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A diamond ring sparks a paradigm shift

Trapping four silicon atoms into a short-lived, diamond-shaped complex gives surprising insights into aromaticity

The sweet smell of benzene gave birth to the term 'aromatic' molecules, but it is the chemical bonds within these compounds that have fascinated researchers for almost 200 years. Encasing alternating double- and single-bonded carbon atoms inside a flat ring allows so-called 'pi'-electrons to delocalize and move around the cyclic framework. And thanks to the curious rules of quantum mechanics, this pi-electron sharing has radical consequences for differently sized rings. While aromaticity makes hexagonal systems like benzene exceptionally stable, 'anti'-aromaticity makes four-membered rings like cyclobutadiene show opposite tendencies—the delocalized electrons try to rip the molecule apart.

To this day, understandings of anti-aromatic molecules remain controversial. Katsunori Suzuki, Tsukasa Matsuo, Kohei Tamao and colleagues from the RIKEN Advanced Science Institute in Wako created their own controversy when they attempted to gain a new perspective on these compounds by synthesizing the first analog of cyclobutadiene made from silicon (Si) atoms. After racing against time to characterize the unstable specimen, the team stared at their analytical results in disbelief. It appeared the four silicon atoms had arranged into a flat planar rhomboid (Fig. 1)—a diamond-shaped ring—that had been predicted theoretically, but never observed in reality.

"When we found the diamond-like Si_4 structure, we were very surprised," says Suzuki. "What is this? Why is it rhombic?" The team's answers to these questions, published recently in *Science*[1], shed light on how atoms rearrange to avoid pi-electron repulsions, and set the stage for new explorations of pi-conjugated silicon materials.

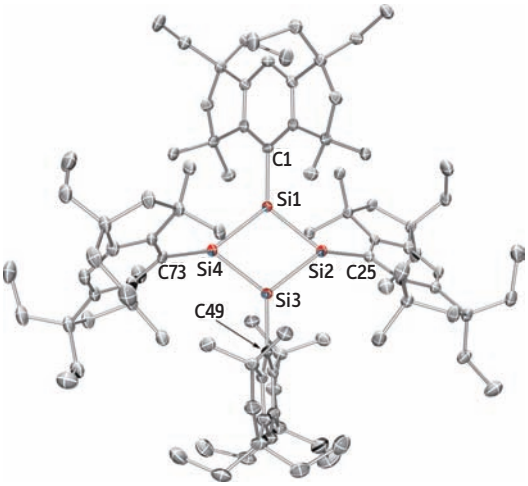


Figure 1: The x-ray molecular structure of a diamond-shaped silicon analog of cyclobutadiene (red atoms) surrounded by Rind protecting groups.

Putting the pieces together

Isolating cyclobutadiene-based compounds is a tricky affair that typically requires extremely cold temperatures, not far from absolute zero, to trap the short-lived substances. Producing a silicon version of cyclobutadiene is especially daunting. The pi-electrons in silicon double bonds are held less tightly than in carbon units, making this species even more reactive.

Fortunately, the researchers recently developed molecules known as substituted s-hydrindacenes, or 'Rind' groups for short, that stabilize silicon double bonds in ways never seen before. With an inner skeleton of three fused hydrocarbon rings surrounded by finger-like alkyl chains, Rind groups can fit together like puzzle pieces and lock silicon double bonds into planar crystals with unique light-emitting capabilities[2].

"In sharp contrast to previously developed protecting groups, our Rind groups are size-controllable, easy to prepare, and have tunable solvent compatibility," says Matsuo. "In light of our previous observations, we anticipated that Rind groups could stabilize a planar cyclic pi-conjugated silicon system."

By using a lithium reagent to add electrons to a Rind-substituted silicon precursor called (EMind)$SiBr_3$, and employing meticulous care to exclude any air or moisture from the reaction, Suzuki and colleagues successfully isolated a small amount of pure orange Si_4(EMind)$_4$ crystals. X-ray analysis revealed an unprecedented Si_4 planar rhomboid, imprisoned by four Rind groups meshed together like a molecular gear (Fig. 2).

Observing the shift

Ideally, cyclobutadiene should appear as a flat square, with carbon atoms on each corner. However, theoretical and experimental studies have shown that cyclobutadiene breaks its molecular symmetry, through a process known as

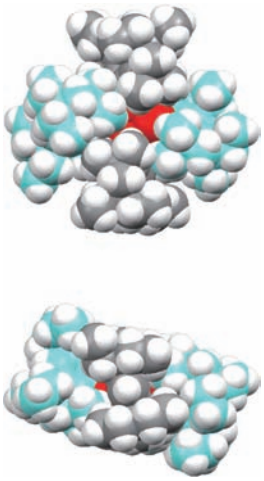


Figure 2: Space-filling models show that the Rind groups (blue, grey, and white spheres) fit together in a gear-like arrangement.

a covalent Jahn-Teller distortion, and reshapes itself into a rectangle to minimize anti-aromatic repulsions. To determine why the Si_4 analog crystallized into a diamond arrangement, the researchers turned to nuclear magnetic resonance (NMR) spectroscopy, a highly sensitive technique for monitoring molecular conformational changes.

Running NMR experiments, however, proved difficult because $Si_4(EMind)_4$ is thermally unstable, with a half life of only three days at 25 °C. Nevertheless, the team persevered and observed that, in a room temperature solution, the diamond-like Si_4 skeleton was actually shifting between two longitudinal and lateral rhombic isomers at an extremely swift speed. This geometric conversion, which was facilitated by the gear-like Rind groups, persisted to low temperatures until crystallization occurred.

Squaring off against aromaticity

Next, the team employed sophisticated theoretical calculations to gain an electronic understanding of their new structure. These computations indicated that several isomers, including rhombic, rectangular, and square structures, could result from a $Si_4(Rind)_4$ complex. In agreement with the experiments, however, the researchers saw that planar rhomboid was the most stable isomer energetically.

While silicon double bonds usually share their pi-electrons equally, the researchers found that the rhombic shape arises from a Jahn-Teller distortion that polarizes electronic charges. By separating the unstable pi-electrons into alternating positive and negative charges on each corner of the silicon diamond, the molecule can convert from an anti-aromatic to a non-aromatic state. This remarkable charge-separation was confirmed by the appearance of two peaks in solid-state silicon NMR measurement—clear evidence that identical silicon atoms experienced two separate electronic environments.

"Synthesizing a rhombic-shaped cyclobutadiene is quite difficult, because the carbon–carbon pi-bond is very strong," explains Matsuo. But since silicon double bonds are weaker and therefore more flexible, they can stretch apart to generate the diamond-like arrangement. "The exquisite geometric effects of Rind groups and the elemental character of silicon atoms make the rhomboid analog possible," he says.

These findings not only reveal some fundamental differences between silicon and carbon atoms, but also how they can be overcome. For instance, by modifying the bulkiness of the Rind ligands, the team is confident that a hexagonal benzene-like silicon compound could soon materialize.

According to Matsuo, this diamond-shaped ring also provides a starting point for new functional materials based on pi-conjugated silicon. "One of our target materials is a polyacetylene–silicon analog,"—a compound with potent light-emitting and electron-conducting capabilities—"and we now have a chance to make it with the power of Rind ligands," he says. ■

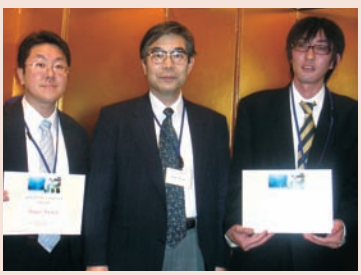
1. Suzuki, K., Matsuo, T., Hashizume, D., Fueno, H., Tanaka, K. & Tamao, K. A planar rhombic charge-separated tetrasilacyclobutadiene. *Science* **331**, 1306–1309 (2011).
2. Kobayashi, M., Matsuo, T., Fukunaga, T., Hashizume, D., Fueno, H., Tanaka, K. & Tamao, K. Air-stable, room-temperature emissive disilenes with *π*-extended aromatic groups. *Journal of the American Chemical Society* **132**, 15162–15163 (2010).

About the researchers

Kohei Tamao received his Dr of Eng. from Kyoto University under the direction of Prof. Makoto Kumada in 1971 after which he rose steadily through the ranks of the same institution becoming Full Professor in 1993. In 2005, he moved to RIKEN as Director of the Frontier Research System and is currently Director of the RIKEN Advanced Science Institute and a unit leader of the Functional Elemento-Organic Chemistry Unit at RIKEN. He received the American Chemical Society Frederic Stanley Kipping Award in 2002. His current research interests are organosilicon and related elemento-organic chemistry.

Tsukasa Matsuo graduated from Tohoku University with BSc (1994) and MSc (1996) degrees under the direction of Prof. Hideki Sakurai and Prof. Mitsuo Kira. He received his PhD (1999), supervised by Prof. Akira Sekiguchi, from the University of Tsukuba and became Assistant Professor at the Tsukuba Advanced Research Alliance in 1999. In 2001 he moved to the Institute for Molecular Science as Assistant Professor and in 2007 was appointed Deputy Unit Leader at RIKEN. His research interests are the structures, reactivities and physical properties of elementoorganic compounds.

