism by increasing blood perfusion, unloading oxygen from hemoglobin, inducing growth of new blood vessels, and stimulating the biogenesis of mitochondria. High levels of NO, on the other hand, inhibit mitochondrial oxygen consumption directly. The diverse interactions between NO and mitochondria will continue to fascinate us for some time to come.

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MATERIALS SCIENCE

Oxygen in Crystals—Seeing Is Believing

John C. H. Spence

On page 870 of this issue, Jia *et al.* (1) present the first really clear images of oxygen-atom columns and their vacancies in crystals (1). The importance of this work can be judged from the industrial significance of a wide range of oxide materials, the intellectual challenges in understanding their properties at the atomic level, and the history of oxygen on Earth.

The development of photosynthesis by cyanobacteria about 3.4 billion years ago initiated the oxidation of many chemical elements (2). Today, Earth's crust and mantle consist almost entirely of oxides to a depth of 2900 km. These oxides, mainly silicates, form a multitude of crystalline structures of variable stoichiometry. Phase

transformations between them have variously liberated or absorbed oxygen under the different thermodynamic conditions that have existed on Earth.

Oxides now form the basis of our largest industries, from the reduction of oxides to iron and aluminum to the manufacture of paints, catalysts, and digital recording media. Transition metal oxides and their defects are at the center of some of the hottest topics in condensed matter physics. In strongly correlated materials, oxide superconductors, and colossal magnetoresistance, electron charge-carrier density depends sensitively on the oxygen occupancy of particular crystal sites. New ferroelectrics and dielectrics based on transition metal oxides hold promise for a new generation of devices.

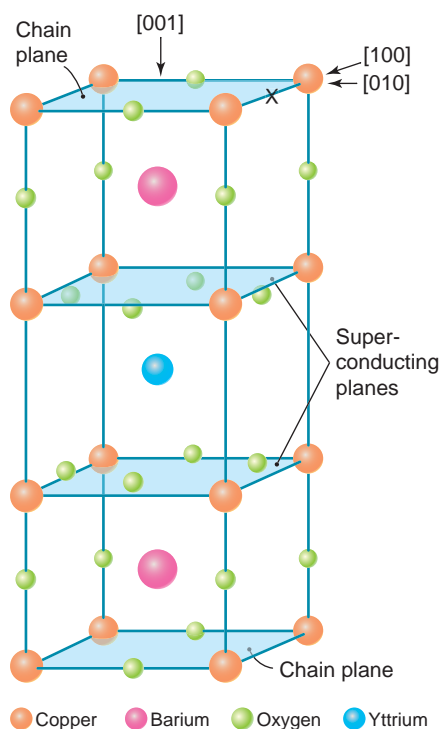
Nevertheless, understanding at the atomic level of the processes of oxidation and reduction in the solid state remains lim-

ited. It has been 200 years since Prout established that chemical compounds consist of elements mixed in fixed proportions. Yet, defects must be involved in oxidation reactions. How is the resulting nonstoichiometry accommodated? And what is the nature of the crystal defects? These questions have been a long-standing puzzle.

Attempts to see oxygen atoms directly inside crystals have proven largely unsuccessful because of its weak scattering and small size (about 0.1 nm). The first hints that oxides were not perfect crystals came from transmission electron microscopy (TEM) in the late 1960s (3). Wadsley had earlier made the bold proposal that crystallographic shear—in which oxygen octahedra change from corner- to edge-sharing, producing planar faults—was the mechanism of oxygen release in transition metal oxides. The mechanism could accommodate local variations in oxygen content.

The first reasonably sharp image of a "Wadsley defect" was obtained at 0.38-nm resolution by Iijima in 1975 (4). In his study, Iijima deduced oxygen-atom sites from images of the heavier cations. The work led to an explosion of research into oxidation processes by high-resolution TEM. Ingenious proposals were made for

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Oxygen starvation. Jia *et al.* (1) have obtained atomic-resolution views of the $\text{YBa}_2\text{Cu}_3\text{O}_7$ superconductor crystal along the three directions shown, allowing them to identify missing oxygen atoms such as those at X. These oxygen vacancies control superconducting properties.

the structures of these crystalline sponges in work by Hyde, Bursill, and others, including the possibility that the planar faults may order to produce a series of new “infinitely adaptive” crystal structures [see (5) for a review], which adapt to the local thermodynamic conditions (6). These structures are known as Magneli phases. The discovery of oxide superconductors provided an added impetus to image the partially ordered oxygen along the oxygen-copper chains, on which the transition temperature to the superconducting state depends (7).

