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Spotlights on Recent *JACS* Publications

LIGAND-CONTROLLED AGGREGATION OF LITHIUM ENOLATES PREDICTS STEREOSELECTIVITY OF ALKYLATION

The stereoselective alkylation of lithium enolates is a common reaction when building complex molecules like pharmaceuticals. In the transition state of these reactions, cations and weak interactions link the enolate and the incoming alkyl group. Often, the enolate contains a group with fixed stereochemistry, called a chiral auxiliary, which controls the structure of the transition state and thus determines the stereochemical preference of the addition.

However, attaching and removing that chiral group to/from a molecule lengthens a synthesis. So chemists developed an enantioselective enolate alkylation where the chirality comes from a loosely bound ligand, rather than a covalently attached group.

Now David Collum, Armen Zakarian, and their colleagues use calculations, crystallography, and atomic spectroscopy to confirm how that chiral ligand controls the stereoselectivity of an enolate alkylation (DOI: 10.1021/ja403076u). These methods reveal information about how the reactants, chiral ligand, and lithium cations aggregate into defined structures. Those structures provide a model to predict how such reactions lead to enantioselective products.

This study adds to a growing understanding of how lithium enolate aggregation can control the stereoselectivity of a reaction. With that knowledge, chemists might be able to modify other known stereoselective reactions of lithium enolates to use chiral ligands instead of chiral auxiliaries. **Melissae Fellet, Ph.D.**

MYRIOCIN: DELIVERING A DOUBLE-WHAMMY

Dominic Campopiano and co-workers uncover a surprising and unprecedented mechanism by which the fungal natural product myriocin inhibits the activity of an enzyme called serine palmitoyltransferase (SPT) (DOI: 10.1021/ja4059876). SPT helps make sphingolipids, biomolecules that comprise part of the cell membrane. A key regulator of sphingolipid levels in the cell, SPT is also a promising drug target for a variety of diseases. Though myriocin has served as a valuable molecular tool for deciphering SPT biology, how the compounds works at the molecular level has remained elusive.

Using an impressive array of structural and functional characterization methods including ultraviolet spectroscopy, mass spectrometry, X-ray crystallography, and kinetic analysis, the authors determine that myriocin first engages in a tight binding interaction in the SPT active site. Remarkably, the enzyme then facilitates a chemical reaction that transforms myriocin into a "suicide inhibitor" of SPT, in which it becomes irreversibly attached to the enzyme and permanently inhibits its activity.

Myriocin's dual-action inhibition offers an explanation for its high potency and efficacy as an SPT inhibitor. In addition, these findings could help guide the design of a new class of inhibitors and drug leads for SPT and related enzymes. **Eva J. Gordon, Ph.D.**

DESIGNER PROTEIN LOVES METAL

Scientists envision that someday computationally designed proteins could bind metals and catalyze chemical reactions unseen in nature for industrial and medical applications. A team has taken a step in that direction by generating a novel metal-binding protein that incorporates an unnatural amino acid with an exquisite taste for metals (DOI: 10.1021/ja403503m).

The researchers, led by David Baker, use an unnatural amino acid because no single amino acid typically found in proteins can bind metals unaided. They use (2,2′-bipyridin-5-yl)alanine, or Bpy-Ala, which alone has micromolar-level affinities for a variety of metals. The researchers instruct their computer program to place Bpy-Ala within a rigid part of a protein, such as an α-helix, to lock the unnatural amino acid in place.

After expressing the computer-designed protein in bacteria, the team solves its crystal structure and find that it matches the design almost exactly. The team also finds that the designed protein binds cobalt, zinc, iron, and nickel, with affinity for zinc in the picomolar range. **Erika Gebel Berg,** *C&EN*

WATER PROMOTES LANTHANIDE-CATALYZED MUKAIYAMA−ALDOL REACTION

Although the Mukaiyama−Aldol reaction was discovered 40 years ago, the details of its mechanism remain elusive, especially for the lanthanide-catalyzed Kobayashi variation. Experimental and computational studies have aided in making this reaction useful in the asymmetric synthesis of organic molecules. Now, Keiji Morukuma and Miho Hatanaka present a systematic computational investigation that identifies the role of water in the europium-catalyzed Mukaiyama−Aldol reaction between benzaldehyde (BA) and trimethylsilyl (TMS) cyclohexenolate (DOI: 10.1021/ja407357c).

The authors first use an advanced quantum mechanical method to determine the optimal coordination numbers for hydrated Eu^{3+} and its complex with BA. Whereas $Eu^{3+}(H_2O)_8$ and $Eu^{3+}(H_2O)_9$ can coexist as stable species $Eu^{3+}(H_2O)_8(BA)$ is a reactive intermediate. An automated algorithm allows the researchers to elucidate a three-step reaction pathway for this complex encompassing, in order, C−C bond formation, proton transfer, and TMS dissociation.

The authors find that water can enhance the proton transfer and TMS dissociation steps, which drives the reversible C−C bond formation away from cleavage, thereby increasing the overall yield. In addition, they reveal that the entropic effect is crucial for the *syn*-diastereoselectivity in this reaction, because the hydrogen bond that restricts the conformation of the less-favored *anti*-transition state is not present in the *syn*-transition state. **Xin Su**

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