Katsunori Suzuki graduated from the Faculty of Science, Tohoku University, with a BSc in 2002. He subsequently took his MSc (2004) and PhD (2007) degrees under the direction of Prof. Mitsuo Kira from the same university. In 2007, he moved to the Functional Elemento-Organic Chemistry Unit at RIKEN as a Research Scientist. His current research interests include synthetic approaches to cyclic π-conjugated aromatic/antiaromatic systems containing heavy group 14 elements, and the development of synthetic methodologies for π-conjugated silicon-silicon unsaturated frameworks for functional elemento-organic materials.



Tsukasa Matsuo (left), Kohei Tamao (center) and Katsunori Suzuki (right).

New tool for proton spin

Measurements of fundamental particles provide a sensitive method to probe the spin composition of protons

How the particles that constitute a proton give rise to is to its rotation, or 'spin', is an intriguing open question of contemporary particle physics. A technique that could provide some answers has been developed using the world's only polarized proton–proton collider. The work was published by the PHENIX Collaboration, which includes researchers from the RIKEN Brookhaven National Laboratory (BNL) Research Center in Upton, USA[1].

Nowadays, the most popular theory for subatomic particles is the Standard Model: a menagerie of fundamental particles including quarks, which come in six different types or flavors, and four fundamental forces. These forces include the 'weak' force that is mediated by particles called *W* bosons, which are created, albeit only briefly, when protons collide. The researchers discovered that these *W* bosons are a sensitive probe of the quarks that make up a proton.

To investigate proton spin, the PHENIX team fired two beams of high-energy protons at one another using the Relativistic Heavy Ion Collider at BNL. "Most of the interactions that take place when the protons collide are 'strong' interactions," explains Kensuke Okada from RIKEN BNL Research Center Experimental Group. "But our experiment was sensitive enough to detect 'weak' interactions too." The researchers identified two such weak reactions: detection of an electron indicated the decay of a negatively charged *W* boson (Fig. 1); and detection of a positron—a positively charged electron—indicated the decay of a positively charged *W* boson. By counting the number of resulting electrons and positrons, the researchers could calculate the probability of each type of interaction.

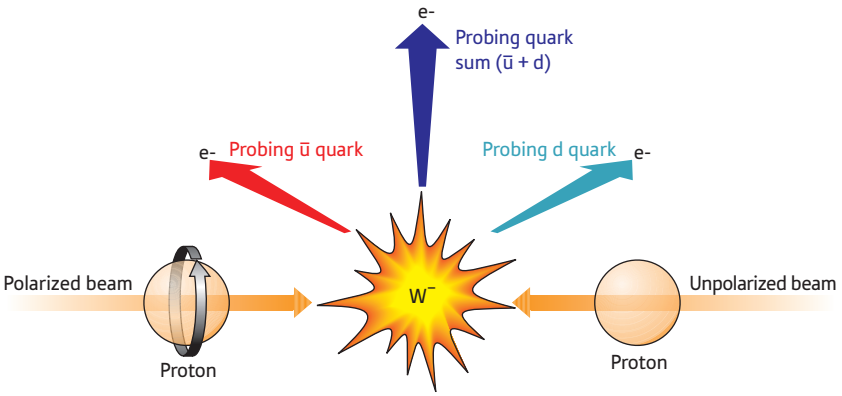


Image courtesy of Brookhaven National Laboratory

Figure 1: When two beams of protons collide (center), the electrons (e^-) produced by the W- boson-mediated interactions provide information about the different 'flavor' quarks of a proton, such as the anti-up (ū) quark and the down (d) quark.

The PHENIX team then performed two experiments simultaneously. In one, they made protons spin parallel to the axis of the beam; and in the other, they made them spin in the opposite direction. The difference in the rate of weak interactions in each experiment provided information about the spin direction of the quarks in the proton. "The asymmetry of the production rates is connected to the probability that the spin of a particular flavor of quark is aligned to the proton spin direction," says Okada. This approach could soon be extended to identify the spin contribution of all the proton's quarks.

Next the team hopes to improve the sensitivity of the experiment. "This time, we only caught electrons and positrons that emerged at 90 degrees to the beam axis," explains Okada. "We are preparing new detectors to extend this detection region for a more complete analysis." ■

1. Adare, A., Afanasiev, S., Aidala, C., Ajitanand, N.N., Akiba, Y., Akimoto, R., Alexander, J., Al-Ta'ani, H., Andrews, K.R., Angerami, A. *et al.* Cross section and parity-violating spin asymmetries of $W^{\pm}$ boson production in polarized $p + p$ collisions at $\sqrt{s}$ = 500 GeV. *Physical Review Letters* **106**, 062001 (2011).

Sugar synthesis hits the sweet spot

Novel tuberculosis treatments could result from success in artificially synthesizing sugar-based structures of the bacterium's cell wall

A new strategy for synthesizing the kind of complex molecules that certain bacteria use to build their protective cell walls has been developed by Akihiro Ishiwata and Yukishige Ito from the RIKEN Advanced Science Institute in Wako[1]. The strategy applies to *Mycobacterium tuberculosis*, the causative agent of tuberculosis (TB), so it could lead to much-needed new medicines to combat the spread of multi-drug-resistant strains of the pathogen.

Disrupting the formation of the cell wall of *M. tuberculosis* is already a proven strategy for treating TB, with several of the current front-line drugs working in this way. However, the cell wall skeleton is a complex, highly branched structure, and its biosynthesis is not yet fully understood.

According to Ito, the compound he and Ishiwata made—a sugar-based structure known as the arabinan motif (Araf_{22}) (Fig.1)—should be a useful biological probe, helping to unravel cell wall biosynthesis. Perhaps more importantly, however, the success of their strategy suggests that larger, more complex cell wall components could be made in the same way.

Sugar-based compounds are notoriously difficult to make. Sugars are bristling with reactive alcohol groups, so molecules made from more than 20 sugar units pose a significant synthetic challenge. Nevertheless, Ishiwata and Ito succeeded in clipping together the branching chain of 22 sugar units needed to make Araf_{22}.

Their strategy involved synthesizing small sub-structures of the mycobacterial cell wall skeleton and building from there. To make the compound, they conceptually broke down Araf_{22}'s structure into several simpler fragments, chemically synthesized those fragments, and then clipped them together to make Araf_{22}. This aspect of the strategy has been applied before, but Ishiwata and Ito built the fragments such that they clipped together at linear rather than branching points in their structure.

The researchers' strategy makes the individual fragments more difficult to build, but it makes the coupling process much more efficient. Crucially, that means the strategy should work just as well as a way to make even larger and more complex components of the cell wall.

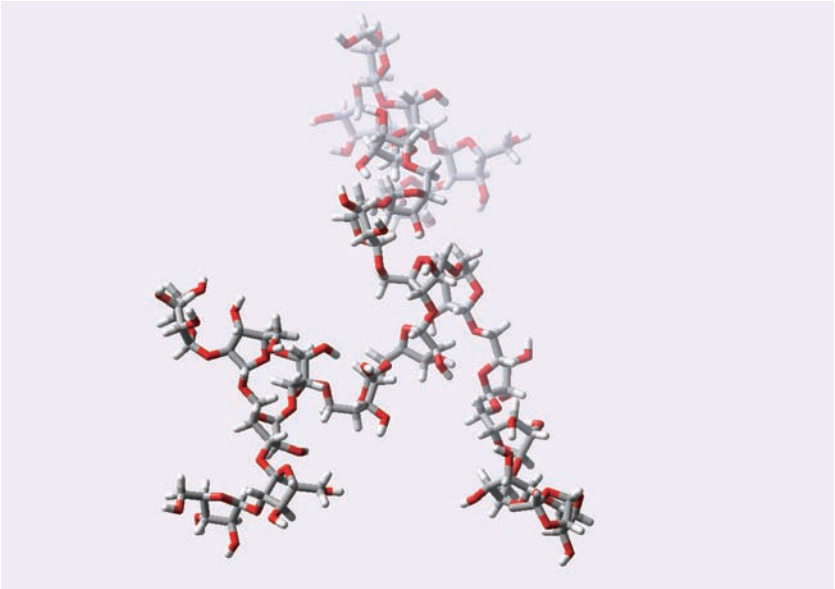


Figure 1: The compound Araf_{22} is a key component of the tuberculosis bacterium's protective cell wall.

"One of the main points of this work is for us to show the way to construct the more complex compounds," says Ishiwata. "We are now planning to synthesize more complex but structurally reliable glycans of cell wall skeletons for biological studies." However, such compounds could even prove to be useful drugs in themselves, if they are able to disrupt the cellular machinery responsible for mycobacterial cell wall biosynthesis. ■

1. Ishiwata A. & Ito Y. Synthesis of docosasaccharide arabinan motif of mycobacterial cell wall. *Journal of the American Chemical Society* **133**, 2275–2291 (2011).

