

vated (7). Moreover, antioxidant treatment of cells that express an oncogenic form of Src (v-Src), or mutation of the oxidation-sensitive cysteine residues of v-Src, reduces the potency of v-Src to transform cells. This redox-dependent activation of Src occurs alongside dephosphorylation of a carboxyl-terminal tyrosine, a modification that is needed to activate Src.

For H_2O_2 to serve as a signal—through modification of signaling proteins—its concentration must increase rapidly above a certain threshold. How can this occur in the presence of antioxidant enzymes such as catalase, glutathione peroxidase, and peroxiredoxin? Whereas catalase is confined to the peroxisome, several peroxiredoxin isoforms are abundant in the cytosol. Therefore, H_2O_2 must be protected from destruction by peroxiredoxin in selected contexts. Indeed, multiple protective mechanisms of this type are being uncovered. During catalysis of H_2O_2 reduction, the active-site residue, Cys-SH, of peroxiredoxin occasionally reacts with two molecules of H_2O_2 , and thus becomes hyperoxidized to Cys-SOOH. Consequently, peroxiredoxins are inactivated (8). This inactivation, which can be reversed by sulfiredoxin, an adenosine triphosphate-dependent enzyme, may represent a built-in mechanism to prevent damping of the H_2O_2 signal. Prokaryotes do not express sulfiredoxin and their peroxiredoxins are resistant to hyperoxidation. Thus, this regulatory mode appears unique to eukaryotes. Peroxiredoxins are also reversibly inactivated upon phosphorylation by cyclin B-dependent kinase during mitosis (9).

Given the toxicity of H_2O_2 , spatial and temporal regulatory strategies must exist to ensure that Nox activation occurs only where needed and that the H_2O_2 signal is terminated in a timely fashion. Recent work on cells stimulated with TNF- α suggests that Nox proteins are assembled in specific subcellular compartments within membranes such as lipid rafts (10). Localized Nox assembly also occurs at focal complexes, points of contact between a moving cell and the extracellular matrix, in response to migratory stimuli (11). The relevant oxidation targets that are presumably enriched in these microenvironments remain to be identified.

Despite the increasingly sophisticated molecular descriptions of H_2O_2 action, disturbingly little is understood about how H_2O_2 is actually delivered to the cytosol. The classical neutrophil studies demonstrate that Nox releases H_2O_2 into the phagosome, which is topologically equivalent to the extracellular space. How, then, does H_2O_2 modulate intracellular signaling? In one scenario, Nox situated at the plasma membrane releases H_2O_2 into the extracellular space as an autocrine factor to be imported into the cell. Alternatively, Nox proteins assembled at organelle membranes discharge H_2O_2 into the luminal space. For example, binding of IL-1 to

its receptor in the plasma membrane triggers Rac-mediated Nox association with the IL-1 receptor and endocytosis (internalization) of the receptor complex (12). This results in superoxide production and conversion into H_2O_2 in the lumen of the endosome. In addition, Nox isoforms and their regulatory subunits have been detected in other cell organelles including the endoplasmic reticulum and nucleus.

Regardless of whether the Nox complex is activated at the cell surface or within an organelle, the resultant H_2O_2 must traverse the lipid bilayer to access the cytosol, where most if not all of its target proteins exist. Although H_2O_2 is believed to diffuse freely across membranes, recent studies indicate that some membranes are poorly permeable to H_2O_2 . Instead, H_2O_2 transport might be regulated by changes in membrane lipid composition or by aquaporins (13), which are diffusion-facilitating channel proteins for noncharged solutes such as water.

The current picture of H_2O_2 -based redox regulation of signaling processes is rapidly expanding beyond those issues focused on here. The development of a sensitive and spe-

cific probe for H_2O_2 that allows quantitative and dynamic assessment in live cells, conspicuously lacking in studies to date, will be a great boon for the study of this misunderstood and maligned molecule.

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MATERIALS SCIENCE

Seeking Room-Temperature Ferromagnetic Semiconductors

Koji Ando

Microelectronic circuits that retain their logic state when the power is off would permit entirely new kinds of computers. Ferromagnetic semiconductors might make this technology possible.

