BIOCHEMISTRY

Scientists get one rung closer to understanding strange ladderane lipids

Peculiar natural products are embedded in organelle membranes inside ammonium-oxidizing bacteria that are crucial to the nitrogen cycle

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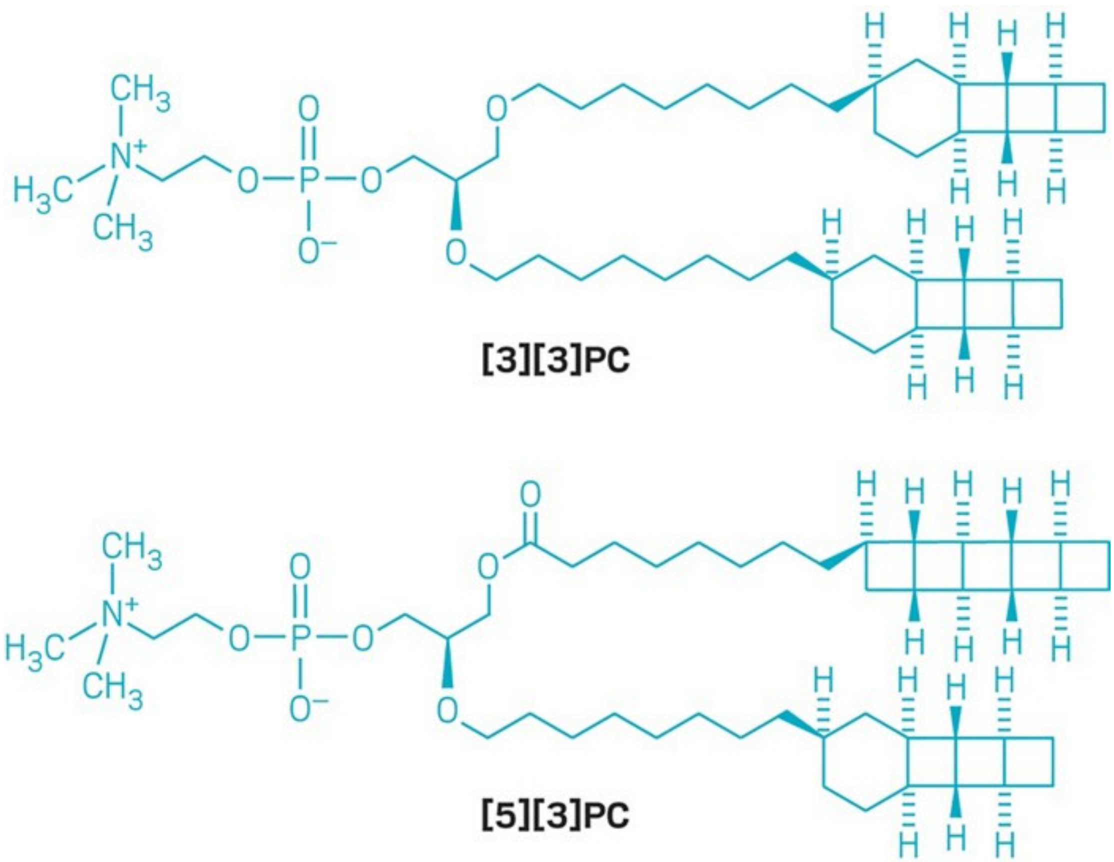
SEPTEMBER 6, 2018 | APPEARED IN **VOLUME 96, ISSUE 36**



These strangely structured ladderane natural products could help scientists understand how anammox bacteria turn ammonium and nitrite into gaseous nitrogen and water.

Since their unlikely discovery in wastewater sludge at the tail end of the past century, anaerobic ammonium oxidation (anammox) bacteria have been spotted in all manner of aquatic settings. These bacteria consume ammonium (NH_4+) and nitrite (NO_2-), churning out gaseous nitrogen (N_2) and water (H_2O). Scientists estimate that this unique process may account for up to half of all oceanic nitrogen.

From the start researchers have sought to harness the microbes to remove ammonium, which is released into the environment by the increasing use of agricultural fertilizers, from wastewater. But studying these microbes, much less manipulating them, hasn't been easy. The bacteria grow slowly, doubling every one to two weeks, and are extremely sensitive to oxygen, which means that scientists wishing to extract certain enzymes have to handle them in airtight gloveboxes.

Now, in a step towards understanding these enigmatic bacteria, researchers at Stanford University have investigated two key molecules found in the membrane of the bacteria's anammoxosome, the organelle where the ammonia-oxidizing process is thought to occur (*Proc. Natl. Acad. Sci. USA* 2018, **DOI: 10.1073/pnas.1810706115**).

Known as ladderane phospholipids, these exotic compounds possess dual strands of hydrocarbons capped with strained, cyclobutane rings bound back-to-back. "I'm shocked that they even exist," study coauthor Noah Z. Burns of Stanford says of the ladderanes. In 2016, his group reported the total synthesis of a ladderane phosphatidylcholine (PC), and last year **they collaborated with Stanford colleague Yan Xia to unzip ladderenes—ladderanes with an alkene at the end—to make semiconducting polymers**.

This time, using Burns's 2016 route, the researchers synthesized two natural ladderanes (shown), as well as an unnatural one, and teamed up with Stanford biophysicist Steven G. Boxer to probe the ladderanes' biophysical properties. The team found that the natural ladderanes form vesicles, small spherical sacs sealed off by a ladderane bilayer membrane, in water at room temperature, which Boxer says he wouldn't have predicted. It's surprising because ladderanes are rigid structures while membranes are generally fluid, he explains.

While analyzing the ladderane vesicles, Burns and Boxer uncovered more surprises. Scientists have hypothesized that the anammoxosome membrane's main job is to protect the rest of the cell from hydrazine, which is a toxic intermediate produced in the reaction. So the researchers made vesicles with either the ladderane lipids or regular straight-chain lipids, and then compared the membranes' ability to let hydrazine and protons diffuse across them. The team found that the vesicles made from ladderane lipids actually had similar hydrazine permeability to normal lipids. They also found that protons moved across the ladderane membranes five to 10 times slower than normal lipids. The authors suggest that keeping protons from diffusing may preserve the proton motive force needed to make energy transfer molecule adenosine triphosphate—essentially the bacteria's way of conserving its energy.

Microbiologist Harry Beller at Microvi Biotechnologies, which develops wastewater solutions, calls the study "elegant and innovative." He says the authors present convincing experimental data that the ladderane lipids' primary role is not keeping hydrazine inside the anammoxosome but instead maintaining the proton motive force across the anammoxosome membrane.

"This is a fantastic example of the power of organic synthesis, and skilled synthetic chemists, to facilitate biophysical experiments," says Dean Tantillo, a theoretical organic chemist at the University of California, Davis who also wasn't involved in the study.

Though Burns says ladderane applications are a long way off, he suggests that they could be used as vesicles that might deliver drugs or high energy fuels, if the compounds could be synthesized on a large scale. The team's findings have only prompted more questions about the ladderanes' biophysical properties, he says, adding "we've barely scratched the surface with these things."

Chemical & Engineering News

ISSN 0009-2347

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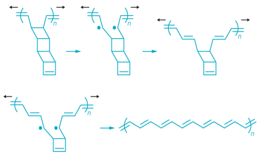

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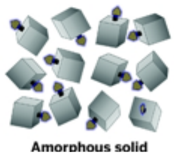

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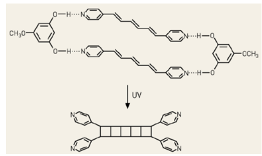

LADDERANES GET A STEP-UP

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