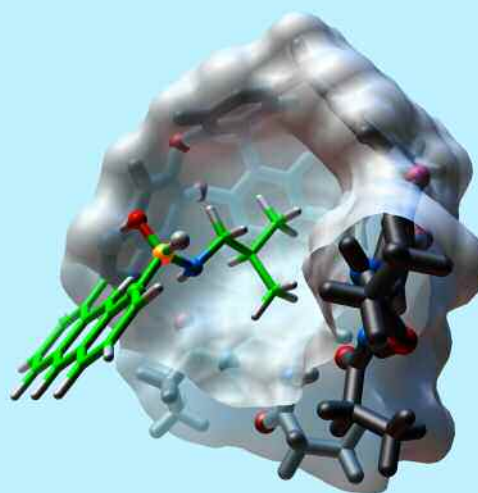


Skaggs Institute for Chemical Biology

Reactive intermediates can be stabilized and isolated in a synthetic receptor. Small amines are bound in a cup-shaped receptor and positioned near an aldehyde. Reaction occurs to give a reactive hemiaminal featuring a new asymmetric center (shown in gold). Graphics obtained with software by AVS, Inc., by Michael Pique, director, Computer Graphics Development, and Michel Sanner, Ph.D., associate professor, Department of Molecular Biology, Scripps Research.





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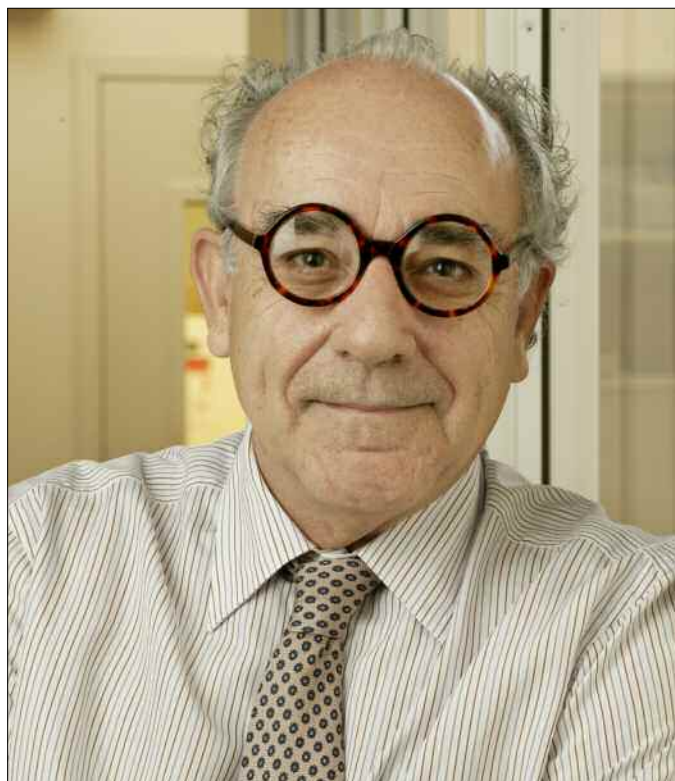
*††††† Research associates in the labo-
ratories of members other than
Dr. Rebek are included in the
lists of the respective depart-
ments in which the associates
hold joint appointments*



THE SKAGGS INSTITUTE FOR CHEMICAL BIOLOGY

In 1996, The Scripps Research Institute established The Skaggs Institute for Chemical Biology, made possible by a gift of more than \$100 million to The Skaggs Institute for Research from Aline W. and L.S. Skaggs.

Scientific members of the Skaggs Institute hold dual appointments in various departments at Scripps Research. These scientists have broad expertise in areas including the structure of biological macromolecules, chemical and antibody catalysis, synthetic and combinatorial chemistry, molecular recognition, and molecular modeling methods. With the achievements of its staff, the Skaggs Institute has assumed its research identity in the United States and throughout the world at the interface of biology and chemistry.



Julius Rebek, Jr., Ph.D.