Tiny probes for living cells

Revealing the inner workings of cells takes a step forward using a newly developed Raman microscopy technique

Living cells are virtuosos of chemistry. At any one time, countless chemical reactions are taking place within any given cell. For researchers trying to understand how cells function, unraveling this complex chemistry is an ongoing challenge. The process, however, could soon become a little more straightforward. Mikiko Sodeoka and colleagues at the RIKEN Advanced Science Institute at Wako, in collaboration with a team led by Katsumasa Fujita and Satoshi Kawata at Osaka University, have demonstrated how to tag molecules of interest in a way that promises to be much more versatile than current methods[1].

Traditionally, researchers looking to study the role of a particular small molecule within a cell have tagged the molecule with a fluorescent marker. Using a fluorescence microscope, the tagged substance can be followed as it moves around the cell. However, fluorescent tags are bulky, and so can disrupt the molecule's normal cellular interactions. To get around this problem, molecules can sometimes be tagged after reaching their destination within the cell, but this technique only works in a limited number of cases.

Sodeoka and her team have now shown that a simple chemical substituent called an alkyne, which consists of just two carbon atoms joined together by a triple bond, can replace the bulky fluorescent tag. Their imaging technique relies on the fact that alkynes scatter a particular wavelength of light when irradiated with a laser—a process known as Raman scattering—which can be detected using a Raman microscope. No other cellular components scatter light at this wavelength, giving a clear picture of the molecule within the cell.

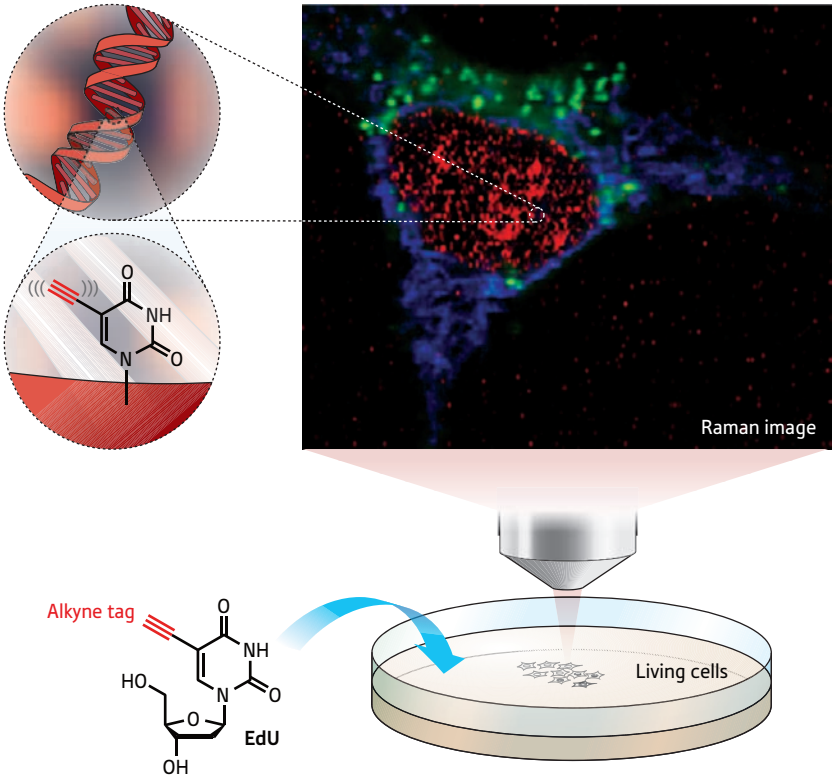


Figure 1: Raman imaging reveals that a molecule known as EdU, colored red in this image, gathers in the cell nucleus. Cytochrome c and lipid are colored in blue and green respectively.

To demonstrate the potential of their technique, the researchers used an alkyne-tagged component of DNA known as EdU. They then used a Raman microscope developed by Fujita and his team to follow a group of replicating cells as they incorporated EdU into their DNA (Fig. 1). The technique took some work to optimize, says Sodeoka. "We were very happy when we could finally see the time-series pictures of the incorporation of EdU to DNA."

The EdU experiment is just a proof of principle, Sodeoka adds. "At this point, the sensitivity of the alkyne tag using Raman microscopy is lower than fluorescent imaging," she says. To improve the sensitivity, the team is working to optimize the attachment of the alkyne tag, and also to improve the Raman microscope itself. "If the sensitivity problem is solved, Raman imaging using alkynes as a small tag could become a powerful tool," she concludes. ■

1. Yamakoshi, H., Dodo, K., Okada, M., Ando, J., Palonpon, A., Fujita, K., Kawata, S. & Sodeoka, M. Imaging of EdU, an alkyne-tagged cell proliferation probe, by Raman microscopy. *Journal of the American Chemical Society* **133**, 6102–6105 (2011).

The new kid on the block

The first cubic-shaped complexes of rare-earth metals and organic carbenes present chemists with a unique structure motif for carbene chemistry study

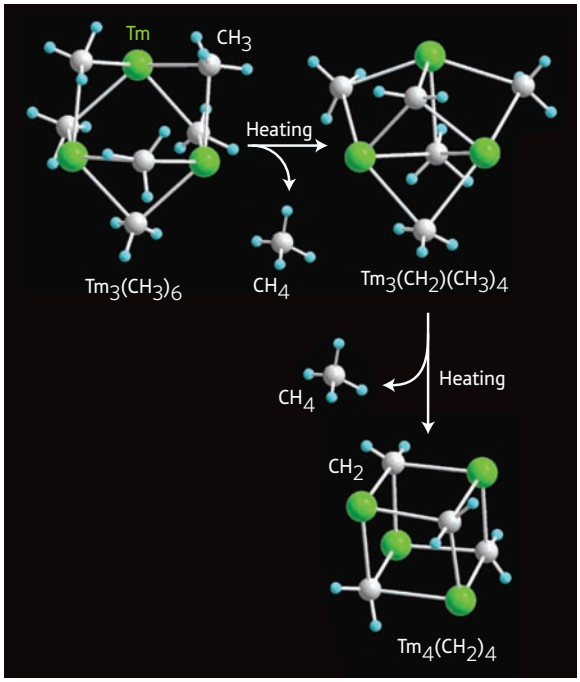


Figure 1: Eliminating methane (CH_4) molecules from polyhedral thulium–methyl crystals ($Tm_3(CH_3)_6$) (top left and right) produces a new cube-shaped rare earth–carbene complex (bottom) with intriguing chemical behavior.

In synthetic chemistry, 'carbene' species—compounds bearing a carbon atom with two unpaired electrons—have a ferocious reputation. Left uncontrolled, they will react with almost any molecule they meet. But by harnessing this vigor with transition metals, chemists can turn carbenes into powerful chemical transformation reagents. Now, Zhaomin Hou and colleagues from the RIKEN Advanced Science Institute in Wako report a new class of compounds that contain multiple carbene units in one extraordinary structure: a cube-shaped molecule stabilized by ligand-protected rare-earth metals[1].

Rare-earth metals hold more electrons within their atomic radii than most other elements, making them essential in high-tech devices such as superconductors and hybrid vehicle batteries. Combining these metals with carbenes could lead to breakthrough procedures in synthetic chemistry. However, rare-earth metal–carbene complexes are usually unstable because the bonds they form are lopsided electronically, and therefore extremely reactive.

To overcome this problem, Hou and colleagues turned to a bulky ligand, based on a five-membered aromatic ring called cyclopentadiene (Cp′), which can trap rare-earth metal–carbene complexes into ordered solids. By mixing Cp′-protected lutetium (Lu) and thulium (Tm) rare-earth metal precursors with a carbon-donating aluminum reagent, they isolated a unique set of hybrid polyhedral crystals. X-ray analysis showed that these materials had a core of three rare-earth metals interconnected by six bridging methyl (CH_3) groups.

An unexpected twist occurred when the researchers tested the thermal stability of the Lu– and Tm–methyl complexes. Heating to 90 °C caused the methyl groups to lose one of their hydrogen atoms, transforming them into carbenes. Then, after the elimination of a methane molecule, the crystal structure rearranged into a perfectly shaped cube featuring four Cp′-protected rare-earth metals and four carbene units (Fig. 1).

The team's experiments revealed that the cubes spontaneously turned benzene–carbonyl molecules into alkenes by swapping their carbene groups for oxygen atoms, yielding a new oxygenated cube in the process. The researchers are now examining the reactivity of the cubes toward other molecules and plan to fine-tune the structure and reactivity of carbene compounds by investigating differently sized rare-earth metals together with different supporting ligands.

"This work demonstrates for the first time that methane can be eliminated rather easily from rare earth complexes containing methyl groups, affording structurally stable but highly reactive multi-carbene species," says Hou. "Further studies along this line should open up a completely new frontier in rare-earth carbene chemistry." ■

1. Zhang, W.-X., Wang, Z., Nishiura, M., Xi, Z. & Hou, Z. $Ln_4(CH_2)_4$ cubane-type rare-earth methylidene complexes consisting of "$(C_5Me_4SiMe_3)LnCH_2$" units (Ln = Tm, Lu). *Journal of the American Chemical Society* **133**, 5712–5715 (2011).

