

using thinner ice. But there's no established method for precisely controlling ice thickness; instead, the NIH researchers had to prepare many specimens and focus their analysis on the ones that produced the best images.

Cancer proteins

Subramaniam and his team recorded cryo-EM structures of three proteins, all of which are relevant to cancer biology. Glutamate dehydrogenase (GDH), the largest of the three at 334 kDa, featured the record-breaking resolution of 1.8 Å. The researchers achieved 2.8 Å resolution of the 145 kDa lactate dehydrogenase (LDH), the enzyme responsible for producing lactic acid in sore, oxygen-starved muscles; cancer cells rely on the same reaction even when plenty of oxygen is available. And they obtained a 3.8-Å-resolution structure of isocitrate dehydrogenase (IDH), which at 93 kDa was the smallest protein yet resolved with cryo-EM. In many cancers, IDH contains a mutation that causes it to fuel malignant cell growth.

Figure 1 shows portions of the two larger proteins with atomic models superposed on the cryo-EM density maps. Because even 1.8 Å is larger than any of the interatomic bond lengths, the atoms appear blurred together. But with the help of structural information from other sources, such as each protein's amino-acid sequence, the atomic models can be positioned with good accuracy. In the 1.8-Å-resolution structure, the amino acids' characteristic shapes are especially apparent, including the holes in the six-atom carbon rings. Some of the individual water molecules (highlighted in yellow in the figure) surrounding the protein are also well resolved.

For the two smaller proteins, LDH and IDH, the researchers looked at the complexes formed between the biomolecules and small-molecule inhibitors that are currently under study as potential cancer-fighting drugs. Says Subramaniam, "We want to see how the molecules work, how they fit together." Figure 2 shows their cryo-EM images of IDH both on its own and bound to an inhibitor molecule known as ML309. Though the 3.8 Å map isn't quite good enough to show detailed atomic information, the researchers could identify the location of the ML309 and glean new information about how the molecules interact. The

ML309 molecule (red) wedges apart the protein's two subunits, shown in yellow and blue, and appears to distort the protein's active site, the region most critical to its metabolic function in cancer cells.

A central remaining challenge for cryo-EM is that biomolecules with identical compositions don't always have identical shapes: Even when folded into the correct structure, many proteins are floppy and can adopt multiple conformations in solution. The algorithms theorists have developed for image analysis⁵ can deal with that structural diversity to a certain extent, but they still need to make assumptions in classifying and

aligning the structural images. But cryo-EM will no doubt continue to improve as researchers test its ability to find structural information about the proteins involved in cancer, brain function, and other frontiers of biology.

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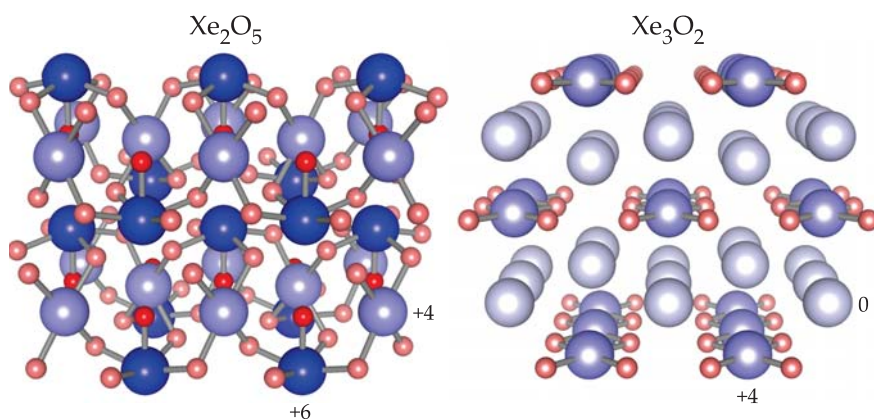
Xenon chemistry under pressure

At geological pressures and temperatures, xenon can form a host of stable oxides.

Like other noble gas elements, xenon strongly resists forming chemical bonds. Indeed, that inertness makes its isotopes important tracers of the evolution of planetary atmospheres and interiors. Yet the fact that the element can react, albeit reluctantly, was predicted a century ago by Walther Kossel (and later, in 1932, by Linus Pauling), who realized that Xe, with its soft, highly polarizable *p* shell and relatively small ionization po-

tential, should form compounds with strongly electronegative atoms such as fluorine or oxygen.