Director's Overview

In 1996, The Skaggs Institute for Chemical Biology was established at Scripps Research through a gift from Sam and Aline Skaggs. Since then, more than \$100 million has been contributed to the research efforts at the institute. This funding supports 30 principal investigators and, in 2007 alone, fellowships for 250 postdoctoral fellows and graduate students. The individual reports of the principal investigators of the institute are provided elsewhere in this report; only a few of the highlights of research from the past year are given here.

Lisa Stowers, a new member of the Skaggs Institute, studies sensory neurons that detect chemical ligands (pheromones) that govern social behaviors. Her studies provide the tools to investigate the molecular mechanisms that underlie human social behavior. Paul Wentworth, Department of Chemistry, has elucidated the universal property of antibody molecules to oxidize water to produce hydrogen peroxide. These studies point to an earlier role of antibodies in immunity as a direct means to kill foreign pathogens through oxidation. Jeff Kelly, dean of the graduate school, is using small synthetic molecules to bind to and stabilize enzymes that prevent Gaucher disease. These molecules act as chaperones

and provide excellent leads for the development of therapeutic agents for treatment of the disease.

Paul Schimmel has traced the origins of Charcot-Marie-Tooth disease to mutations in genes for 2 aminoacyl tRNA synthetases. These results indicate expanded functions for tRNA synthetases in human cells that now include neurogenesis. Dale Boger and his group have synthesized molecules that inhibit fatty acid amide hydrolyase. These inhibitors increase the levels of endogenous analgesics that relieve neuropathic and chronic pain. Dr. Boger and his group have also defined the structural details of vancomycin action and how resistant bacteria elude this antibiotic. Through total synthesis, they have prepared a vancomycin derivative that overcomes this resistance.

Kim Janda, the new director of the Worm Institute for Research and Medicine, has observed a startling aspect of Δ^9 -tetrahydrocannabinol, the active component of marijuana. This molecule inhibits the amyloid aggregation that leads to neurodegeneration in Alzheimer's disease and provides a new lead for development of more conventional therapeutics for treatment of the disease. Ullrich Müller, another new member of the Skaggs Institute, identifies and studies genes that control the function of hearing in mammals. His results have led to animal models for deafness and the pathogenic variance of the proteins that cause it.

Barry Sharpless continues to pursue the application of click chemistry, a reaction that has lowered the obstacles that separate chemistry from biology and is widely used by chemical biologists. He has also discovered that organic reactions that occur on water's surface offer many advantages in synthesis. M. Reza Ghadiri uses rationally designed small-molecule peptide scaffolds that present chemical functional groups in predictable 3-dimensional directions. These cyclic pseudopeptides provide a new platform for drug design. Elizabeth Getzoff has studied the 3-dimensional structures of the enzymes superoxide dismutase and nitric oxide synthase. These catalysts are involved in neuronal cell death and are key therapeutic targets for the pharmaceutical industry.

My own research in collaboration with Tamas Bartfai, Molecular and Integrative Neurosciences Department, has led to small-molecule modulators of the immune system. These modulators have excellent activity in animal models of pain and fever. In other studies, members of my laboratory are synthesizing mimics of protein surfaces to provide tools for determining how molecules fit together in biological systems.

Although this overview covers just a few of the advances made in the past year, all of us in the Skaggs Institute are dedicated to reducing human suffering by finding cures for diseases. We are grateful to the Skaggs Institute for Research for encouraging our studies at the frontiers of science and to the Skaggs family for their continued support.