But at the low resolution of these studies, the images were dominated by the more strongly scattering cations, and oxygen-atom columns could not be seen in the images, which show a projection through a thickness of about 10 nm of crystal (8). Image resolution has improved steadily since then, providing tantalizing glimpses of oxygen atoms in images produced with either elaborate image-processing techniques (9) or very high voltage machines. The latter are, however, limited by the radiation damage they cause (10). Equally important has been the development of environmental cells within the microscope, allowing real-time video recording of chemical reactions at near-atmospheric pressures and ~0.2-nm resolution (11).

A revolution of sorts in electron microscopy is now allowing the first direct images of oxygen atoms. The images obtained by Jia *et al.* (1) are the first of many breakthroughs we can expect, made possible by the development of the aberration-corrected electron lens (12). This lens is taking the image resolution below 0.1 nm in the annular dark-field scanning transmission electron microscopy (ADF STEM) mode (13). But it is the ability to tune the spherical aberration coefficient to negative values that enabled the remarkable images of strings of oxygen atoms in SrTiO_3 and the superconductor $\text{YBa}_2\text{Cu}_3\text{O}_7$.

Negative spherical aberration produces bright atom images, in this case on a dark background, under “bright-field” weak-scattering conditions (the opposite of normal imaging contrast, and similar to the ADF STEM mode). In the additional presence of a small amount of multiple scattering within the sample, contrast is greatly improved, producing sharp, bright images of the oxygen columns with a resolution of 0.13 nm. It is to be hoped that the sample dependence of this effect is weak.

But it is the oxygen vacancies and dopants themselves, rather than images of the projected atomic structure, that are of greatest interest to scientists. Recently, the first credible TEM images of individual dopant atoms were published (14), again seen in projection. Jia *et al.*'s images of $\text{YBa}_2\text{Cu}_3\text{O}_7$ are remarkable in that they managed to obtain images of the defective oxygen-atom columns in three orthogonal projections (see the figure), although each projection was taken from a slightly different region of the crystal. The images show

both the CuO -chain planes and the CuO_2 superconducting planes in three projections. If we assume similar disorder in the three sample regions, it is possible to conclude that the Cu-O-Cu-O chains are highly ordered along the [010] direction. In contrast, oxygen atoms are missing along [100], creating ordered Cu-X-Cu-X- (with X denoting a vacancy). The projection image along [100] also shows a planar fault in response to stoichiometric constraints (1).

The prospects for developing this “tomographic” imaging of oxygen ordering during chemical reactions inside an environmental cell are tantalizing, promising a true atomic-resolution solid-state chemical observatory for the future. This tool may enable the role of the various types of point, line, and planar defects to be elucidated in solid-state chemical reactions, and the atomic mechanisms involved in oxide catalysis finally to be understood at the atomic level.

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PHYSICS

Coherent Power Booster

Heiner Linke

In the early 19th century, Sadi Carnot realized that a heat engine requires two heat baths to operate: a warm source of heat and a cooler dump for waste heat. The temperature difference drives the heat engine and determines its maximum efficiency. If the two baths have the same temperature (or if there is only one bath), no power output is possible. This insight is the essence of the Second Law of Thermodynamics (1).

On page 862 of this issue, Scully *et al.* propose a quantum-electrodynamic heat engine that uses quantum coherence to extract work

from a single, warm gas (see the figure) (2). Rather than violate the Second Law, this and similar thought experiments highlight differences in the thermodynamics of classical and quantum systems. Quantum mechanics may even help to improve some real engines.

The centerpiece of the proposed quantum heat engine is a microlaser cavity formed by two mirrors. One mirror acts as a piston driven by photon pressure, enabling a Carnot-like, cyclic process to produce work. Thermal contact with a heat reservoir is established via a beam of atoms whose electron energy levels are populated according to the reservoir temperature. The atoms are resonant with the photon mode.

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