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Spotlights on Recent *JACS* Publications

QUANTUM DOTS UNCAGE THERAPEUTIC MOLECULE

Peter Ford and colleagues have found a way to unlock a potentially therapeutic molecule with targeted visible light (DOI: 10.1021/ja4083599). The molecule is carbon disulfide (CS_2), and though exactly how it behaves biologically is imperfectly understood, there is evidence that it may be a powerful anticancer and anti-inflammatory agent. Other research has shown, for example, that CS_2 can react within the body to form molecules known to inhibit inflammatory and tumor-promoting targets.

While researchers have increasingly acknowledged the physiological importance of small molecules such as nitric oxide, carbon monoxide, reactive oxygen, and perhaps CS_2, delivery to targeted tissues has remained a limiting obstacle. And while CS_2 is a likely therapeutic agent, it is also toxic at high concentrations, which means control is critical.

The scientists use light to generate CS_2. They attach a molecule called dithiooxalate (DTO) to quantum dots. When hit with a beam of visible light, the photosensitive dots catalyze a reaction that changes DTO into carbon dioxide and CS_2. Red light is sometimes used for photodynamic therapy, and it can penetrate through tissue, allowing for controlled and targeted CS_2 production. According to the authors, this work represents the first demonstrated photochemical release of this potentially therapeutic small molecule.

Jenny Morber, Ph.D.

CONVERGENCE FOR DIVERSITY

Under the brand name Blenoxane, bleomycin A_2 is a glycopeptide-based anticancer agent that can effectively induce DNA cleavage. Despite high potency, bleomycin A_2 is often limited by its side effects. Potential improvements, however, can be made by modifications based on its key subunit, (−)-pyrimidoblamic acid.

In conventional synthetic routes to (−)-pyrimidoblamic acid, chiral peripherals are installed after the pyrimidine cores are made, which fails to allow full stereochemical control. Inspired by the recent discovery of [4+2] cycloadditions between electron-deficient 1,2,3-triazines and dienophiles, Adam Duerfeldt and Dale Boger develop a convergent approach to (−)-pyrimidoblamic acid, introducing all chiral centers concurrent with formation of the pyrimidine core (DOI: 10.1021/ja412298c).

The efficacy of this reaction is also demonstrated by the total synthesis of P-3A, a peptide derivative of a (−)-pyrimidoblamic acid analogue. The new convergent strategy not only provides complete control over stereochemistry but also provides feasible access to the structural diversity of drugs in the bleomycin family.

Xin Su, Ph.D.

REVEALING THE REAL-TIME DYNAMICS OF MOLECULAR JUNCTIONS

Nanoelectronics are electronic materials or devices that have some components based on nanotechnology. These components are so tiny that their behavior is markedly different from that of larger components with more bulk-state characteristics. Nanoscale junctions between components inside nanoelectronics can be made of redox molecules, which are chemical entities that can gain and lose electrons. Researchers consider redox molecular junctions to be important for engineering nanoelectronics, but unfortunately, not much is understood about them.

Now Yoram Selzer and co-workers have developed a new experimental system that can track the redox state of molecular junctions in real time (DOI: 10.1021/ja412668f). This system allows researchers to carry out statistical analyses of the kinetics of these dynamic single-electron transfer events. Earlier studies did not permit researchers to do statistical analyses because they were done in solution at elevated temperatures. Selzer and colleagues conduct their experiments in a vacuum at a temperature of 77 K and show that, under these conditions, there is a measurable change in the coherent conduction of molecular junctions, such as a ferrocene-based one, when the redox state changes.

The investigators say their method can be readily applied to other types of molecular junctions, which should allow researchers to better understand the properties of these nanoelectronic components.

Rajendrani Mukhopadhyay, Ph.D.

FUZZY NMR STRUCTURES GET SHARPER

For protein structure determination, X-ray crystallography often beats nuclear magnetic resonance (NMR) spectroscopy in terms of accuracy, mainly because NMR analyzes proteins in solution where the protein's atoms are freer to move around than in the crystalline state. However, solution structures of proteins, rather than structures in a crystal lattice, may more realistically represent the conformation of active proteins within a cell.

Gaetano Montelione, David Baker, and co-workers use a computer program called Rosetta to refine the NMR structures of a few dozen proteins with NMR restraints and find that, in most cases, the resulting structures become more accurate relative to their corresponding X-ray structures (DOI: 10.1021/ja409845w). Using basic physical chemistry principles and information about stable protein folds found in a digital database of known protein structures, Rosetta minimizes the energy of protein structures determined by NMR and can improve its accuracy.

The researchers then conduct molecular replacement (MR) solution of X-ray diffraction data using Rosetta-refined NMR structures. In all 38 cases tested, the optimized NMR structures are sufficiently accurate to identify correct MR solutions. Knowing the precise structure of a protein is crucial to understanding its function. Hence, improving the accuracy of NMR structure determination can expand the range of proteins for which accurate structures can be obtained.

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