Unraveling plant reactions to injury

Identification of a key compound that regulates plant responses to wounding could provide benefits on three fronts

Better understanding of plant defense systems, and the potential to generate stress-tolerant plants and even new malaria drugs, may all stem from the documentation of a molecular mechanism that plays a significant role in the response of plants to physical injuries, such as cuts. A team of agricultural researchers in Japan, led by Fuminori Takahashi of the RIKEN Plant Science Center in Tsukuba, found that the key protein in the complex mechanism is MPK8, which is fully activated by two signaling pathways working in concert[1].

The researchers showed that MPK8 is activated while the wounded plant mounts an initial emergency response to an injury. Around the fresh wound, the plant produces reactive oxygen species (ROS), such as hydrogen peroxide. These highly toxic compounds kill any pathogens that could access internal tissues via the wound site. However, since ROS can also harm plant tissue they require close regulation. Takahashi and his team—from RIKEN and three Japanese universities—found that the regulator is MPK8.

In addition to the initial response, the injury stimulates the release of calcium ions and starts a cascade of phosphorylation or phosphate-adding compounds. The compounds involved are called mitogen-activated protein kinases (MAPKs). MPK8 is one of the MAPKs of the model plant *Arabidopsis*.

Takahashi and his colleagues used *Arabidopsis* plants to investigate how both signaling and the levels of ROS are regulated after physical injury. Using plants into which they had introduced additional copies of the *MPK8* gene, the researchers showed that MPK8 was activated under stress, particularly from physical wounding. MPK8 was strongly activated by MKK3, another MAP kinase from higher up the cascade. But it was also activated by calcium ions, specifically when they were bound to proteins called calmodulins. In addition, the researchers determined that the production of MPK8 was associated with regulation of ROS, lowering its accumulation.

A region of MPK8 known as TDY is known to interact or be phosphorylated with both MKK3 and calcium-bound calmodulins. By inhibiting each of these compounds in turn, the researchers showed that full activation of MPK8 demanded activating both of them at once, bringing the signaling pathways together. Finally, by examining the expression of genes, they found that MPK8 regulates the production of ROS by repressing the gene that stimulates their production (Fig 1).

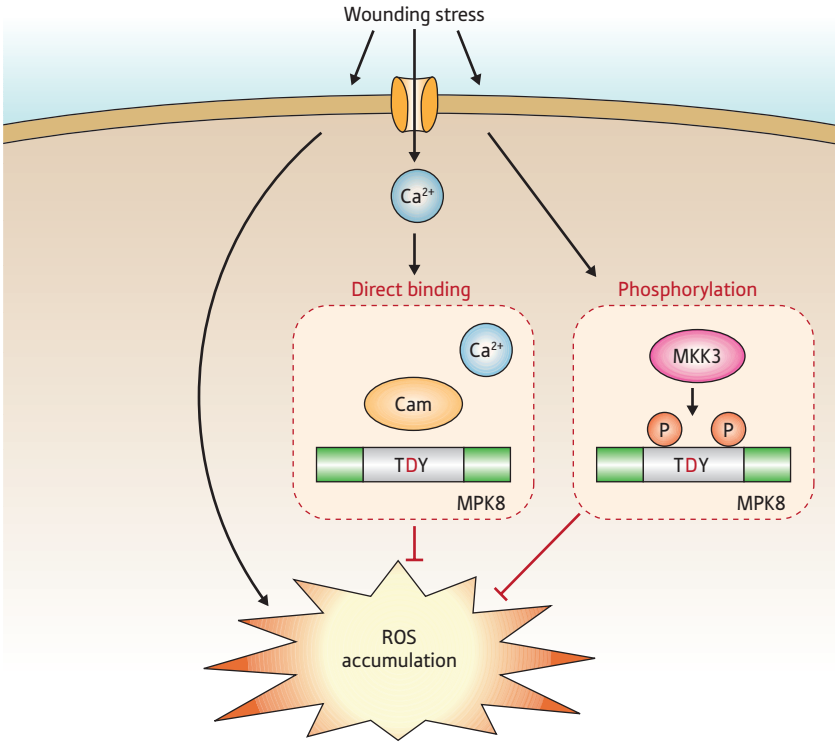


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Figure 1: After a plant is wounded, direct binding and phosphorylation, which are two responses that follow the initial emergency response, converge at MPK8 to monitor or reduce the level of ROS that protect the plant from pathogens but can damage healthy tissue.

"We think our findings might eventually lead to designing a drug treatment for malaria infection," says Takahashi, "because the *Plasmodium* parasite involved uses the same kind of MAPKs." ■

1. Takahashi, F., Mizoguchi, T., Yoshida, R., Ichimura, K. & Shinozaki, K. Calmodulin-dependent activation of MAP kinase for ROS homeostasis in *Arabidopsis*. *Molecular Cell* **41**, 649–660(2011).

Know your tomatoes

Assessing the chemical diversity of genetically modified organisms is an important first step for evaluating their safety

Genetically modified (GM) tomatoes look much the same as traditional varieties (Fig. 1). But are they? By comparing the chemical diversity of strains of GM tomatoes with a control strain and traditional reference cultivars, a research team in Japan has developed a way to distinguish between them[1].

Consumers need to be confident that GM tomatoes are safe, so initial risk assessments must show that they are 'substantially equivalent' to traditional varieties in their chemical make-up. Scientists can then focus on those chemicals, or 'metabolites', found only in particular GM varieties for toxicological testing.

As a case study, the team—led by Kazuki Saito of the RIKEN Plant Science Center in Yokohama—focused on GM tomatoes over-expressing a foreign gene encoding miraculin, a substance normally found in a tropical plant but not tomatoes. Miraculin is a glycoprotein—a protein with short carbohydrate side chains. It has the remarkable ability to make sour foods taste sweet. "Miraculin has fewer calories than sugar and has potential as a natural sweetener and flavor enhancer," Saito notes.

Metabolism refers to the processes involved in maintaining life, including the building and breakdown of proteins, nucleic acids and carbohydrates. Complex metabolic pathways involve many enzymes and the chemical constituents of cells and tissues are in constant flux.

Whereas genomics provides an overview of the genetic composition of an organism, 'metabolomics' can give a snapshot of biochemical status.

Figure 1: Genetically modified (GM) and natural cultivar tomatoes. From left to right: Moneymaker (parental control), GM (56B), GM (7C), Aichi First, Alisa Craig, M82, Micro-Tom and Rutgers.

"We applied metabolomic techniques to compare the chemical diversity of GM tomatoes to that of traditional varieties," Saito explains. Because there is currently no single technique for separating and characterizing all metabolites, the researchers used a range of metabolomic techniques to assess the chemical diversity of GM tomatoes over-expressing miraculin.

"Our multi-platform approach allowed us to identify metabolites in both types of tomato in an automated manner, and to evaluate variation between them using robust statistical methods," says Saito.

The researchers found that the ripening GM tomatoes had a reproducible metabolic signature, and that over 92% of their metabolites showed an acceptable range of variation similar to that of the traditional varieties.

"Our aim was not to show that the GM tomatoes are safe, but rather to examine the chemical diversity of GM tomatoes compared with natural variants, and to possibly narrow down the list of potentially problematic metabolites as a guide to further investigation," explains Saito.

The team believes that their multi-platform approach could be applied to any GM organism as a start to objective risk assessment. ■

1. Kusano, M., Redestig, H., Hirai, T., Oikawa, A., Matsuda, F., Fukushima, A., Arita, M., Watanabe, S., Yano, M., Hiwasa-Tanse, K., Ezura, H. & Saito, K. Covering chemical diversity of genetically-modified tomatoes using metabolomics for objective substantial equivalence assessment. *PLoS ONE* **6**, e16989 (2011).

How plants self heal

Identification a master regulator of the response of plants to injury sheds light on organ regeneration

Many animals and plants regenerate tissues or even whole organs after injury. Typically, specialized cells at the wound site revert to a 'pluripotent' state–via a process called dedifferentiation—which means they regain the ability to develop into the various cell types required for regeneration. The dedifferentiated cells rapidly divide to form a callus from which the damaged tissue or organ will regenerate. Now, a research team from the RIKEN Plant Science Center in Yokohama has identified a master regulator of the response of plants to injury[1].

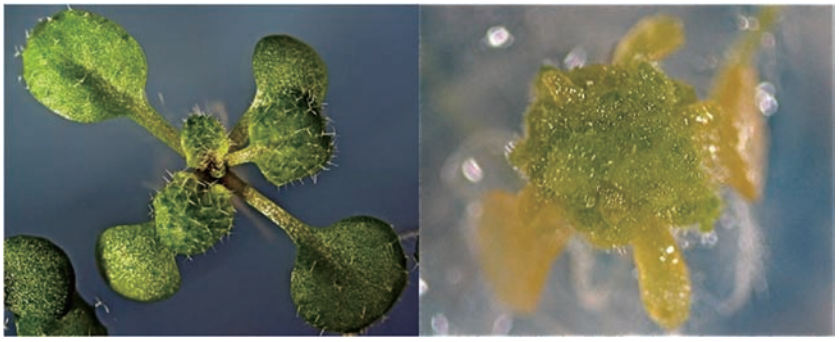

Figure 1: *Arabidopsis* plants grown without plant hormones. Compared to the wild-type plants (left) those over expressing WIND1 (right) can exhibit a range of developmental abnormalities including dedifferentiated callus-like cells masses instead of roots and shoots.