That prediction was borne out in 1962 when Neil Bartlett noticed an orange-yellow solid precipitate as soon as he exposed Xe to platinum hexafluoride gas. Syntheses of dozens of Xe compounds soon followed, nearly all containing fluorine or oxygen. But all the xenon oxides produced in the half century since that



XENON OXIDES, IN EXTREMIS. When xenon gas is mixed with free oxygen at mantle-like temperatures and pressures, it reacts to form stable compounds of Xe_2O_5 and Xe_3O_2 . In each structure Xe and O atoms exhibit mixed-valence states. The Xe atoms (blue) are shaded according to their oxidation state (+6, +4, or 0). O atoms are represented by two shades of red, depending on whether they bond with one or two Xe atoms. (Adapted from ref. 4.)

first demonstration of reactivity have proven unstable at ambient conditions, and some are dangerously explosive.

Applying pressure can forestall the instability. At 100 GPa the change in internal energy of a material may reach several eV per atom. Under such a harsh squeeze, existing chemical bonds can be broken and new ones formed.¹ At 50 GPa an atomic crystal of Xe, which melts at -112°C at ambient pressure, turns into a compact solid that melts at 3000°C .

In 2013 Stony Brook University theorists Qiang Zhu, Artem Oganov, and their colleagues predicted that above 80 GPa a sequence of XeO_n compounds (with integers n) would become stable against decomposition into atomic constituents.² A year later Andreas Hermann and Peter Schwerdtfeger predicted that a host of other candidates, including Xe_3O_2 , should also be stable above roughly the same pressure.³

Agnès Dewaele at France's Atomic Energy Commission (CEA) in Arpajon and her colleagues have now synthesized the predicted Xe_3O_2 material and a new, unpredicted one, Xe_2O_5 . In their

experiments, conducted at the European Synchrotron Radiation Facility (ESRF), oxygen-rich and oxygen-poor mixtures of Xe and O_2 were loaded into diamond anvil cells, compressed to near 100 GPa, and heated to 2000 K with an IR laser to induce reactions.⁴ The new syntheses, which the group monitored using x-ray diffraction and absorption spectroscopy, represent the first stable xenon oxides made under pressure. The figure on page 15 shows their lattice structures.

Missing xenon

Interest in the xenon oxides is driven partly by a long-standing mystery: Xe's scarcity in Earth's atmosphere. At a concentration of less than one part in 20 million, the element is an order of magnitude rarer than expected from the composition of stony, so-called chondritic meteorites. If the gas wasn't somehow lost to space during Earth's early, hot accretion, then it must have become sequestered in the planet's interior. All the near-surface entrapping suspects have been ruled out: Searches for Xe in

ices, sediments, shales, and clathrates have turned up far too little to account for what's missing. The deeper crust and mantle are more appealing as candidate reservoirs because the usually inert element becomes increasingly reactive as pressure and temperature rise.

In 2005 geophysicist Chrystèle Sanel (now at Pierre and Marie Curie University) and her colleagues squeezed Xe into quartz (SiO_2) at thermodynamic conditions on par with those in the crust.⁵ They found evidence from x-ray diffraction at ESRF that Xe atoms displace silicon atoms—possibly forming networks of oxide structures, they hypothesized. A few years later, McMaster University chemists David Brock and Gary Schrobilgen strengthened that hypothesis with their ambient-pressure synthesis of XeO_2 , whose proposed network structure is made up of square-planar XeO_4 units, which are thought to replace tetrahedral SiO_4 units in quartz. They added crystals of xenon tetrafluoride to water at its freezing point and produced a substance whose vibrational spectra identified it as the sought-for

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XeO₂ (though its crystal structure has not yet been resolved).⁶

Dewaele's new experiment offers a different formation route. It directly exposes Xe to oxygen, the most abundant element in Earth's lower mantle, at pressures and temperatures within the range of what's experienced there. Even so, the experiment doesn't solve the missing Xe problem. For one thing, Xe is so scarce that the element seems unlikely to accumulate in sufficient quantities to be accommodated into deep mineral phases. For another, the O atoms in those deep phases are themselves bound as interstitial components of the minerals, not the free O₂ molecules present in the new experiments.

