

To catch an intermediate

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A new technique for capturing the short-lived but critical "intermediate" compounds that help carry chemical reactions which take place in aqueous solution from their starting point to the final product has been developed by researchers with the U.S. Department of Energy's Lawrence Berkeley National Laboratory (Berkeley Lab). This technique basically entails temporarily trapping the elusive transients inside molecular pyramids.

"Nature is very effective at making local chemical environments inside a protein that are very different from the surrounding aqueous solution. This is a key to binding substrate molecules and to modifying their behavior, particularly for catalysis," said chemist Ken Raymond. "We have now demonstrated that similar confined, modified chemical environments in a water soluble supramolecular metal complex cluster can catalyze substrate molecules by dramatically stabilizing the reactive intermediate, similar to what an enzyme does."

Raymond was a co-leader of this research with chemist Robert Bergman. Both hold joint appointments with Berkeley Lab's Chemical Sciences Division and the University of California at Berkeley's Chemistry Department. Raymond is a leading authority on chemical sequestering agents. Bergman is an expert on chemical reaction mechanisms.

From starting ingredients to final product, the path of a chemical reaction often includes multiple intermediate steps, especially in aqueous solution. These intermediate steps involve the formation of numerous chemical compounds that may only exist briefly and in tiny

concentrations. Despite their fleeting presence, these intermediates can have a profound impact on the outcome of a reaction. Scientists would like to know more about them, especially since water is the primary solvent in which nearly all enzymatic and other biological reactions take place. The study of intermediates that are unstable at high concentrations in water, however, presents an obvious challenge and scientists are eager to find new ways of isolating these compounds from other molecules and prevent them from continuing down the reaction pathway.

Said Bergman, "By encapsulating intermediate ions, one can generate them in much higher concentrations than are accessible in ordinary aqueous solution. In doing this, it becomes possible to use intermediates in reactions that might otherwise be subject to side reactions, which take over when the target compound is present in too low a concentration. In addition, being able to generate high concentrations of the intermediates allows us to directly study their fundamental physical and chemical properties."

Raymond and Bergman, in a study carried out with previous coworkers Vy Dong and Barbara Carl (postdoctoral fellows) and Dorothea Fiedler (Ph.D. student) studied imines. These are chemical compounds derived from ammonia and containing a carbon-nitrogen double bond, which serve as important intermediates in a wide number of enzyme-catalyzed chemical and biological reactions. Of particular interest were positively charged ions (cations) of imines that form when amines react with ketone molecules.

"Methods to efficiently generate iminium ion species in situ typically require acidic conditions and/or organic solvents," said Raymond. "In aqueous solution, iminium ions exist only transiently due to their high reactivity toward hydrolysis. Intrigued by the ability of covalent and self-assembled hosts to sequester a number of reactive species, we sought to use host-guest chemistry as a novel means of accessing iminium ions."

Raymond and his group had previously developed a water-soluble tetrahedral or pyramid-shaped assembly that featured a hydrophobic cavity which had a strong propensity for binding with, and thereby encapsulating, cations. Some of these trapped cation "guests" would be rendered inert for extended periods of time, while others would exhibit unusual cavity-controlled reactivity.

"On the basis of the affinity of this nano-sized vessel for cationic species, we envisioned that the assembly could favor the encapsulation of iminium ions generated in situ from amines and ketones in water," said Raymond. "If it were possible, this would represent a unique strategy for generating iminium ions inside the chiral pocket of a water-soluble nanovessel."

Raymond, Bergman and their collaborators found that the iminium cation-capturing tetrahedra formed spontaneously in water from a mix of gallium ions, amines and ketones. These tetrahedra immediately and effectively encapsulated iminium cations within their cavities. Based on NMR spectroscopy, anywhere from 30- to 90-percent of the tetrahedral cavities trapped iminium cations, depending upon the size of the amine and ketone molecules in the tetrahedra.

"Once encapsulated, the iminium ions remained stable for months at room temperature," said Bergman. "This technique should provide us with the ability to study the reactions of individual molecules in isolated and controlled environments."

The tetrahedral encapsulation technique developed by Raymond and Bergman has many of the same essential features as enzymatic catalysis, including the creation of cavities that allow for the recognition and control of molecular asymmetry in reactions. Such asymmetric capabilities are essential for preparing compounds that have biological activity. Raymond and Bergman's technique also holds implications for

nanoscience by making it possible for scientists to organize molecules within molecules, and for information storage. With this technique, it may also be possible to develop chemical reactions that could not previously have been done in aqueous solution.

Said Bergman, "Our highest priorities now are to widen the scope of materials that can be encapsulated by developing synthesis of nanovessels with larger cavities, to use the chirality of the nanovessels to catalyze selective reactions, and to encapsulate catalytically active metal complexes and control their selectivity using the shape and size of the cavity."

Source: Lawrence Berkeley National Laboratory

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