Developmental biologists have evidence that the mammalian wound response is genetically programmed, involving transcription factors—proteins that regulate gene expression. However, the precise molecular mechanisms underlying the cell dedifferentiation and redifferentiation are poorly understood for both animals and plants, explains team leader Keiko Sugimoto.

Akira Iwase, a special postdoctoral researcher in Sugimoto's laboratory, previously identified the transcription factor WIND1 that was expressed in cultured *Arabidopsis* cells but not in healthy seedlings. His findings suggested that WIND1 might be involved in the wound response. Using transgenic seedlings, Iwase along with Sugimoto and their colleagues have now demonstrated that WIND1 expression increases markedly at wound sites within hours of injury and continues throughout callus development.

Iwase, Sugimoto and colleagues further showed that *Arabidopsis* seedlings that were genetically engineered to over express WIND1 exhibited a range of developmental abnormalities (Fig. 1). They found that the most severe defects were associated with particularly high levels of WIND1 expression. These included aborted development after germination and the growth of undifferentiated callus-like cell masses at the places where roots or shoots would normally form.

In addition, the researchers found that the callus-like cell masses continued to proliferate rapidly when removed from the plant and grown in culture. This occurred even in the absence in the culture medium of auxin and cytokinin, two plant hormones long known to be involved in the normal regeneration process. Further experiments also confirmed the importance of WIND1 in callus formation *in vivo*.

The researchers then investigated the mode of action of WIND1. They found that wounding induced a cytokinin response involving increased expression of the so-called 'B-type *Arabidopsis* response regulator' (ARR). Further experiments confirmed that WIND1 acts via the ARR-dependent signaling pathway to promote cell dedifferentiation.

"Our findings clearly demonstrate that WIND1 functions as a key molecular switch triggering cell dedifferentiation in *Arabidopsis*," explains Sugimoto. "The discovery of WIND1 should allow us to establish specific role of transcriptional regulators in cell dedifferentiation." ■

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The beginnings of the brain

A single protein is sufficient to switch on the various genes that kick off the development of the embryonic nervous system

All of the tissues and organs of the body arise from one of three embryonic precursors: the ectoderm, mesoderm and endoderm. The ectoderm contributes to several tissues, including the nervous system and the skin, but some studies have suggested that development into neurons requires nothing more than the absence of specific inhibitory signals.

This phenomenon has led biologists to formulate what is called the 'neural default model'. "The simplest interpretation of the neural default model is that the neural fate is a 'left-over' choice, passively determined by the elimination of other pathways of differentiation," explains Yoshiki Sasai of the RIKEN Center for Developmental Biology in Kobe. This model fails to address the identities of the factors that actively drive neuronal development, but new findings from Sasai and colleagues have spotlighted a single protein that appears to set this process into motion[1].

His team had previously designed a culture system that promotes neural differentiation of mouse embryonic stem (mES) cells[2], and they used this technique to identify genes that are specifically switched on in these cells. They identified one intriguing candidate, *Zfp521*, which activated several other genes involved in neural development, even when the mES cells were cultured in the presence of factors that would normally curb this process (Fig. 1).

When Sasai and colleagues examined expression in developing mouse embryos, they noted that the spatial and temporal distribution of *Zfp521* activity closely mirrored known sites of neural differentiation. Likewise, early stage mouse embryos injected with mES cells in which *Zfp521* expression was abrogated largely failed to incorporate these cells into the developing nervous system. By systematically identifying the genes whose expression is disrupted in the absence of *Zfp521*, the researchers were able to determine that this gene acts as a driver for the maturation of ectodermal cells into neuroectoderm, the developmental stage that immediately precedes formation of actual neural progenitors.

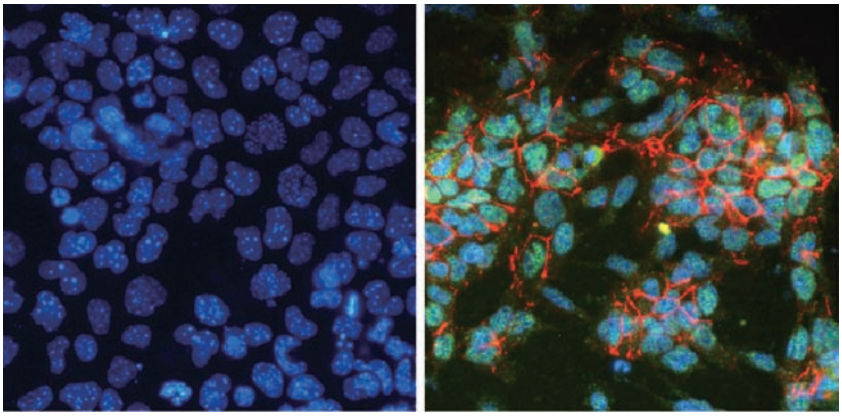

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Figure 1: mES cells cultured in serum (left) are exposed to diverse factors that generally inhibit neural development. However, forced overexpression of *Zfp521* in serum-exposed mES cells strongly induces production of Sox1 (green) and N-cadherin (red), two proteins closely associated with neural differentiation (right). Blue stain indicates cell nuclei.

"The most important message of this study is that the neural fate is acquired by an active determination process," says Sasai. Understanding how this developmental switch works could ultimately provide scientists with a powerful tool for efficiently transforming human stem cells into mature nervous tissue suitable for experimental use or even transplantation, although it remains to be determined whether human ES cells obey the exact same principles. "We have preliminary data showing a conserved essential role for *Zfp521* in both species," says Sasai, "but we need to analyze the similarities and differences in greater depth." ■

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Keeping traffic moving

An enzyme helps control the extension of cellular tendrils by regulating the delivery of supplies needed for growth

The body of the adult fruit fly is covered with hair-like bristles (Fig. 1) that act as sensory organs for detecting tactile stimuli. Each one consists of a single cell that has gradually elongated over the course of pupal development, reinforced by bundles of actin protein filaments.

The signaling protein IKKε helps to regulate this process by controlling the organization of these actin bundles, but a recent study from Shigeo Hayashi and colleagues at the RIKEN Center for Development Biology in Kobe has revealed that IKKε also promotes bristle growth by managing the trafficking of cellular cargoes[1].

Initial experiments by Hayashi and team showed that activated IKKε is primarily found at the tips of developing bristles, where growth-associated cargoes are most likely to be unloaded. "Membranes and associated proteins are water-insoluble and thus do not easily diffuse to distant sites, and one model is that distal trafficking actively delivers such insoluble materials as packages," explains Hayashi.

Membrane-enclosed bubbles known as endosomes are a core component in this process, using so-called motor proteins to travel along routes defined by a microscopic 'railway' of fibers known as microtubules. The researchers found that this trafficking is severely disrupted in the absence of IKKε, with endosomes remaining trapped at the ends of the bristle rather than being distributed throughout the cell.

Hayashi and colleagues determined that IKKε interacts with a protein called Nuf, which links the motor protein Dynein with a key endosome-associated protein and thus contributes to directional transport of cargoes toward the tip of the growing bristle. Upon arrival at the tip, IKKε-mediated inactivation of Nuf sends the newly emptied endosomes on a return trip, thereby completing a 'recycling' process. "Such endosomal movement occurs in other cell types, but the shape of bristles makes this shuttling very prominent," says Hayashi. "I think this is a very good example of how a highly specialized cell and its shape can reveal a mechanism of general significance."

Many other cells grow in a similar fashion, ranging from the tiny branches that help connect neurons to the hairs on plant roots that assist in water absorption, and Hayashi speculates that similar regulatory mechanisms may also operate in these contexts. Moving forward, he and his colleagues will further explore the apparently central coordinating role of IKKε. "We are currently studying actin as a target," says Hayashi, "and we are also studying upstream regulators of IKKε, hoping to uncover a comprehensive view of this signaling pathway." ■

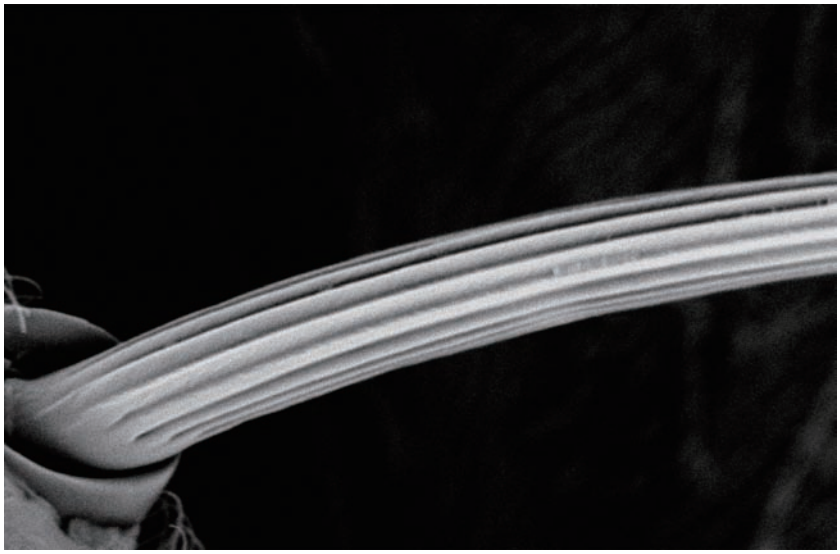

Figure 1: An electron microscope image of a sensory bristle from the body of the fruit fly *Drosophila melanogaster.*

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Measuring evolution's waistline

Gene expression data offer surprising evidence that embryos of different vertebrate species are most similar at intermediate stages of development

Nearly 150 years ago, noted German biologist Ernst Haeckel made the bold assertion that 'ontogeny recapitulates phylogeny': in other words, morphological changes that occur during an organism's embryonic development mirror its evolutionary history.