Nonvolatile digital circuits that retain their logic states even when their power sources are rapidly switched on and off would make possible a new type of computer. Although appearing to operate normally, these devices would actually be turned off most of the time, potentially changing the way we use digital devices. Such devices would allow, for example, year-long operation of mobile computers, an enormous number of tiny computers embedded all around us to help our daily lives, and ultrahigh-density integrated circuits free from heat generation problems. To make this dream a reality, nonvolatile transistors are needed, but unfortunately this technology is nonexistent. Because transistors are composed of semiconductor materials, the ideal way to make nonvolatile transistors would be to use semiconductor materials that are intrinsically nonvolatile.

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Among several physical phenomena that produce nonvolatility, the most enticing is that of ferromagnetic hysteresis. In this effect, the material retains its magnetic state until reversed by a suitable magnetic field. Ferromagnetism has been verified to offer high-speed, unlimited magnetization reversal, so it is perfect for transistor applications. However, the ferromagnetic materials used in digital devices such as hard disks and magnetic random access memory chips—iron, cobalt, and nickel and their alloys—are not semiconductor materials. Hence, there is a continuing search for semiconductor materials that display ferromagnetic properties.

By replacing some of the positive ions of the parent nonmagnetic semiconductors by magnetic ions, one can make ferromagnetic semiconductors such as (In,Mn)As and (Ga,Mn)As (1). But their ferromagnetic Curie temperatures (T_c)—the temperature at which the ferromagnetism disappears—are 61 K (2) and 173 K (3), respectively, much lower than room temperature. In 2000, Dietl et al. (4) used a simple theory to estimate the T_c of

ferromagnetic semiconductors, and they predicted that room-temperature ferromagnetic semiconductors might be created by substituting manganese ions in wide-band gap semiconductors such as GaN and ZnO. Reports of GaN- and ZnO-based room-temperature ferromagnetic semiconductors (5, 6) soon followed. A Curie temperature as high as 940 K was reported for GaN with less than 10% manganese (5). Before long, reports began appearing of room-temperature ferromagnetic semiconductors extended to materials based on other useful oxide insulators such as TiO_2 (7). Eventually there appeared a report of room-temperature ferromagnetism of pure HfO_2 (8), which contains no magnetic ions at

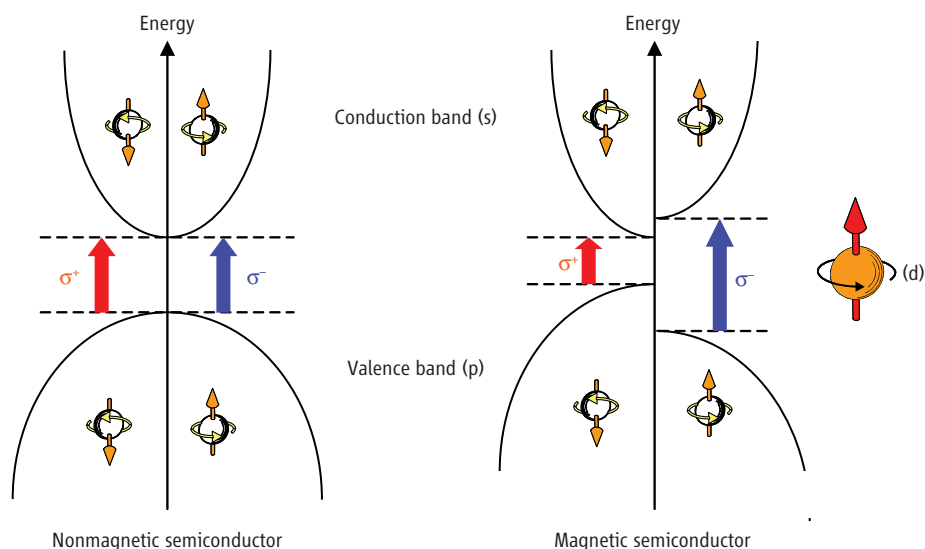
ductor" is typically only 10^{-5} emu. Still, this level of weak magnetization can be easily detected by extremely high-sensitivity SQUIDs (superconducting quantum interference devices). However, careful attention should be paid to the fact that even tiny amounts of iron—as little as 1 part per 2000 of the typical sample volume used in SQUID measurements—can generate these kinds of magnetic signals. A recent report (13) cautioned that nonmagnetic HfO_2 thin films generate clear, ferromagnetic signals after contact with stainless steel tweezers. Because new, unexpected ferromagnetic materials can be synthesized in the nonequilibrium growth method, the possible presence of very small amounts of

one can control the magnetization by the electrical field (14) or control the semiconductor optical characteristics by the magnetic field (15), for example. Because of the s, p-d exchange interaction, the energies of the s and p electrons in a magnetic semiconductor become dependent on their spin state [up or down (see the figure)]. Therefore, confirmation of a spin-polarized semiconductor band is the litmus test of the existence of a magnetic semiconductor.

