Reaction Mechanisms Conference (RMC) 2022
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Boulder, Colorado

Abstracts

Plenary and Short talks

Heterobimetallic d8-d10 Complexes as Intermediates, Transition States, and Transition State Analogs for the Transmetalation Step in Sonogashira and Negishi Coupling Reactions

Prof. Dr. Peter Chen, Raphael Oeschger and Raphael Bissig

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We report an experimental study, with accompanying DFT calculations, on a series of heterobimetallic complexes with Pd(II) and Cu(I), Ag(I), or Au(I). The isolable complexes, for which we have extensive structural data in the solid state, in solution, and in the gas phase, are models for the intermediates and transition state for the transmetalation step in Sonagashira and Negishi coupling reactions, among which, according to the DFT calculations, only the transition state has the two metal centers within bonding distance. The d8-d10 metal-metal interaction has been proposed to be a stabilizing factor lowering the transition state for transmetalation, which naturally then becomes relevant to cross-coupling by shifting the turnover-limiting step to one of the other elementary reactions in the catalytic cycle. Furthermore, we report a substituted version of an analogous heterobimetallic complex in which a competing dissociation sets an upper-bound on the strength of the d8-d10 metal-metal bond. Analysis of the structures in the solid state and in solution, and the competitive dissociation experiment in the gas phase, indicate that the dispersion-corrected DFT methods used in the study appears to overestimate the strength of the metal-metal interaction, thus distorting the shape of the computed potential energy surface systematically for transmetalation.

Keywords: bimetallic, transmetalation, cross-coupling

Isomerization, Cracking, and Dehydrogenation of Cyclohexane by Group 10 Metal Cationic Complexes in the Gas-Phase

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Cyclic hydrocarbons comprise a significant portion of petroleum reserves. Their transformation into high-commodity chemicals like hydrogen, ethylene, and propylene constitutes a large economic portion of the petroleum industry. For example, cyclohexane can be thermally "cracked" to produce ethylene and 2-butene or two molecules of propylene. The cracking process requires high temperatures (> 700 °C) and pressures, and even the use of catalysts does not afford significantly lower temperatures.

Recently, we showed that [(phen)M(X)]+ complexes (where phen is 1,10-phenanthroline, M = Ni, Pd, Pt, and X=H or CH3) can activating C-H and C-C bonds in hydrocarbons. Here we explore the utility of mass spectrometry to study catalytic processes of cracking and dehydrogenation of cyclohexane.

DFT calculations revealed that for cyclohexane both axial and equatorial positions are accessible for C-H activation. Upon collisional activation two key competing processes operate. The first (Pd, Ni) involves ring opening followed by "chain walking" of the metal ion along the hexyl chain which in turn is followed by "cracking" of the hexenyl chain, accompanied by the release of alkenes. The resultant product ions can be fragmented further under multi-stage CID conditions to ultimately reform the hydride or methide complexes, which can react with cyclohexane again, thereby closing catalytic cycles. The second type of process involves sequential dehydrogenation reactions. (Dominant for Pt). Cyclohexane can be dehydrogenated all the way to benzene. These results highlight once again how the choice of the metal can influence the selectivity in C-H and C-C bond activation reactions.

Crystals at Work

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Recent findings highlight crystals that can be flexible and when subject to external stimuli, e.g., light or pressure, can bend, hop, or twist. Irradiation of azido compounds causes them to release N_2 gas, that can cause photodynamic response of the azido crystals. Herein, we compare photolysis of organic azido derivatives in various crystal lattices to gauge how intermolecular forces affect their photodynamic behavior.

Carbonyl-Olefin Metathesis

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Mechanistic-Driven Development of Fe-Catalyzed Multicomponent Cross Coupling Reactions

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Despite advances in high-throughput screening methods leading to a surge in the discovery of catalytic reactions, our knowledge of the molecular-level interactions in the rate- and selectivity-determining steps of catalytic reactions, especially those involving highly unstable and reactive open-shell intermediates, is rudimentary. These knowledge gaps prevent control, suppression or enhancement, of competing reaction channels that can drive development of unprecedented catalytic reactions. In this talk, I will focus on our use of high-level quantum mechanical calculations, rigorously calibrated against experimental data, to interrogate the mechanisms and to guide the development of new catalysts and reagents for currently sluggish or unselective reactions. In particular, I will focus on our use of combined experimental and computational tools to understand and develop new (asymmetric) three-component iron-catalyzed radical cascade/cross-coupling reactions.