This concept has long since been debunked, but has nevertheless provided useful starting points for considering the yet-unsolved question of how the developmental process has evolved. Naoki Irie of the RIKEN Center for Development Biology (CDB) in Kobe has pondered this problem since graduate school. "My main interest then and now has been to understand the basic or common rules of how animal bodies develop," he says.

Now, as a postdoctoral fellow in Shigeru Kuratani's laboratory at CDB, Irie has conducted an ambitious comparative analysis of four vertebrate species with the aim of resolving an ongoing debate over two prevailing evolutionary models[1] (Fig. 1). The 'funnel-like' model, informed in part by Haeckel's thinking, suggests that the process of vertebrate embryonic development is very similar across species at the earliest stages, but increasingly differs at later stages. In contrast, the 'hourglass' model suggests that the earliest and latest stages of development differ considerably, whereas the greatest similarity is observed at the intermediate stages where organ development and body patterning take place.

To resolve this so-called 'evo-devo' debate, Irie and Kuratani analyzed changes in expression levels of thousands of evolutionarily conserved genes at different developmental points in the mouse, chicken, frog and zebrafish. The data provided striking support for the hourglass model, with gene transcription levels most similar at the intermediate stage known as 'pharyngula', where the animal has developed primitive precursors of the heart, kidney, brain and other tissues. They observed particularly strong conservation of activity among the Hox genes, which contribute to limb development, as well as several growth factor genes.

These findings offer new fuel for the evo-devo debate, but also raise complicated questions. "It is puzzling for me how vertebrate embryos established differences in early developmental stages while conserving the mid-embryonic stages," says Irie. "It's obvious that later developmental stages will not exist if earlier stages fail to develop successfully."

Irie now hopes to obtain further support for the hourglass model by expanding his approach to include well-characterized invertebrate species, such as the fruit fly. He also intends to dig deeper into the nuts and bolts of development. "We would like to go down to the level of tissues and primordial organs to find which structures have been conserved during evolution," he says. ■

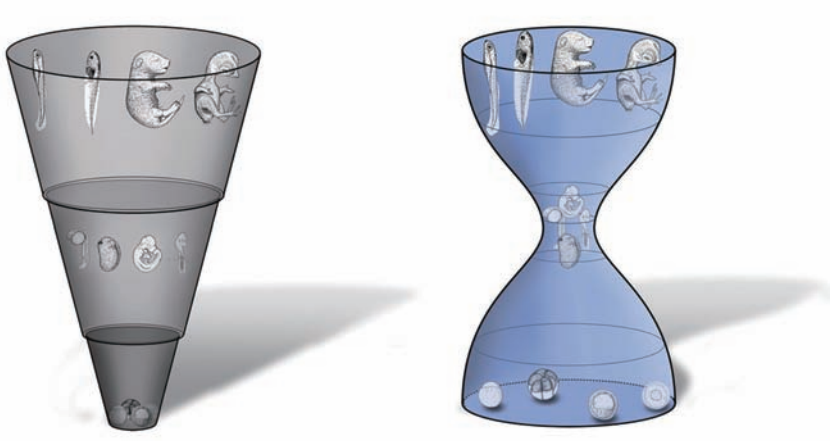

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Figure 1: The funnel-like model (left) and the hourglass model (right) are two competing theories that explain how developmental processes are conserved during evolution. In the funnel-like model, conservation occurs at the earliest embryonic stage (bottom) but in the hourglass model it occurs during the middle 'pharyngula' stage.

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Seeing the world of nanotechnology from a single-molecule perspective

Yousoo Kim

Associate Chief Scientist
Surface and Interface Science Laboratory
RIKEN Advanced Science Institute

Researchers around the world have been exploring the possibilities of nanotechnology for about ten years, with high expectations for many novel applications. "These expectations, however, are now on the verge of fading because the findings have fallen short of what was promised. What is actually going on in the molecular or nanometer regime? Unfortunately, we are finding it extremely difficult to conduct experiments that can lead to an understanding of the essence of the nanoworld," says Yousoo Kim, associate chief scientist at the Surface and Interface Science Laboratory of the RIKEN Advanced Science Institute. Kim has developed a unique technique to study the nature of individual molecules on surfaces, and he is taking advantage of these new tools to open a new frontier in nanoscience to link study results to practical applications such as organic solar cells and photocatalysts.

Observing the chemical reactions of single molecules

"When I was in junior high school, I learned the chemical formula for the electrolysis of water," says Kim. That formula is $H_2O \rightarrow H_2 + 1/2O_2$. "I asked my teacher why we need to multiply the O_2 by half. The teacher answered that the oxygen is multiplied by half because when water is electrolyzed, hydrogen and oxygen are produced in the proportion of two to one. However, I thought, what if a single water molecule is electrolyzed? This question gave me the incentive to observe the process of a chemical reaction on the scale of a single molecule."

Kim went on to the Department of Chemistry at Seoul National University where he majored in electrochemistry. "At that time, I conducted experiments that used an electrical circuit, like in the electrolysis of water, to control a chemical reaction in a solution and to examine the chemical reaction from the reaction products. This approach, however, does not provide information on how individual molecules are involved in a chemical reaction. We can only conjecture."

After finishing his master degree program at Seoul National University, he visited Japan in 1996 and started research at The University of Tokyo under the supervision of Akira Fujishima, now president of the Tokyo University of Science, who was known as the 'father of the photocatalyst'. Photocatalysis is a process by which molecules can be broken down on the surface of a photoactive material, such as titanium oxide, on exposure to light. "I originally planned to make a thorough study of photocatalysts. However, Prof. Fujishima suggested that I do more basic research because my background was in science. So I decided to study the physical phenomena that occur when the surface of a substance is exposed to light."

Reacting a single molecule

"When I was in the third year of my doctoral program, I came across a very intriguing paper reporting that a scanning tunneling microscope had been successfully used to observe the 'molecular vibration' of a single molecule. I immediately thought that this was what I really wanted to do."

A scanning tunneling microscope (STM) is an imaging technique that allows the microscopic surface structure of a substance to be mapped at

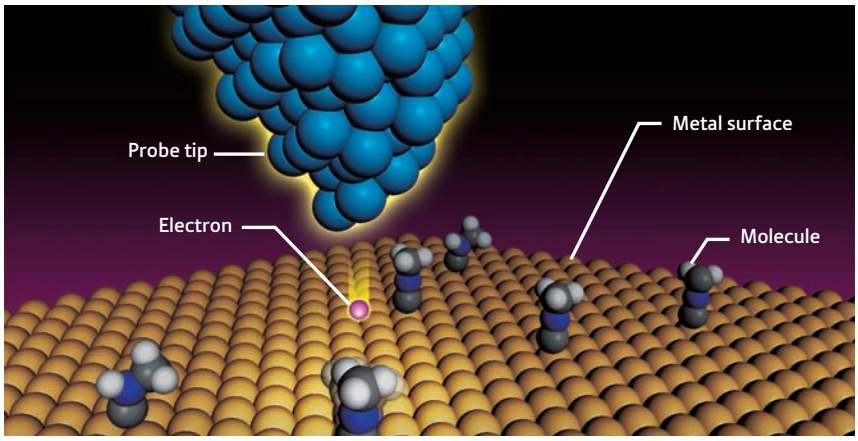

Figure 1: The principle of scanning tunneling microscopy.
When a voltage is applied to an atomically sharp STM tip that is brought close to a molecule on a metal surface, a tunneling current flows between the tip and the molecule, injecting electrons into the molecule and inducing a molecular vibration. The intensity of the molecular vibration at a given voltage can be used to identify the molecule. This technique can also be used to induce a chemical reaction.

resolutions approaching the scale of individual atoms. But this is not the only function of STM; it can also be used to identify the types of molecules present based on the molecular vibration.

In STM, a voltage is applied to a very sharp probe tip that is brought very close to a molecule on a surface (Fig. 1). Electrons from the probe flow to the target molecule, producing what is called a 'tunneling current', referring to the way electrons seem to 'tunnel' through the classical energy barrier needed for such a current to flow. This current induces a molecular vibration, causing all the individual atoms of the target molecule to become displaced from their equilibrium positions. The intensity of the molecular vibration corresponding to a given voltage depends on the type of molecule or the chemical bonds within the molecule. The type of molecule can therefore be identified by observing the molecular vibration.

