Nanoreactors: Small Spaces, Big Implications in Chemistry

In recent years, chemists have worked to understand how fundamental chemical principles change when systems are confined to spaces with nanoscale dimensions or sub-microliter volumes. "Nanoreactors" offer a means of creating unique nanoscale chemical environments partitioned from the surrounding bulk space. The rise of nanoscience and nanotechnology has offered the opportunity for exploring chemistry in a variety of different types of nanoreactors—those that are synthetically generated, such as nanopores and nanoholes, hollow nanoparticles and porous architectures, and tubular nanostructures, as well as those that are native to biological structures, such as protein pores and channels. Such systems, through assorted avenues, enable the number of atoms or molecules under study to be tuned and controlled in ways not possible with bulk systems. Nanoreactors change the basic chemical nature of molecules and moieties within them, and alter how they behave in chemical reactions. In this way, nanoreactors can be exploited not only to speed up a reaction or make a new type of nanoparticle, but also to gain new fundamental understanding of a chemical system or process or to develop an analytical tool based upon this insight. This *ACS Select* virtual issue highlights recent publications in the *Journal of the American Chemical Society* that introduce novel nanoreactor systems and explores the many ways they can deepen and enhance our understanding of the world around us.

The unique, highly confined environment of a nanoreactor can result in significant changes to chemistry in comparison to that observed in the bulk solution. For example, **Roy, Skinner, and co-workers** investigated changes to water dynamics within the gyroid phase of a gemini surfactant.[1] The dynamics of water molecules trapped inside carboxylate-lined channels (between 1.4 and 1.6 nm in diameter) were found by both experiment and simulation to be an order of magnitude slower than in bulk solution and highly dependent on the curvature at the water—surfactant interface. Confinement has also been found to alter the fluorescent or Raman response of molecules. Specifically, **Shustova and co-workers** reported the construction of a metal—organic framework that is capable of imitating the emission properties of a system where benzylidene molecules are confined inside a protein β-barrel; similar fluorescence was observed for the system involving the synthetic construct and the naturally occurring protein, highlighting how confinement can be used to selectively control the interactions of molecules that give rise to fundamental physical properties.[2] **Haddon and colleagues** noted a significant Raman spectral response from a single-wall carbon nanotube upon incorporation of sulfur.[3] S_2 molecules were speculated to polymerize within the nanotube, producing chains of sulfur diradicals that interact substantially through van der Waals interactions with the walls and leading to unique Raman bands that were a direct consequence of confinement. Theoretical analyses by **Szleifer and Tagliazucchi** have highlighted the fact that ligand—receptor binding in nanoconfined environments is qualitatively and quantitatively different from the common description used in bulk solution, leading to dramatic changes in apparent dissociation constants;

their model system involved protein binding under geometrically confined environments and is guiding the design of nanochannel/nanopore-based sensors operating via changes in ionic conductance.[4]

Protein pores and channels are popular nanoreactors because they can be formed in lipid bilayers and have consistent and well-defined volumes. **Oiki and colleagues** reported on highly proton-conductive, single-file water molecule chains confined within protein nanotubes.[5] Rectification in proton conduction through polytheonamide B was observed, with the proton flux 1.6 times higher from the C-terminal to the N-terminal compared to the reverse; this behavior was attributed to changes to the orientation of the water molecules within the nanopore and the protein side chains. The similarities of the internal dimensions of the protein pore α-hemolysin vestibule to those of a DNA duplex make it an ideal nanoreactor for studying conformational changes in double-stranded DNA. **Burrows, White, and co-workers** measured the kinetics for the base-flipping process of a single cytosine base at a DNA mismatch site in a single DNA duplex confined at the 2.6 nm diameter "latch" constriction within the α-hemolysin channel.[6] They found the base-flipping at the mismatch sites to be pH dependent for the case of a cytosine—cytosine mismatch, where protonation of the cytosine pair results in greater stability of the intra-helical state through the formation of an additional hydrogen bond. Protonation of the cytosine—cytosine pair was not observed within the protein channel due to the vanishingly small number of protons that pass through the pore while DNA is inside the channel. This work highlights how confinement within a nanoreactor can drastically alter acid/base equilibria from that observed in bulk solution. The versatility of the α-hemolysin nanoreactor was also demonstrated in a recent report by **White and Macazo**, where the protein pore was incorporated into a scanning ion conductance microscopy (SICM) device.[7] As a proof of concept, the authors imaged β-cyclodextrin flux from a 25-μm pore on a glass substrate. The coupling of a nanoreactor capable of selective chemical imaging to a SICM device presents unique opportunities to map ion conductance while simultaneously acquiring chemical information.