Metalloradical Catalysis for Asymmetric Radical Reactions

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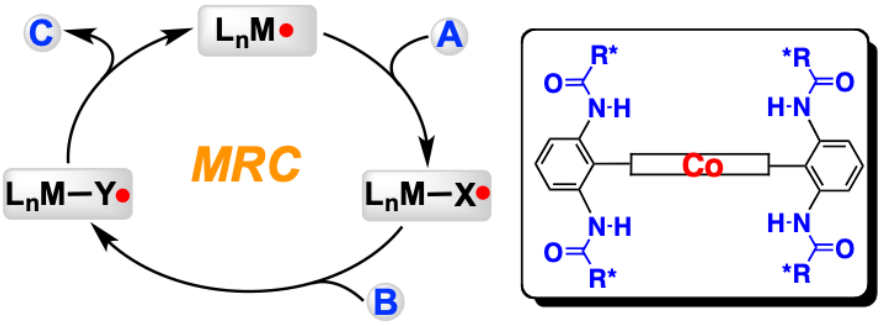
Organic synthesis has been dominated by the development of chemical reactions that are based on two-electron heterolytic ionic processes, either stoichiometrically or in catalytic fashion. While one-electron homolytic radical chemistry is equally rich and has been demonstrated with a number of unique features, its application in practical synthesis of organic molecules has been hampered by several enduring challenges. Over the past two decades, my laboratory has been in the process of formulating metalloradical catalysis (MRC) as a general concept to guide the development of fundamentally new approaches for controlling both reactivity and stereoselectivity of radical reactions. In essence, metalloradical catalysis aims for the development of metalloradical-based systems for catalytic generation of carbon-, nitrogen-, and oxygen-centered radicals from common organic compounds without the need of radical initiators or the use of light. The subsequent reactions of the resulting organic radical intermediates, which remain covalently bonded or closely associated with the metal center, can be selectively controlled by the catalyst. For achieving enantioselective radical reactions via MRC, we have developed a family of unique chiral metalloradical catalysts based on structurally well-defined Co(II) complexes of D_2-symmetric chiral porphyrins with tunable electronic, steric, and chiral environments. These Co(II)-based metalloradical catalysts have been shown to be highly effective for a wide range of stereoselective organic reactions, including olefin cyclopropanation, olefin aziridination, C–H alkylation and C–H amination. Due to their distinctive stepwise radical mechanisms that involve unprecedented α-metalloalkyl, α-metalloaminyl and α-metalloxyl radical intermediates, the Co(II)-based metalloradical systems enable addressing some long-standing problems in these important organic transformations.



Hybrid Pd-radical Chemistry: New Mechanism, New Possibilities

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We have uncovered new reactivity of hybrid Pd-radical species, generated at room temperature under visible light without exogenous photosensitizers, which lead to development of novel transformations, including new types of Heck reaction, aliphatic C–H functionalization methods, as well as new cascade transformations. These methods employ easily installable/removable silicon-based, amide, and sulfonamide linkers.

The scope of these transformations will be demonstrated, and the mechanisms will be discussed.

Recent Studies on the Mechanism of BHAS Reactions

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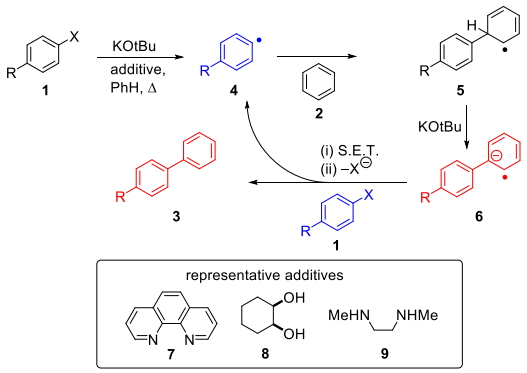
Base-induced homolytic aromatic substitution (BHAS) reactions, forming biaryls from aryl halides and arenes, have become recognised as widespread since their discovery in 2008.1-6 Three proposals for their initiation have been made: (i) by organic super-electron donors, formed by reaction of KOtBu (or, in some cases, NaOtBu) with diverse organic additives, (ii) by reaction of arenes with benzynes that are derived from the aryl halides and (iii) by ground state electron transfer from KOtBu to aryl halides.



This presentation will discuss our recent research on the mechanism of initiation and propagation of these reactions.