As a result of the quantum mechanical selection rules for optical absorption, the spin polarization of a semiconductor band is directly connected with the appearance of magnetic circular dichroism (MCD) (15). MCD is an effect in which clockwise-polarized and counterclockwise-polarized light are absorbed differently. The important point here is that, whereas all magnetic materials can produce an MCD signal, a magnetic semiconductor should not only have a strong MCD signal but should also display an MCD spectral shape that reflects the band structure of the parent semiconductor (15). If the MCD spectral shape is different from what is expected, it is possible that the detected MCD signal is being produced by a magnetic material other than the expected magnetic semiconductor. When the magnetic field dependence of the MCD signal of a magnetic semiconductor behaves ferromagnetically, we can conclude that we have a ferromagnetic semiconductor.

Up to now, studies of the spin-polarized semiconductor band structures of materials claimed to be "ferromagnetic semiconductors" have been limited despite their importance. In the cases of GaN:Mn, GaAs:Cr, and ZnO:Ni—all of which produced ferromagnetic SQUID signals—no magnetic MCD signals were observed (16). It is very likely that some material other than a magnetic semiconductor was responsible for the observed ferromagnetic SQUID signal. The MCD spectral shape displayed by a ferromagnetic ZnO:Co was very different from that of paramagnetic (Zn,Co)O (16). In the case of $\text{TiO}_2\cdot\text{Co}$, no clear correspondence between the shape of the ferromagnetic MCD spectra (17) and the expected band structure has been established. On the other hand, MCD spectral analysis has verified that (In,Mn)As (18), (Ga,Mn)As (19), and (Zn,Cr)Te (20) are intrinsic ferromagnetic semiconductors.

To make one's way in a wilderness, a compass is necessary. In the quest for ferromagnetic semiconductors, that compass is MCD analysis and theoretical materials design. Recently, the number of experimental MCD studies has been increasing, but hardly any theoretical work has been done on interpreting the spectral shapes in MCD. On the other hand, there have been substantial improvements in theories for predicting the T_c of ferromagnetic semiconductors (21, 22). It seems that the wide-band gap semiconductors do not necessarily have an advantage in achieving high T_c . An alternative would be to look more



Magnetism in semiconductors. (Left) In normal, nonmagnetic semiconductors, electronic energy does not depend on the spin direction. It is not possible to distinguish between spin-up and spin-down electrons. (Right) In magnetic semiconductors, the d electrons of magnetic ions influence the s and p electrons, and the conduction band and valence band are split depending on the spin direction (Zeeman splitting). This spin-polarized semiconductor band structure alters the absorption of clockwise-polarized (σ^+) and counterclockwise-polarized (σ^-) light (the MCD effect). For this reason, a magnetic semiconductor should display an MCD spectrum that reflects the band structure of the parent semiconductor.

all. In the physics world it was long held that ferromagnetism at room temperature could only be achieved with materials containing very high concentrations of magnetic ions, so these reports came as a big surprise.

Are we close to realizing the dream of non-volatile transistors? Half a decade has already passed since the first report of the high- T_c ferromagnetic semiconductor, but debate on the nature of the observed ferromagnetic signals still continues to rage (9–12). Now that the excitement has passed, efforts are increasingly shifting to the task of thinking calmly about ways to evaluate ferromagnetic semiconductors.