In another approach to combining electrochemistry with specific chemical detection, **Ren and colleagues** developed an electrochemical tip-enhanced Raman spectroscopy method capable of monitoring electrochemically driven conformational changes in surface-confined aromatic molecules.[8] They were able to acquire spectra from less than 600 molecules within a nanoreactor defined by the distance between the probe tip and substrate surface (<10 nm). **Braunschweig and co-workers** utilized the solution volume between elastomeric tips and a surface as nanoreactors to investigate the effect of applied force and chain length on the reaction rate of the copper-free Huisgen cycloaddition between an alkyne and a surface-bound azide.[9] This nanoreactor system presents a highly controlled

Published: June 22, 2016

way to study the effects of such parameters in fields spanning biology to materials science. Likewise, **Mirkin and co-workers** utilized scanning probe block copolymer lithography to deliver attoliter-scale volumes of metal-coordinated block copolymers to a desired location.[10] These nanoreactors, which were typically smaller than 350 nm in diameter, were used to synthesize arrays of single alloy (bi- and trimetallic) nanoparticles (10−20 nm in diameter) on a surface and therefore create particle libraries that could be used to examine a host of industrially important catalytic reactions, among others.

Electrochemistry in confinement has been explored by **Bohn and co-workers**, who reported on the redox cycling of a ruthenium(II/III) couple at a recessed ring-disk nanoelectrode array in the absence of a supporting electrolyte (each nanopore was ∼600 nm in diameter).[11] Ion accumulation within the confined geometry of the pores and the short (150 nm) interelectrode distance gave rise to redox shuttling effects that resulted in a 2000-fold increase in the measured current. Such work has important implications in the development of sensitive electrochemical sensors. **Coutanceau, Atanassov, and colleagues** found that electro-oxidation within nanopores (30−100 nm in diameter) prepared in Pd−Bi substrates differed markedly from that observed in bulk catalysts.[12] In the context of glycerol oxidation in alkaline media, the diffusion of products, intermediates, and reactants into and out of the nanopores was significantly perturbed; the pores permitted product selectivity as a function of potential. Continuing the theme of electrocatalysis, **Pan, Bao, and co-workers** developed a model of "confinement energy" that can be used to predict the catalytic properties of different transition metals confined within a carbon nanotube.[13] Confinement within a carbon nanotube was found to shift the optimal catalytic behavior to metals with a higher binding energy because the confined environment weakens substrate adsorption interactions.

Researchers are also interested in using nanoreactors in other types of catalytic reactions. **Zhang, Dai, and co-workers** prepared nanospheres consisting of a core of metal (Pd and Pt) clusters inside an outer microporous silica shell tens of nanometers in size.[14] The Pd clusters (between 1.1 and 2.3 nm in size by transmission electron microscopy) were found to catalyze allylic oxidations of substrates small enough to enter the porous shell of the nanoreactor (i.e., cyclohexene ∼0.5 nm vs cholesteryl acetate ∼1.91 nm). Further, **Wang, Li, and co-workers** developed a hollow-structured zeolitic imidazolate framework (ZIF-8-H, ∼515 nm in diameter) as a nanoreactor for the catalysis of [3+3] cycloaddition reactions.[15] The positioning of the acidic Zn^{2+} species and basic imidazolate moieties in close proximity allows them to be activated cooperatively, and this nanoreactor also likely creates an environment that products prefer to vacate, allowing new substrates to enter. A team led by **Mirkin** uncovered that DNA-directed assembly, silica encapsulation, and subsequent calcination reactions can be used to generate body-centered-cubic superlattices of 5-nm gold nanoparticles fixed in a porous solid-state environment that are catalytically active in alcohol oxidation.[16] They found that the DNA-templated pores are important for providing access to the particle surface with the unsupported particles and the uncalcined system not showing catalytic activity. **Astruc and co-workers** employed an amphiphilic dendrimer as a catalytic nanoreactor to accelerate CuI-catalyzed alkyne−azide cycloaddition (CuAAC) "click" reactions.[17] The encapsulation and activation exhibited by this nanoreactor allows for part-per-million catalysis with turnover numbers up to 510 000.

Tomas and colleagues showed that, like catalytic reactions, biological reactions can also be promoted inside nanoreactors.[18] They found that activated amino acid derivatives trapped in the cavities of liposomes were protected against hydrolysis, reacting nearly quantitatively with other building blocks that were membrane-permeable and free in solution to form the dipeptide; hydrolysis was the prevalent reaction outside the liposomal nanoreactor. Further, **Pileni and co-workers** revealed that the applicability of nanoreactors is not limited to chemical reactions between molecules.[19] In their system, nanocrystal growth into complex colloidal supracrystals was achieved through superlattice-matched epitaxial overgrowth along existing colloidosomal nanoreactors. Lastly, **Palivan, Meier, and co-workers** introduced another important type of nanoreactor—a polymer template in which binding sites are between 4.3 and 31.5 nm apart.[20] Using such a template, molecules can be placed into close proximity to facilitate a chemical reaction or interaction less likely or unlikely to occur if a template were not used.

The selected publications are representative of some of the important topics within this broad field, deeply rooted in chemistry at the interface of nanoscience and technology, biology, materials science, and physics. We hope that this *ACS Select* collection will call the attention of the community to this exciting area of research and serve as an overview that directs the reader toward interesting new research directions and significant unanswered questions that are worthy of exploration.

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■ AUTHOR INFORMATION

Notes

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