INVESTIGATOR'S REPORT

The Behavior of Surrounded Molecules

J. Rebek, Jr., D. Ajami, E. Barrett, T.J. Dale, N. Gombosuren, R.J. Hooley, J.-L. Hou, T. Iwasawa, E. Mann, L. Moisan, S. Odermatt, F.R. Pinacho Crisotomo, P. Restorp, M. Schramm, S. Shenoy, C. Turner, H. Van Anda

STABILIZATION AND OBSERVATION OF TRANSIENT REACTION INTERMEDIATES

Cavitands are synthetic receptors that more or less surround small-molecule targets. The cavitand provides a means to isolate molecules from the bulk medium, and the labile tetrahedral intermediates in the reaction of primary amines with aldehydes to give imines can be observed (Fig. 1). The reaction proceeds

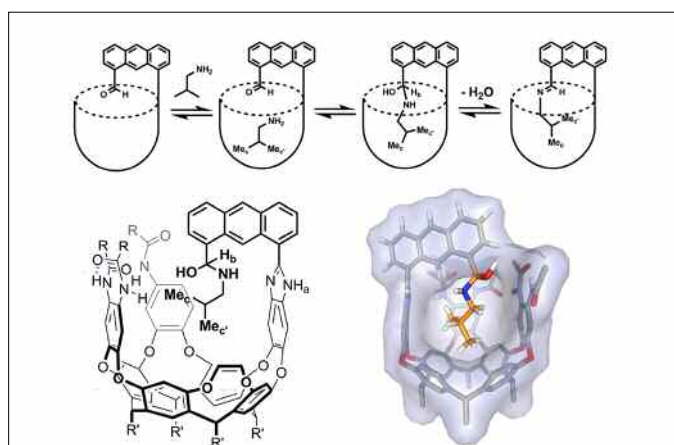


Fig. 1. Top, Illustration of the reaction taking place inside the cavity. Bottom, Structure (left) and energy-minimized representation (right) of the reactive intermediate hemiaminal. Some groups have been removed for clarity.

through an intermediate hemiaminal, which, except in special cases, does not occur in free solution. The receptor recognizes and surrounds amines of appropriate size and shape and then presents them with a covalently attached aldehyde group. The small volume of the receptor amplifies the concentration of amine reactant, and the bound hemiaminal intermediates can be detected at ambient temperatures by using conventional nuclear magnetic resonance spectroscopy. Extra stabilization is provided by hydrogen-bonding interactions. Depending on the amine added, these hemiaminals can have half-lives of up to 100 hours; in equivalent reactions in free solution, no hemiaminals occur. The receptor has

all the hallmarks of an enzyme: it presents the intermediate with complementary hydrogen-bonding groups and isolates the intermediate in a well-defined limited space, leading to selective stabilization. The synthetic receptor provides a window into an enzymelike reaction chamber.

CAVITANDS IN MICELLES

Other cavitands have served as small-molecule hosts with guest selectivity, guest exchange, reaction acceleration, and even catalysis. The deepened hydrophobic interiors facilitate sequestration of both neutral and charged organic molecules from bulk solution, most commonly via the hydrophobic effect. To develop a general cavitand for guest recognition in aqueous micelles, we prepared a hydrophobic cavitand (Fig. 2). We found

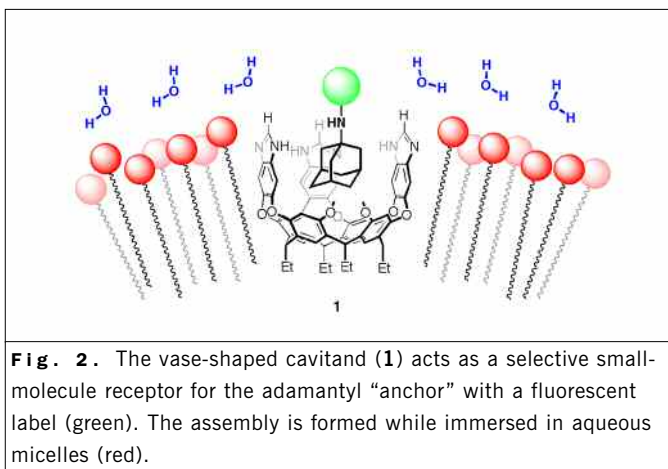


Fig. 2. The vase-shaped cavitand (1) acts as a selective small-molecule receptor for the adamantyl "anchor" with a fluorescent label (green). The assembly is formed while immersed in aqueous micelles (red).

that the cavitand is incorporated in aqueous phosphocholine micelles, folds into the vase shape, and functions as a small-molecule host. Hydrophobic guest "anchors" are held deep in its interior. These anchors include cycloalkanes, adamantanes, and nitrogen heterocycles that compete favorably with the large excess of phosphocholine alkyl side chains that make up the micelle interior. The adamantyl anchor shown in Figure 2 was further functionalized with fluorophores and dipeptides, and both guests retained their recognition properties.

