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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Spotlights on Recent *JACS* Publications

CESIUM'S SWEET 16: AN UNPRECEDENTED HIGH COORDINATION NUMBER

Coordination number—the number of atoms, ions, or molecules that a central ion holds as its nearest neighbors by direct bonding—is one of the organizing principles of chemistry. Ions in most compounds have coordination numbers ranging from 2 to 12, and higher coordination numbers are extremely rare. The highest coordination number yet discovered, in Th-$(H_3BNMe_2BH_3)_4$, is 15. In a recent study, Klaus-Richard Pörschke and co-workers break this record, showing that the cesium ion in $Cs[H_2NB_2(C_6F_5)_6]$ has an unprecedented coordination number of 16 (DOI: 10.1021/jacs.6b02590).

The researchers prepare this compound by reacting sodium salt with cesium fluoride in dichloromethane or water. By subjecting the resulting colorless crystals to a variety of analytical methods, the researchers find that the cesium ions in this compound are connected to 16 fluorine atoms. A similar compound formed with rubidium instead of cesium shows a coordination of only 10 for this cation, demonstrating the effect of the lower ionic radius and higher electrophilicity of rubidium.

Further experiments show that $Cs[H_2NB_2(C_6F_5)_6]$ is virtually insoluble in water. Consequently, the authors suggest potential applications for this compound in cesium removal from nuclear waste solutions, as an antidote for cesium poisoning, or as a brachytherapy agent to treat cancer with radioactive cesium.

Christen Brownlee

ELECTROPHILE EXCHANGE YIELDS TRYPTOPHAN ANALOGUES IN ONE STEP

Andrew Buller, Frances Arnold, and colleagues have streamlined synthesis of the non-standard amino acid β-methyltryptophan using an enzyme produced via directed evolution (DOI: 10.1021/jacs.6b04836).

Non-standard amino acids are used to synthesize commercial chemicals and pharmaceutical small molecules. However, existing routes to such compounds are not very efficient, making large-scale production difficult. Biosynthesis of the β-branched amino acid β-methyltryptophan, for example, involves three different enzymes.

In an earlier study, this team used directed evolution to engineer an enzyme that improves on this pathway. It is a bacterially produced variant of a subunit of tryptophan synthase, the enzyme that catalyzes formation of L-tryptophan from indole and L-serine. In an effort to optimize this system, the researchers now show that L-threonine can substitute for L-serine as an electrophile in catalysis by tryptophan synthase.

The variant has 1000-fold greater activity for the reaction with threonine than the wild-type subunit reaction with serine. By making this swap, they use the enzyme variant to produce β-methyltryptophan in just one step. In addition to improving the potential for large-scale production of this amino acid, the approach could be expanded to help synthesize other non-standard amino acids.

Deirdre Lockwood, Ph.D.

UNTANGLING AQUEOUS INSTABILITY OF ORGANOBORONIC ACIDS

Organic boronic acids are the key component in many useful synthetic reactions. However, they have long been believed to be unstable in aqueous organic media, solvent systems often involved in the widely used Suzuki−Miyaura coupling. But, the decomposition of boronic acids, especially the *in situ* aqueous protodeboronation of heteroaryl boronic acids, is still not well understood.

To gain a systematic understanding of the aqueous C−B bond cleavage process in heteroaryl boronic acids, Guy Lloyd-Jones and his team establish a mechanistic model for aqueous−organic protodeboronation based on experimental kinetics analysis and density functional theory calculations (DOI: 10.1021/jacs.6b03283). The reaction rates are found to be dominated by pH but can vary significantly, depending on the heterocycle structures. In addition to these factors that cause instability, the researchers further identify competing processes.

These results shed new light on a long overdue problem with organic boronic acids. The work also contributes to the general knowledge of organoboron chemistry, as well as C−B bond stability. In practice, the findings will be helpful to synthetic chemists for determining the best choice of reaction conditions involving heteroaryl boronic acids.

Xin Su, Ph.D.

