Researchers describe 'implausible' chemistry that produces herbicidal compound

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A soil microbe that uses chemical warfare to fight off competitors employs an unusual chemical pathway in the manufacture of its arsenal, researchers report, making use of an enzyme that can do what no other enzyme is known to do: break a non-activated carbon-carbon bond in a single step.

Their study, appearing this week in the journal *Nature*, provides the first three-dimensional structure of the enzyme, hydroxyethylphosphonate dioxygenase (HEPD) and proposes a mechanism by which it performs its task.

University of Illinois researchers first reported the enzyme in *Nature Chemical Biology* in 2007, said Wilfred van der Donk, an author on both papers with microbiologist William Metcalf.

"Our team discovered this very implausible chemical reaction," van der Donk said. "And the more we learned about it the more unusual it became. The enzyme is unusual because it breaks a carbon-carbon bond without needing anything except oxygen."

The study is important because HEPD catalyzes a critical step in the chemical pathway that produces phosphinothricin (PT), a bacterial compound that is widely used as an agricultural herbicide. This compound, which is a component of two top-selling weed killers (Liberty and Basta), is effective when used with transgenic crops that have a PT-resistance gene inserted into their DNA. The resistance gene

also comes from the bacteria that produce PT. It allows the bacteria (which belong to the genus Streptomyces) to emit the antibiotic to kill off their competitors without killing themselves. Similarly, corn and other crops that contain the resistance gene are able to withstand PT-based herbicides that kill the weeds around them.

The new findings are part of an ongoing exploration at Illinois of naturally produced molecules that contain carbon-phosphorus (C-P) bonds. Although little understood, these phosphonates (which contain C-P bonds) and phosphinates (with C-P-C bonds) are already widely used in agriculture and medicine. This class of compounds includes the herbicide glyphosate, the osteoporosis treatment alendronate, the antimalarial drug fosmidomycin and the antibiotics fosfomycin, dehydrophos and plumbemycin.

Whether man-made or naturally produced, phosphonates and phosphinates are structurally similar to other compounds used by enzymes in nature. They sometimes bind to the same enzymes and thus can inhibit ordinary cellular processes in bacteria or other organisms. This makes them attractive candidates for the development of new antibiotics, said van der Donk, a principal investigator on the study with Metcalf and biochemistry professor Satish Nair.

Understanding how bacteria synthesize these compounds also enables the scientists to predict how bacteria might develop resistance to any new drugs that are developed, he said.

"Knowing how a compound is made may allow you to make an analog that can overcome that resistance," van der Donk said. "That's the game that's been played with penicillin for the last 40 years. Every time a bacterial strain becomes resistant to one penicillin, scientists tinker with the structure so that the organism is susceptible again."

The researchers hope the new findings will spur the development of much smaller, cheaper and more efficient synthetic catalysts that can also sever C-C bonds in one step.

"Every time we find something new in nature it's an inspiration to see if we can copy that reactivity with a small molecule," van der Donk said.

Source: University of Illinois at Urbana-Champaign (news : web)