Alternatively, Xe may not form part of a mineral phase at all. Like most other atoms, Xe can be retained at grain boundaries or other defect sites in mantle silicates and oxides. But why the atoms did not then outgas to the atmosphere over geologic time is its own mystery.

Theory to the rescue

The new work is also driven by pure curiosity. The synthesis and identification of new compounds are at the heart of chemistry. Although at first glance the reaction of two gases could hardly be simpler, its interpretation wasn't. The x-ray beamlines at ESRF are among the most intense in the world, but the diffraction peaks Dewaele and her team observed didn't yield enough detail for them to reconstruct the number and position of O atoms in the newly produced materials. With its number of electrons less than one-seventh that of Xe, O scatters too few incident photons.

Dewaele also examined absorption spectra of the material to convince herself of the presence of Xe–O bonds and the absence of any bonds between Xe and the carbon in the diamond anvils or the metal in the cell's gasket.

What's more, the structures of high-pressure phases can defy chemical intuition. One might suspect that when squeezed tightly together, elements should favor close-packed configurations. After all, atomic Xe sluggishly transforms from one close-packed variant (face-centered cubic) into another (hexagonal-close packed) before it eventually becomes metallic above 130 GPa. But work from the past two decades has proven that supposition wrong.¹ The

problem of energy-efficient packing is even more complicated if the spheres are unequal in size.

To resolve the structure and stoichiometry of the new oxides, Dewaele asked Cambridge University's Richard Needs to predict, using first-principles methods, the most stable, low-energy lattice configurations that should exist under a range of pressures. Reassuringly, the diffraction-peak positions Needs and colleagues Nicholas Worth and Chris Pickard calculated from two of the candidate structures matched the positions visible in the experimental patterns.

To achieve that match, the theorists had to consider Xe's *d*-shell electrons as part of the valence shell. The compression essentially opens that otherwise closed core shell thanks to the spatial overlap of the 4*d* orbitals with the higher-energy 5*s* and 5*p* ones. Xe atoms adopt different oxidation states—the number

of Xe electrons associated with bonding—in the same compound (see the figure). Although such mixed valency is common in high-pressure chemistry, it is rare in the noble gases.

More practically, the theoretical treatment of the 4*d* orbitals produced a more accurate and lower prediction for the pressure at which the new oxides would be stable. As a result, Xe and O₂ are more reactive under pressure than theorists had previously realized.

Mark Wilson

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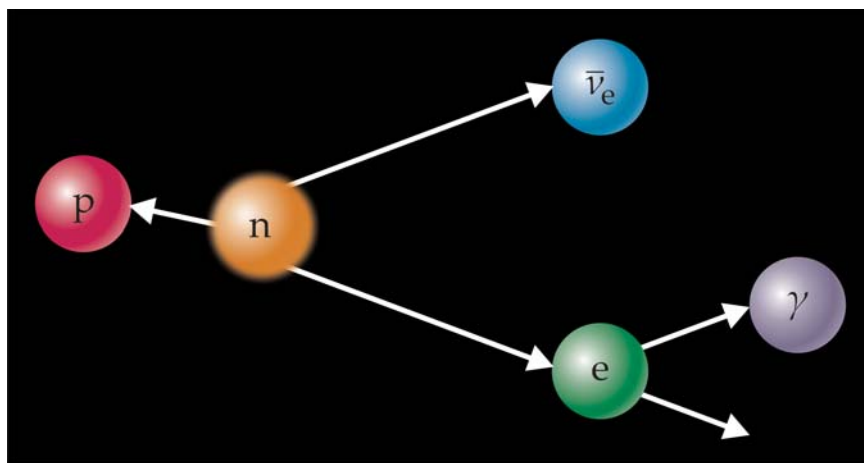
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The colors of radiative beta decay

The energy distribution of photons produced in a rare neutron-decay mode has now been measured.

The neutron, though an essential component of most stable nuclei, is itself unstable: After a mean lifetime of about 15 minutes, a free neutron decays into a proton, an electron, and an elec-

tron antineutrino. Because the process depends on only a handful of parameters, it's an ideal testing ground for understanding the fundamental physics of the weak interaction.



WHEN A DECAYING NEUTRON produces a photon—in addition to the usual proton, electron, and electron antineutrino—the photon is usually associated with the creation of the electron. The energy distribution of those photons can be predicted by quantum electrodynamics; that prediction has now been experimentally confirmed.