The concentration of magnetic ions that can be introduced into a parent semiconductor is at most 10%, even with the use of a nonequilibrium film growth method. For this reason, the magnetization displayed by thin-film specimens of what is claimed to be a "ferromagnetic semicon-

ductor" is typically only 10^{-5} emu. Still, this level of weak magnetization can be easily detected by extremely high-sensitivity SQUIDs (superconducting quantum interference devices). However, careful attention should be paid to the fact that even tiny amounts of iron—as little as 1 part per 2000 of the typical sample volume used in SQUID measurements—can generate these kinds of magnetic signals. A recent report (13) cautioned that nonmagnetic HfO_2 thin films generate clear, ferromagnetic signals after contact with stainless steel tweezers. Because new, unexpected ferromagnetic materials can be synthesized in the nonequilibrium growth method, the possible presence of very small amounts of

an impurity phase is a critical problem that cannot be avoided in research on ferromagnetic semiconductors. Crystallographic evaluation methods, such as x-ray diffraction and transmission electron microscopy, are often used in claims of the absence of impurities, but their detection sensitivity is extremely low relative to that of SQUID, and so they cannot be taken to provide conclusive evidence. To clear up this confusion, it is useful to consider the essential character of a magnetic semiconductor. If magnetic properties and semiconductor properties existed independently of each other, magnetic semiconductors would have absolutely no value. It is the mutual interaction between magnetic properties (supported by the d electrons of the magnetic ions) and the semiconductor properties (supported by the s and p electrons) that is the essence of a magnetic semiconductor. With this s, p-d exchange interaction,

closely at materials having a longer exchange interaction distance between magnetic ions and a higher concentration of magnetic ions. All of the (In,Mn)As, (Ga,Mn)As, and (Zn,Cr)Te materials belong to this category. Recently, the T_c of (Ga,Mn)As has been increasing from an initial value of 110 K (1) up to 173 K (3) by improving the growth procedures, and that of (Zn,Cr)Te has reached 300 K (20).

Many different characteristics are considered when searching for the ferromagnetic semiconductors needed for nonvolatile transistors, including high T_c , high carrier mobility, and intrinsic insulation conditions for carrier doping. To find our goal, it seems we must continue wandering, with the compass of MCD in one hand.

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CHEMISTRY

Targeting Specific C-H Bonds for Oxidation

Rubén Mas-Ballesté and Lawrence Que Jr.

A main challenge in chemistry is the design of catalysts that can carry out a desired chemical transformation only upon chosen specific targets. These specific targets can be one molecule in a mixture of chemical substances or—perhaps even more difficult—one specific site in a molecule with several reactive sites. On page 1941 of this issue, Das *et al.* (1) report an innovative approach to the design of a bio-inspired catalyst for the highly selective oxidation of CH bonds.

Nature uses different strategies to achieve selective oxidations. For instance, the enzyme methane monooxygenase (MMO) selectively oxidizes methane to methanol, even in the presence of other hydrocarbons with weaker C-H bonds (2). This specificity arises from a sieve-like phenomenon that hampers the access of molecules bigger than methane to the active site of the enzyme (see the figure, left panel) (3, 4). Besides size (and shape), enzymes can confer specificity by means of noncovalent interactions that orient the substrate in a particular manner (see the figure, right panel). Fatty acid desaturases use a functional group within the enzyme active site to anchor the carboxylate end of a fatty acid and achieve dehydrogenation at two specific carbon atoms (5).

Finding inspiration in nature, chemists have designed synthetic systems to emulate the specificity of biological oxidations. An initial approach reported by Breslow used steroid sub-

strates with a dangling, covalently attached photosensitizing group to carry out light-activated remote oxidations at particular sites of the substrate (6). In the same vein, Stuk *et al.* appended a substrate to a manganese catalyst to achieve selective oxidation at specific sites of the substrate (7). These examples demonstrated the possibility of selective oxidations in a biomimetic system, but the covalent binding of substrate to the oxidant constrained the chemistry to a maximum of a single turnover, such that only stoichiometric (rather than catalytic) oxidation could be achieved.

Subsequent efforts have incorporated into the catalyst design moieties that can recognize substrates through noncovalent interactions. An approach extensively explored in the past used a metalloporphyrin as the catalytic center, with modifications at its periphery to confer substrate selectivity.

For example, Bhyrappa *et al.* attached dendrimers to the metalloporphyrin to favor the oxidation of less sterically hindered linear alkanes over cyclic alkanes (8); this approach emulates the size-recognition strategy of MMO. Mimicking the anchoring strategy of fatty acid desaturases, Groves and Neumann (9) embedded a metallo-

Enzymes use two main strategies—size/shape selectivity and substrate orientation—to achieve selective oxidation. Chemists have now developed a simple catalyst that mimics substrate orientation.



Size/shape recognition versus substrate orientation. Schematic representation of the two main strategies used by enzymes to achieve selectivity.

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