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Spotlights

Spotlights on Recent *JACS* Publications

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IN PROTEIN FOLDING AS IN LIFE, THERE ARE MANY PATHS TO SUCCESS

To adopt the unique structure that dictates its function, a protein must fold into its active conformation. While traditional thinking holds that the process of folding occurs through a single pathway for each protein, there is growing evidence that the same folded protein can be arrived at by several distinct routes. However, a shortage of studies that rigorously characterize parallel protein folding pathways has left this matter unresolved within the scientific community.

Now, Jayant B. Udgaonkar and colleagues provide an in-depth structural analysis of the multiple folding pathways that yield the monellin-derived protein MNEI (DOI: 10.1021/jacs.0c11097). The researchers created four versions of MNEI with a fluorescent donor and acceptor pair installed at different sites and measured distant-dependent energy transfer over time to track the protein's structural features as it transitioned from an unfolded to a folded state. They found that MNEI first exists as a "collapsed ensemble" that, while unfolded overall, contains subregions of structural definition. The protein then diverges into four separate pathways in which individual segments fold at various times and through diverse mechanisms. In averaging the four pathways, the team observed that local features are formed before global protein structure is finalized, with α helix formation, core consolidation, and β-sheet formation preceding end-to-end protein distance reduction. As MNEI is commonly used as a model in protein folding studies, this work provides generalizable insights into the folding process and serves as an important, well-characterized example of parallel pathways in protein folding.

Sarah Anderson

TRAPPING NITROGEN OXIDES IN CAR EXHAUSTS DURING A COLD START WITH A METAL−ORGANIC FRAMEWORK

Nitrogen oxides, emitted into the atmosphere by combustion engines mainly in the form of NO and NO_2 (represented as NO_x), are an important pollutant having a lasting negative impact on the environment and human health. One approach for preventing the release of these noxious nitrogen oxides is catalyzed disproportionation reactions, whereby a catalyst causes the NO_x molecules to undergo simultaneously oxidation and reduction reactions. Unfortunately, the currently used catalysts in vehicle exhaust systems only work efficiently at temperatures above 200 °C, resulting in an increased NO_x emission for several minutes after a cold start.

Now, Ashley Wright, Chenyue Sun, and Mircea Dincă have found a solution to this problem by capturing the NO_x molecules in a metal−organic framework (MOF) and then releasing it when the temperature is sufficiently high, allowing the disproportionation reactions that render the NO_x molecule innocuous (DOI: 10.1021/jacs.0c12134). The MOF they investigated, Cu-MFU-4*l*, is a porous crystalline material that contains copper metal sites. The researchers found that copper showed a reactivity toward small molecules like NO, initially forming an intermediate copper-nitrosyl. Above 200 °C, the NO molecules are restituted and the MOF catalyzes the NO disproportionation reaction, whereby the original copper MOF was restored and readied for the next cycle of NO disproportionation.

Alexander Hellemans

INCORPORATING AN UNNATURAL AMINO ACID TO IMPROVE NMR

The enzyme pyrrolysyl-tRNA synthetase (PyIRS) and its cognate pyrrolysyl-tRNA have been used extensively to add unnatural amino acids to the genetic code of bacterial and eukaryotic cells. However, despite the potential of this system for studying proteins, protein yields of most pyIRS variants have been generally modest, limiting their application in biomolecular NMR.

Gottfried Otting and co-workers show new potential for this system, using it for site-specific incorporation of a high-signal lysine derivative into proteins with high yield (DOI: 10.1021/jacs.0c11971). This variant, (((trimethylsilyl)methoxy)-carbonyl)-L-lysine (TMSK), consists of a trimethylsilyl group at the end of a lysine side chain. With nine equivalent protons, TMSK is able to produce intense singlets in ^{1}H NMR spectra near 0 ppm, where few other proton resonances occur. The researchers demonstrate this system's ability to detect ligand binding, measure the rate of conformational change, and assess protein dimerization by paramagnetic relaxation enhancement. They also show the ability to incorporate both TMSK and *O*-*tert*-butyl-tyrosine, another unnatural amino acid, in the same protein in quantities sufficient for NMR spectroscopy. The close proximity of these two noncanonical amino acids was readily detected by nuclear Overhauser effects. The authors

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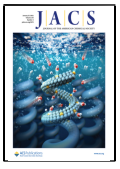

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suggest that small and flexible probes like TMSK have excellent potential for site-specific protein studies.

Christen Brownlee

TOGETHER WE GLOW: DETECTING BIOFILMS VIA AGGREGATION-INDUCED EMISSIONS

Bacterial biofilms are complex, matrix-enclosed bacterial populations within a sticky exopolysaccharide (EPS) layer that adheres to surfaces and cause infections in implants and prosthetic devices. Generally pathogenic, up to 80% of all chronic infections are associated with biofilm formation. As biofilms protect bacteria against host defense mechanisms and antibiotics, approaches aimed at both detecting biofilms and subsequently eliminating them are of immense interest.

By modifying an FDA-approved iron chelator deferasirox (ExJade), Xiao-Peng He, Jonathan Sessler, and co-workers have developed a novel system to detect biofilms via the aggregation-induced fluorescence of modified chelator molecules (DOI: 10.1021/jacs.0c11641). Molecules that fluoresce upon aggregation or Aggregation-Induced Emission luminogens (referred to as AIEgens) are of immense interest for their ability to exhibit enhanced fluorescence in an aggregated state and have been used extensively as bioprobes and in gathering high-resolution in vivo images. The researchers extended the use of these AIEgens to detect and treat bacterial biofilms.

In introducing modifications to the chelator molecule, the authors have developed a library of molecules with unique aggregation-induced emission characteristics and studied their structure−property relationships. By introducing a combination of two different pro-chelator molecules, the authors have demonstrated the detection and treatment of biofilms of bacterium *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). As medical device and nondevice, associated infections continue to grow, and hospital-acquired (nosocomial) bacterial infections continue to rise globally, the early detection and treatment of biofilms can play a significant role in ensuring favorable public health outcomes.

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