These small-molecule cavitand hosts are themselves guests within the hydrophobic interior of the micelle and are thus simple biomimetic receptors. The next steps of this research program will be to transport fluorophores and druglike molecules into more complicated lipid bilayer and cellular systems.

ENERGY TRANSFER

Another aspect of our research involves modeling natural photosynthesis by using knowledge of noncovalent interacting systems. The photosynthetic pathway

involves the absorption of light, a series of electron-transfer events, and, finally, conversion of the light energy into chemical work. These electron-transfer reactions occur between a series of electron donors and electron acceptors, ultimately producing a charge-separated state. By attaching suitable electron-transfer donors and acceptors noncovalently, the desired charge-separated state from the electron-transfer event has a longer lifetime than do similar systems in which covalent attachments are used. The long charge-separated lifetime is desirable because it facilitates conversion of the absorbed light energy into chemical work.

We have attached a porphyrin to the outside of a cylindrical capsule to act as both the light absorber and the electron acceptor (Fig. 3). When a suitable electron

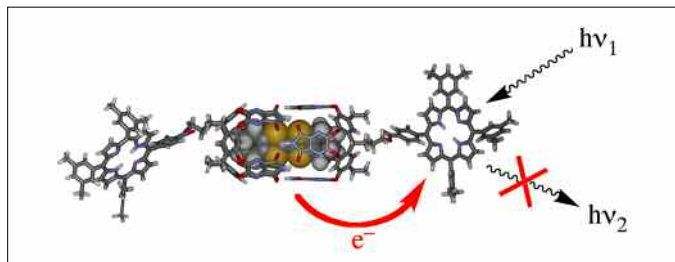


Fig. 3. Electron transfer from an encapsulated molecule to an appended porphyrin.

donor is encapsulated inside the capsule, the absorption of light by the porphyrin induces a transfer of electrons across the capsular boundary to the porphyrin and produces the desired charge-separated state. We are studying this system in an attempt to harness the captured light energy as an energy source.

CAPSULE DYNAMICS

We showed that 2 capsules of vastly different sizes, shapes, and hydrogen-bonding patterns formed not only their respective host-guest assemblies in solution but also a hybrid assembly (Fig. 4). We used fluorescence resonance energy transfer to study the formation of

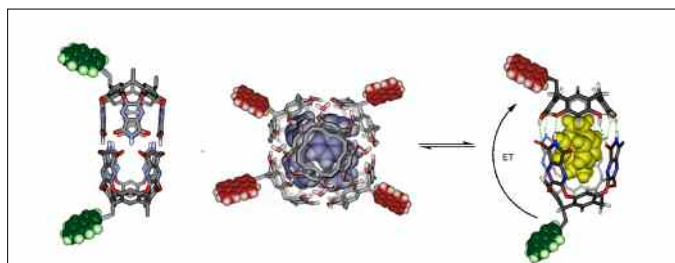


Fig. 4. Representation of the donor-labeled cylindrical capsule and the acceptor-labeled hexameric capsule in equilibrium with a hybrid capsule. Fluorescence resonance energy transfer occurs only when donor and acceptor are parts of the same assembly. ET = electron transfer.

the hybrid assembly. Fluorescence resonance energy transfer, although common in the study of dynamic processes in biology, is rarely used in synthetic supramolecular systems. It allows study of subunit exchange and guest exchange at nanomolar concentrations, providing information unattainable from experiments done at millimolar concentrations. The modules that make up the capsules were synthesized with either a donor or an acceptor fluorophore. Fluorescence resonance energy transfer occurs only when the hybrid capsule is assembled, a process that takes several days to complete.

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