NUCLEOTIDE ANALOGUE MINIMIZES OFF-TARGET RNA INTERFERENCE

RNA interference, or RNAi, uses a short double-stranded RNA to target complementary mRNA for digestion, thereby blocking protein synthesis and producing a genetic knockout. But the system also permits extensive and undesirable off-target gene regulation, limiting its utility. Now Ian MacRae, Peter Beal, and colleagues describe a strategy to minimize that concern (DOI: 10.1021/jacs.6b06137).

This team previously reported a nucleotide analogue (1-ER triazole I) that could be inserted at the guide RNA 5′ end without disrupting RNAi efficiency. Here, they report the 2.3 Å crystallographic structure of human Argonaute 2 (hAgo2, the RNAi nuclease) with a modified guide RNA and test its impact on off-target RNAs.

1-ER triazole I extends into the hAgo2 "central cleft", where it disrupts binding to off-target mRNAs. That modification boosts on-target potency 2-fold relative to natural nucleotides while decreasing off-targeting 4-fold. A further modified base exhibits 3-fold lower potency against on-targets, but 2 orders of magnitude lower potency against off-targets.

"Our results directly demonstrate that hAgo2 function can be modulated by projection of substituent groups into the hAgo2 central cleft, thus revealing a new approach to tuning target selectivity and controlling human RNAi," they conclude.

Jeffrey M. Perkel

Published: August 3, 2016

DOI: 10.1021/jacs.6b07707
J. Am. Chem. Soc. 2016, 138, 9325−9326

LOCALIZED SURFACE PLASMON RESONANCE BEYOND NOBLE METALS SEES THE VISIBLE LIGHT

Interest continues to grow in nanostructures that exhibit localized surface plasmon resonance, an oscillation of surface electrons upon light excitation. This phenomenon has promise in a variety of areas, including biological detection and energy storage/conversion. Though noble metals are the best-studied, highly doped semiconductors have recently emerged as an alternative material. However, these semiconductors tend to display plasmon frequencies in the infrared spectrum, and manipulating them toward shorter wavelengths in the visible region remains a challenge.

In a recent study, Hefeng Cheng, Baibiao Huang, Hiromi Yamashita, and co-workers demonstrate a technique that tunes metal oxide semiconductors to visible light wavelengths-pinning plasmoic materials (DOI: 10.1021/jacs.6b05396). The researchers take advantage of a method called hydrogen spillover to dope MoO_3 and WO_3 with hydrogen, creating hydrogen bronzes, and the introduced abundant delocalized electrons, revealed by theoretical calculations, sustain their surface plasmons. By varying their stoichiometry through reduction temperatures, metal species, the nature and size of metal oxide supports, and oxidation treatments after hydrogen doping, tunable plasmon resonance is observed in a wide range. These new materials show promise for heterogeneous catalysis, speeding *p*-nitrophenol reduction with visible light. The authors suggest the potential of using low-cost and Earth-abundant plasmonic materials for broader practical applications.

Christen Brownlee

INTRAMOLECULAR OLEFIN HYDROAMINOMETHYLATION GONE ASYMMETRIC

Hydroaminomethylation (HAM), an important transformation for complex amines, typically involves alkene hydroformylation, amine condensation, and hydrogenation. However, asymmetric HAM reactions are rarely reported, because racemization often occurs upon the dehydration of the condensation products.

In a HAM reaction, if the alkanolamine intermediate can be stabilized, the stereogenic center will remain intact during further conversion. Based on this premise, Hui Lv, Xiu-Qin Dong, Xumu Zhang, and colleagues have developed a rhodium-catalyzed stereoselective interrupted intramolecular HAM through a stable and chiral five-membered-ring hemiacetal intermediate (DOI: 10.1021/jacs.6b03596). Starting from 1,2-distributed olefins, the authors are able to obtain in a single operation chiral pyrrolidinones and pyrrolidines, valuable molecular motifs extensively found in popular drugs and important natural products.

The hemiacetal intermediates prove to be highly versatile, as they enable a variety of direct transformation, demonstrating the synthetic utility of the reported methodology. In addition, this strategy, as an uncommon example of asymmetric HAM, provides convenient access to chiral pyrrolidinones and pyrrolidines, which may simplify existing routes to compounds of pharmaceutical interest containing these units.

Xin Su, Ph.D.

DOI: 10.1021/jacs.6b07707
J. Am. Chem. Soc. 2016, 138, 9325−9326