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Spotlights on Recent *JACS* Publications

ENZYMES BREAK IT DOWN FOR DRUG DELIVERY

Most stimuli-responsive materials reported to date respond to changes in a combination of pH, temperature, and light. Now, Roey J. Amir and colleagues report a new class of functional nanostructures whose breakdown is triggered by enzymes, offering researchers a new level of control and specificity for potential applications in drug delivery (DOI: 10.1021/ja413036q)

The team reports an enzyme-responsive amphiphilic hybrid nanostructure composed of two types of molecules: linear poly(ethylene glycol) (PEG) and a stimulus-responsive dendron with hydrophobic end groups that can be cleaved off with enzymes. The PEG-dendron hybrids self-assemble to form micelles in water. Upon the addition of the activating enzyme, the hydrophobic end groups are cleaved from the dendron, making the complex more hydrophilic and unstable, and thus prone to disassembly and subsequent release of any cargo encapsulated within the hydrophobic core.

The team demonstrates the ability to fine-tune the disassembly rate of the micelles by adjusting the length of the linear PEG block. By exploiting the overexpression of certain enzymes by diseased cells, the team envisions enzyme-responsive drug delivery vehicles that one day may help target drugs specifically to diseased cells, minimizing harm to healthy tissue.

Christine Herman, Ph.D.

NICKEL HYDROXIDE BEATS OUT EXPENSIVE CATALYST FOR WATER SPLITTING

Efficient and cheap water splitting, which produces both oxygen and hydrogen gas, is one of the most pursued goals in the realm of chemical research to date because such a reaction would provide the basis for using hydrogen as an energy source. Without a catalyst, however, water splitting is both slow and inefficient. The most successful candidates developed for water oxidation so far have been oxides of ruthenium or iridium, metals that are both scarce and expensive.

Now, using cheap and abundant nickel, Yushan Yan and co-workers have synthesized an α-nickel hydroxide nanostructure that is an incredibly active and stable water-splitting catalyst (DOI: 10.1021/ja502128j). The compound works better than the established ruthenium or iridium oxides and is easier to make.

The researchers make a series of nickel nanostructures, including hollow spheres, nanoplates, and nanoparticles. The hollow spheres are able to catalyze the reaction at a very small overpotential of 0.331 V and a current density of 10 mA cm^{-2}, numbers that compare favorably to the ruthenium catalyst. The nickel catalyst however is much more robust after many cycles of the water-splitting reaction. This development may lead to a cheaper and more efficient way to create hydrogen to be used for cleaner energy production.

Leigh Krietsch Boerner, Ph.D.

MOLECULAR DYNAMICS EXPOSE ATP SYNTHASE SECRETS

Mitochondria create molecular energy by coupling a proton gradient to the synthesis of adenosine triphosphate (ATP). The enzyme at the heart of that transformation is ATP synthase, an enzyme that resembles a tree with a narrow trunk or shaft. Researchers already knew that ATP synthesis occurs by rotation of the head of that structure about the shaft, but the precise molecular details of the process have remained elusive. Now, thanks to work by Jacek Czub and Helmut Grubmüller, they have a clearer picture of how it works (DOI: 10.1021/ja500120m).

Czub and Grubmüller use all-atom molecular dynamics simulations to model ATP synthase molecular transformations as the enzyme rotates 120° over 300 ns. The authors also assess the role of predicted electrostatic interactions in the enzyme mechanism by simulating specific binding-site mutations.

The data resolve whether the enzyme's nucleotide binding pocket closes via an "induced fit" mechanism or "conformational selection" caused by rotation of the enzyme (γ) shaft. The authors conclude that in response to the γ-shaft rotation, [the empty β subunit], initially in the open state, undergoes fast spontaneous closure to a half-open conformation.

Jeffrey M. Perkel

MOTION AND MECHANISM IN ENZYME CATALYSIS

Rudolf K. Allemann and co-workers uncover an unexpected difference in how protein dynamics affect enzyme catalysis in two versions of dihydrofolate reductase (DHFR), an enzyme important for the synthesis of certain nucleobases and amino acids (DOI:10.1021/ja502673h). The authors probe the role of protein motions, such as bond vibrations and structural changes, in the kinetics of dihydrofolate reductase (DHFR) from the hyperthermophile *Thermotoga maritima*, which thrives in extremely hot environments but has lower catalytic activity than DHFR from *Escherichia coli*.

Using kinetic isotope effect studies, in which carbon, nitrogen, and hydrogen atoms in the enzyme are replaced with their heavy isotope counterparts, the authors find that, while prior studies showed that isotope substitution distinctly alters the rate of the chemical reaction in the *E. coli* enzyme, the same is not true with DHFR from *T. maritima*. They propose that the increased structural rigidity inherent in the *T. maritima* enzyme leads to a loss of conformational sampling and prevents active site closure.

This study suggests that proteins motions are not universally coupled to reaction kinetics. More generally, these findings offer clues into the types of evolutionary trade-offs that may occur in enzymes to gain properties such as thermal stability.

Eva J. Gordon, Ph.D.

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CONTROLLING GOLD NANOPARTICLE FORMATION, A FEW ATOMS AT A TIME

Nanoparticles' diminutive size makes them interesting and useful. It also makes them sensitive to structural variation, and their synthesis can be difficult to control precisely. Nanoparticle properties often depend on size, structure, and composition, but managing these variables is challenging. Gold nanoparticles in particular work well as chemical catalysts and growth promoters for other nanostructures—applications in which the right size, structure, and composition can be essential.

Richard Palmer and co-workers gain tight control over the atomic structure of gold nanoparticles by systematically varying their formation conditions (DOI: 10.1021/ja502769v). With state-of-the-art microscopy, the researchers match the proportions of nanoparticles produced with each of three atomic structures to specific reaction parameters. The team finds that the proportion of one common structure can be varied, to zero if desired, by controlling the concentration of gold vapor during their formation.

The authors suggest that their approach may allow others to prepare batches of structurally pure particles, which would in turn enable researchers to correlate nanoparticle properties to size and atomic configuration. Additionally, the results can help researchers create particles with precisely engineered nanostructures for structurally sensitive biomedical, chemical, electronic, and optical applications.

Jenny Morber, Ph.D.

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