"I was searching for a research laboratory where I could use STM in Japan when Prof. Fujishima introduced me to the Surface Chemistry Laboratory at RIKEN, headed at that time by Chief Scientist Maki Kawai, who is now an Executive Director of RIKEN."

After joining the Surface Chemistry Laboratory in 1999, Kim developed STM technologies together with Tadahiro Komeda, a research scientist in the laboratory and now a professor at Tohoku University. There, Kim observed molecular vibrations to successfully identify individual molecules on this basis (Fig. 2). He also succeeded in injecting electrons into a specific site of a molecule, thus changing it into a different molecule (Fig. 3).

"We removed two hydrogen atoms from a trans-2-butene molecule consisting of four carbon and eight hydrogen atoms to produce a 1,3-butadiene molecule consisting of four carbon and six hydrogen atoms. We used STM to cause a chemical reaction as intended within a single molecule, observed the vibrational signals before and after the reaction, and identified the type of molecule successfully for the first time."

Kim attributes the success in eliciting the desired chemical reaction to the laboratory's earlier work in catalysis. "We placed a molecule on the surface of palladium, which served as a catalyst for the chemical reaction. The Surface Chemistry Laboratory originally started as a catalyst research laboratory, and we owe much to the huge accumulation of knowledge on molecules and catalysts on the surface of substances."

Controlling individual molecules

There still remained a technical challenge to be overcome in observing molecular vibrations by STM. "When electrons are injected from an STM probe tip into a molecule, some molecules start moving before their molecular vibrations are observed. Finding an effective way to observe these unstable molecules was a big problem for us."

Kim and his laboratory colleagues examined what electron energy level causes the molecule to move. "As a result, we found that the molecule moves at an injected electron energy level equal to that causing the strongest molecular vibration." Based on these experiments, they established a unique measurement method called 'action spectroscopy'. "This measurement method made it possible for us to identify all types of molecules, both stable and unstable molecules, and to examine their essential characteristics."

When electrons are injected from an STM probe tip into a molecule, the molecule can move in many directions. "We cannot control the direction of a

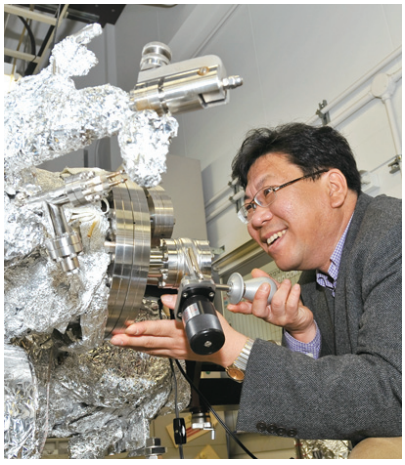

Figure 2: Yousoo Kim adjusting a scanning tunneling microscope.

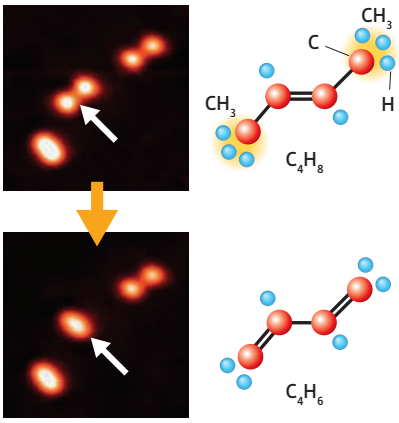

Figure 3: Chemical reactions on a single-molecular level.
Electrons were injected from an STM tip into the two methyl groups (CH_3) of a trans-2-butene (C_4H_8) molecule (upper), which released a single hydrogen atom (H) from each of the methyl groups and turned into a 1,3-butadiene (C_4H_6) molecule (lower). Arrows point to the molecule that caused the chemical reaction.

molecule's movement, but we encounter this problem only when the STM probe tip is placed right above the molecule. So we placed the STM probe tip obliquely upward and used the electrostatic force acting between the probe tip and the molecule. This approach also enabled us to control the direction of movement of the molecule successfully."

Kim's team has used this technique to draw letters by moving molecules (Fig. 4). In the late 1980s, a paper was published describing an experiment in which the atoms forming a molecule were moved by STM to construct letters. In that experiment, the letters were created by drawing the atoms closer to the probe tip or by using the tip to shape the atoms. "We constructed our letters by moving the molecules themselves in the desired direction on a surface. This cannot be achieved without a complete understanding of the nature of molecules and the interaction between electrons and molecules." In the future, this technique will be applied in the fabrication of computer circuits by arranging molecules.

Electrolyzing single water molecules

In 2009, Kim started the experiment that he first imagined when he was in junior high school—the experiment to electrolyze a single water molecule. "In electrolyzing a single water molecule, there are two possible reaction pathways," he says. Those pathways are $H_2O \rightarrow 2H + O$, and $H_2O \rightarrow H + OH$. In the former reaction, the two hydrogen atoms are separated from the single oxygen atom, and can be achieved by injecting electrons with high energy. The difficulty is how to produce the other reaction pathway.

Electrons injected into a molecule from an STM tip cause the molecule to start vibrating in an excited state. If the duration of the excited state (vibrational lifetime) is long enough, the molecular vibration causes the bonds between the atoms to break down, which increases the probability of a chemical reaction occurring. "When a single water molecule is placed on the surface of a metal, the water molecule cannot be broken down because of its short vibrational lifetime. This is because the water molecule binds chemically to the metal surface, and the energy of the injected electrons is easily dissipated into the metal surface."

Placing a water molecule on the surface of an insulator instead of a metal can increase the vibrational lifetime because no chemical reactions can occur and no electronic energy is absorbed. However, a tunneling current cannot flow from the STM probe tip in this case because the water molecule is on an insulator. "To cope with this problem, we developed a metal surface coated with an ultrathin film of magnesium oxide just two atoms thick. A water molecule on this surface produces a small tunneling current in STM."

Theoretically, a water molecule can be electrolyzed when injected with an electron having an energy of 0.77 electronvolts or more. On the ultrathin MgO film, however, the water molecule broke down at just 0.45 electronvolts. "We attributed this to a multi-step excitation process in which the water molecule is excited by the first injected electron and then by the following injected electron while the water molecule is still in the vibrationally excited state, because the electron energy is slowly dissipated owing to the ultrathin insulating film surface and hence the vibrational lifetime is increased."

The results of their experiments showed exactly what they were looking for (Fig. 5). "Using this approach, we succeeded in separating a single hydrogen atom from a single water molecule," says Kim. These results confirmed the $H_2O \rightarrow H + OH$ reaction pathway experimentally for the first time, and could lead to the development of technologies for producing hydrogen fuel with the minimum consumption of energy.

Practical applications of single-molecule experiments

In 2010, Kim started the Surface and Interface Science Laboratory at the RIKEN Advanced Science Institute. "We are working on new research into the interaction between light and substances. Many researchers have already

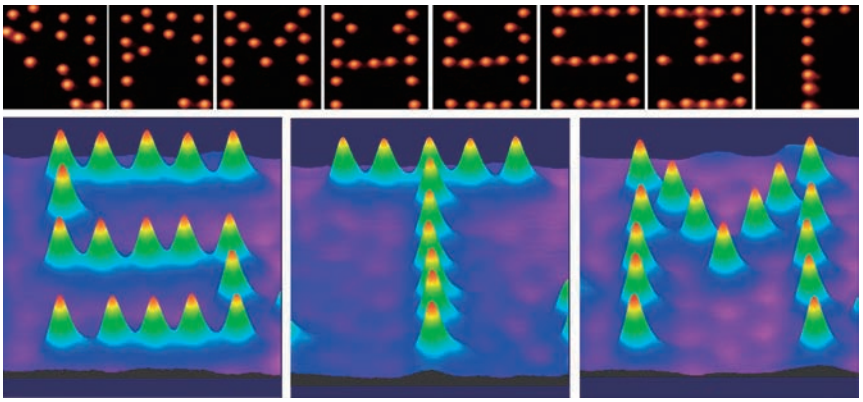

Figure 4: Letters drawn using an STM tip to move molecules.
Electrostatic force between organic molecules (CH_3S) and the STM tip was used to move the organic molecules to form the letters S, T and M (lower). The upper pictures show the drawing process for each letter.

