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Spotlights on Recent *JACS* Publications

NMR REVEALS INNER WORKINGS OF CELLULAR GARBAGE DISPOSAL

Over time, cells can accumulate misfolded and damaged proteins that must be removed to maintain proper cellular functioning. The barrel-shaped proteasome, a protein complex, degrades protein garbage by cleaving peptide bonds. Inhibiting the proteasome in cancer cells may induce cell death, making the complex an attractive drug target. However, drug development is stymied by the fact that scientists still do not fully understand how the proteasome breaks peptide bonds.

Crystal structures have indicated that a side-chain oxygen of a particular threonine residue attacks the ill-fated peptide bond, but they do not show what base accepts the leftover hydrogen from the first step in the cleavage. Now, Algirdas Velyvis and Lewis Kay use nuclear magnetic resonance spectroscopy to identify that hydrogen acceptor (DOI: 10.1021/ja403091c).

Studying massive protein complexes, such as the proteasome, by NMR is a challenge because the numerous signals overwhelm the spectra. To simplify the proteasome spectra, the researchers replace its hydrogen atoms with NMR-silent deuterons. NMR-active $^{13}CH_3$ methyl groups are then introduced into the proteasome at specific locations, allowing the researchers to determine the pK_A of chemical groups in threonine side chains by NMR. The team finds that the catalytic threonine's amino group has a pK_A of 6.3, strongly indicating that it is deprotonated under physiological conditions and thus ripe to accept a hydrogen during peptide bond cleavage. **Erika Gebel, Ph.D.**

PHASE TRANSITIONS ON THE ROCKS, WITH SALT

Many atmospheric, geologic, and marine processes, including cloud and rock formation, involve freezing and thawing of salty water on surfaces. Until now, there have been no detailed experimental measurements of how the process occurs. Ali Dhinojwala and colleagues have found that saltwater freezes on a substrate in two distinct steps, rather than a single transition (DOI: 10.1021/ja403437c).

Dhinojwala's team uses infrared−visible sum frequency generation (SFG) spectroscopy to monitor the heating and cooling of a salt solution in contact with a sapphire substrate. As the solution cools to a temperature at which ice and brine coexist, a concentrated briny layer forms on the sapphire surface. The SFG results indicate that sodium ions interfere with hydrogen bonding. As the solution is cooled further, frozen hydrates form at the substrate surface.

The results clarify our understanding of saltwater phase transitions on surfaces, and could help researchers reconstruct conditions of geologic formation on Earth and other planets. The work could also help scientists test hypotheses about the potential of salty, icy environments, such as those of early Earth and Mars, to incubate life. **Deirdre Lockwood**

MOLECULAR SENSOR MEASURES MITOCHONDRIAL VISCOSITY

Mitochondria are the power stations of biological cells and are important in the cellular suicide program called apoptosis. Movement of molecules through the mitochondrial interior depends on its viscosity, which is a parameter thought to be a critical indicator of the organelle's ability to function.

Chulhun Kang, Jong Seung Kim, and colleagues now have developed a sensor to measure mitochondrial viscosity (DOI: 10.1021/ja403851p). A moiety called triphenylphosphonium targets the sensor to the mitochondria. The sensor also has two fluorescent molecules connected by a phenyl spacer, coumarin and the boron-dipyrromethene (BODIPY). When mitochondrial viscosity is low, the C−C bond between the spacer and BODIPY freely rotates and quenches BODIPY fluorescence; when the mitochondrial viscosity increases, the bond stops rotating and BODIPY fluoresces. The ratio of fluorescence between BODIPY and coumarin, whose fluorescence is independent of viscosity, gives a self-calibrated signal that is directly proportional to mitochondrial viscosity.

By testing their sensor in live HeLa cells, the investigators determine that the average mitochondrial viscosity is 62 cP. When the cells are treated with two different drugs that trigger apoptosis, a higher viscosity of 110 cP is measured. The investigators suggest that their sensor will be useful in studying mitochondrial viscosity and its role in mitochondrial-based diseases. **Rajendrani Mukhopadhyay, Ph.D.**

EFFICIENT SYNTHESIS OF A COMPLEX MARINE ALKALOID

David Evans and co-workers have completed a highly convergent total synthesis of (−)-nakadomarin A, a marine natural product that has long been considered a very complex target (DOI: 10.1021/ja404673s). (−)-Nakadomarin A is a polycyclic alkaloid in the manzamine family and has a wide range of potential therapeutic attributes, including cytotoxic, antimicrobial, and antibacterial activities.

The researchers construct a 15-membered macrocyclic lactam early in the synthesis, in eight steps, on a multigram scale. Another key lactam intermediate is constructed in five steps. This bicyclic lactam contains a single stereocenter that critically controls the subsequent stereochemical outcome of the product assembly. A triflate-mediated double Michael/cycloaddition reaction joins these two intermediates, and only one further step is required to yield the final natural product.

Although (−)-nakadomarin A is a highly complex natural product, this extraordinarily efficient synthesis almost makes the target look simple. The opportunity to scale up this synthesis and possibly to construct derivatives could facilitate the further investigation of this marine alkaloid's therapeutic potential. **Sonja Krane, Ph.D.**

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