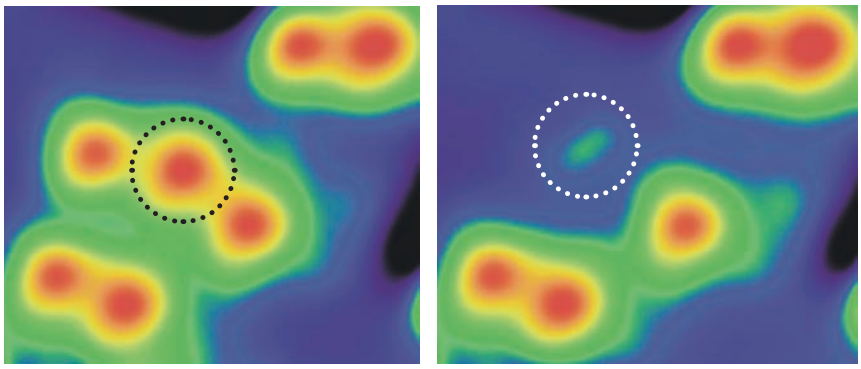

Figure 5: Electrolysis of a single water molecule by a new reaction pathway.
Electrons were injected from an STM tip into a single water molecule on the surface of an MgO film (at the point indicated by a circle in the picture on the left) to cause the water molecule to vibrate. The single water molecule was successfully electrolyzed in this way according to the reaction pathway: $H_2O \rightarrow H + OH$. The circle in the picture on the right indicates an OH group as an electrolyzed product.

investigated this subject. However, there have been virtually no reports on experiments that examine the interaction between light and substances while observing individual molecules."

Photocatalysts are a firm research target. "In Prof. Fujishima's laboratory, I used to watch how he advanced his own research into photocatalysts around him. This time, I intend to conduct research into the essence of photocatalysts in my own right based on the technology and experience I gained over the years at RIKEN."

On a single-molecular scale, nobody knew the position on titanium oxide at which a photocatalytic reaction occurs. "It has been considered for years that the photocatalytic reaction occurs at positions where oxygen atoms are missing on the surface of titanium oxide because electrons concentrate at those positions. Our experiments with an STM probe tip clarified that photocatalytic reactions actually occur across wide electronically active areas around the positions where oxygen atoms are missing."

The Surface and Interface Science Laboratory is also conducting research into organic solar cells. "What types of molecules are most effective and how should we arrange them to increase power generation efficiency? Many researchers from around the world have wanted to perform single-molecule experiments while observing individual molecules, but such experiments have been too difficult to handle. We have accumulated STM technology that I am confident will enable such experiments."

Toward 'sci-engineering'

"So far, I have focused on research into the essence of chemistry. In the future I also plan to start research that helps us link that knowledge to practical applications. This idea was triggered by a meeting with Dr Takanori Fukushima from the Energy Conversion Research Team. He specializes in organic synthesis and can synthesize any organic molecule. I always have a good time with him, talking about our dreams."

Molecules and matter exhibit different characteristics on the nanometer or molecular scale compared with the macroscale behavior scientists are most familiar with. This is the reason for the widespread scientific interest in nanotechnology over the past ten years, and the origin of the expectations for a nanotechnology revolution.

"These expectations, however, are now on the point of fading because the findings to date have fallen short of society's expectations. Although many theoretical papers have been published on what is actually going on in the nanometer world, only a few study have been reported because of the technical difficulty in directly observing the nature and functions of individual molecules. Many conventional application studies have been conducted without fully understanding the basic mechanisms of nanotechnology. I plan to make use of the STM to study the nature of individual molecules and open a new frontier in nanoscience that will allow us to explore the essence of the nanoworld.

"RIKEN launched systematic research into nanoscience before anywhere else in the world," Kim points out. "In 1993, Dr Kawai, now an Executive Director of RIKEN, started the Atomic Scale Sci-engineering Research and Promotion Group together with Chief Scientist Masakazu Aono, now a fellow at the National Institute for Materials Science, and Chief Scientist Katsunobu Aoyagi, who is now professor at Ritsumeikan University. 'Sci-engineering' is a term implying that research into the essence of a phenomenon should come first, and then engineering should follow from the results. I would like to follow the research concept of sci-engineering in the Surface and Interface Science Laboratory. ■

Yousoo Kim

Yousoo Kim was born in Seoul, Korea, in 1968. In 1991, he graduated from the Department of Chemistry, Seoul National University, where he also obtained a master's degree in 1993. In 1999, he earned a PhD in applied chemistry at The University of Tokyo. In the same year, he joined the Surface Chemistry Laboratory at the RIKEN Discovery Research Institute as a research associate, and six months later became a special postdoctoral researcher. He was promoted to research scientist in 2002, and to senior research scientist in 2006 at the same laboratory, where he studied single-molecule chemistry by scanning tunneling microscopy. Since 2010, he has been the principal investigator of the Surface and Interface Science Laboratory. His research focuses on describing the details of energy transport and conversion on solid surfaces and interfaces in the nanoscale regime. To understand the basic mechanisms at a single molecule or atom level, he carries out combined study of scanning probe microscopy/spectroscopy and density functional theory calculation on well-defined surfaces under ultrahigh vacuum conditions.

Strengthening ties with the Max Planck Society

The year 2011 marks the 150th anniversary of Japan–Germany relations as well as the centennial of the Max Planck Society (MPG), an important international partner for RIKEN. In anticipation of the important year, RIKEN and the MPG have been working toward further deepening the cultural and scientific interaction between the two organizations and countries. RIKEN and the MPG have been cooperating in a diverse range of fields including physics, chemistry and biology for more than a quarter century since they first entered into a collaborative agreement in June 1984.

To celebrate the 25th anniversary of their cooperation, the two organizations held a joint conference on 21–23 January 2009 at the MPG administrative headquarters in Munich, covering their collaborations in the three fields of physics, materials science and the life sciences. At this conference it was decided that an invaluable global resource for chemical compounds could be created by combining two chemical compound banks led by Hiroyuki Osada and Herbert Waldmann, respectively.

On 19 January 2010, RIKEN President Ryoji Noyori and Kohei Tamao, director of the RIKEN Advanced Science Institute (ASI), visited MPG President Peter Gruss in Germany. During this visit, it was decided that the cooperative ties between the two organizations should be strengthened and developed, and to this end a Memorandum of Understanding was signed for research collaboration in the field of systems chemical biology. This MoU led to research involving the exchange of researchers and students, and in February 2010 a RIKEN–Max Planck joint research team was created in preparation for the later establishment of a joint research center.

RIKEN President Ryoji Noyori (left) and RIKEN ASI Director Kohei Tamao (right) with MPG President Peter Gruss (center).

As discussions on the proposed joint research center progressed, it became clear that significant breakthroughs in glycobiology could be achieved through collaboration between the Max Planck Institute of Colloids and Interfaces, headed by Peter Seeberger and known for its automated oligosaccharide synthesis technology, and the RIKEN ASI's Systems Glycobiology Research Group, headed by Naoyuki Taniguchi. It was then decided to create a joint research center that would support and foster the expected synergetic effect of these two groups working together and sharing information.

As a fruit of these efforts, on 27 April 2011, Presidents Noyori and Gruss signed an agreement to strengthen collaboration between the two institutions by establishing a joint research center for systems chemical biology, a field that seeks to achieve a systematic understanding of biological systems from a chemistry perspective.

The joint research center will bring together two libraries—the RIKEN ASI's natural chemical compounds bank (NPDepo), and the biology oriented synthesis library, BIOS, of the Max Planck Institute for Molecular Physiology in the Department of Chemical Biology, under the leadership of Herbert Waldmann. The goal is to create one of the world's leading chemical compound banks for both synthetic and natural compounds.

The agreement also calls for strengthening the ongoing collaboration on disease glycomics and oligosaccharide synthesis.

By bringing together their complementary technology and experience and working in close collaboration, RIKEN and the MPG hope to transcend the boundaries between different research fields to achieve a comprehensive understanding of life phenomena. It is also hoped that the resulting exchange of personnel, both young researchers and students, will foster the development of the next generation of scientists. ■

Dr Franco Nori
Team Leader
Digital Materials Team
RIKEN Advanced Science Institite
Wako, Saitama, Japan

Dear Prof. Nori,

When I was visiting the University of Michigan in the USA in 2001, you offered me the opportunity to join a new research group that you were going to start at RIKEN. Actually, I had never expected to work in Japan before your suggestion, but after arriving at RIKEN, I liked it very much. The green and peaceful campus impressed me. Particularly, when the many cherry blossoms on campus were in full bloom, I was astonished by their beauty. I had never seen before so many pretty flowers in one place.

In addition to its attractive and peaceful campus, RIKEN is also doing great research in many areas of science. In fact, it has attracted top scientists, and I was fortunate to join one of them there. Though I was the first member in your group at that time, I did not feel lonely, because I could often discuss with you and other top visiting scientists you invited. Because of that exciting international environment around me, with many seminars involving heated and insightful discussions, I extended my initially planned one-year stay at RIKEN to nearly three years. Indeed, this allowed you and I to complete several projects on quantum information processing with superconducting circuits. Also, I witnessed the growth of your group from a small team to an internationally famous research center on superconducting quantum computing.

In 2004, after I became a professor at Fudan University in Shanghai, China, I visited your group on several occasions, sometimes with one of my students. This helped my group at Fudan to attract smart students because there were not so many opportunities there to study abroad. Moreover, these visits also helped me produce important academic results, including our highly cited feature article in *Physics Today*.

My collaboration with you is the longest for me, started over 20 years ago, and also the most fruitful one. I greatly appreciate the opportunity to have worked with you over the past two decades, and I look forward to visiting your group again.

Best regards,

Jian-Qiang You
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