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Synthetic Half-Reactions

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This lecture will describe the emerging theory of synthetic half-reactions. Apart from electrochemistry, which offers a convenient formalism to compare electron transfer processes on electrode surfaces, there is no accepted system that dissects organic reactions into components with the goal of matching uphill steps with cognate downhill processes. Such a system would allow one to look at organic reactivity from a different perspective that would deemphasize the role of orbitals in favor of the arguably more intuitive enthalpic arguments. Given the frequent (although often incorrect) use of the term "driving force" in organic chemistry, it stands to reason that such a treatment of reactivity is long overdue. I will attempt to describe the origins of the theory of synthetic half-reactions and demonstrate their utility on examples from our and others' laboratories.

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Nickel-Mediated Radical Pathways and Applications in Cross-Coupling Reactions

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Reactions involving organic radical intermediates have been traditionally regarded as overly reactive and unselective. Nickel complexes can reversibly coordinate to radicals and modulate the reactivity and control the selectivity of reactions involving radical intermediates. Our mechanistic studies answer fundamental questions, such as "how do nickel complexes initiate radical formation from various precursors", "how do radicals interact with nickel complexes", and "How do ligands serve to stabilize open-shell intermediates and facilitate catalytic reactions?" Mechanistic data accounts for selectivity observed in nickel-catalyzed cross-coupling reactions.

Towards Understanding and Controlling Mechanistically Ambiguous Transformations

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Glycosylations represent one of the more sensitive and mechanistically complex organic transformations. The mechanistic path followed, as well as the nature and conformation of intermediate structures, is highly dependent on both the intrinsic properties of the coupling partners and the environmental conditions chosen. To interrogate the identity and influence of these factors, we have used a flow chemistry platform to build a concise dataset exhibiting a broad range of stereoselective outcomes. This dataset was used to train a machine learning algorithm to gain greater insights into the balance of these factors and to predict the stereoselectivities of this model class of glycosylations. In this talk, we will discuss what we have learned about the factors impacting this ambiguous mechanism, and how these can suppress or enhance the intrinsic properties of the coupling partners. Lastly, we will see how these insights may be transferrable, as we seek to understand and control similar variable and divergent transformations such as LA-activated epoxide ring openings.

Photochemical Generation of Alkylidenecarbenes from Phenanthrene-based Methylenecyclopropanes: An Overview

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Several laboratories, including ours, have shown that cyclopropanated phenanthrene precursors can be photolyzed to produce "saturated" carbenes in which the divalent carbon is attached to two separate substituents.[(1)] In this overview, we describe subsequent extensions of this approach to produce "unsaturated" acyclic alkylidenecarbenes, in which the the carbene center is connected to a single substituent by a double bond, from analogous precursors.[(2)] These alkylidenecarbenes typically undergo a Fritsch-Buttenberg-Wiechell (FBW)-type rearrangement[(3)] to produce alkynes. A further extension of this approach to generate strained cycloalkynes is also presented.[(4)]

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Confessions of a Carbocation Addict

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In this talk I will discuss our recent efforts to utilize phenyl and vinyl carbocations in stereoselective C–H functionalization reactions. We will describe how these reactive dicoordinated carbocations can be generated under mild conditions and utilized in the selective C–C bond forming reactions of simple hydrocarbons. Moreover, we will discuss our efforts to understand the mechanism of these reactions through computational chemistry, kinetics, electron microscopy, and isotopic labeling studies. In the second half of the talk we will discuss our efforts to bring electron microscopy to organic chemistry through the use of MicroED and other CryoEM modalities.

Mechanistic Investigations into the Formation of Sulfur-Containing Heterocycles by C–H Functionalization

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The majority of active pharmaceutical ingredients and agrochemicals contain at least one heterocycle in their scaffold. While nitrogen and oxygen heterocycles are most common, sulfur-containing heterocycles are becoming increasingly important.

The Bolliger group has developed a new strategy to prepare both charged (Figure 1a) and neutral (Figure 1b) tricyclic sulfur-containing heterocycles. The target compounds are conveniently obtained from air stable precursor via selective deprotection of a thiol followed by on oxidative cyclization. Using this procedure, it is possible to obtain a variety of tricyclic heteroarenes with diverse functional groups. In this presentation we will highlight our newest investigations into the mechanism of the cyclization reaction and discuss our results with respect to possible radical or ionic reaction pathways.

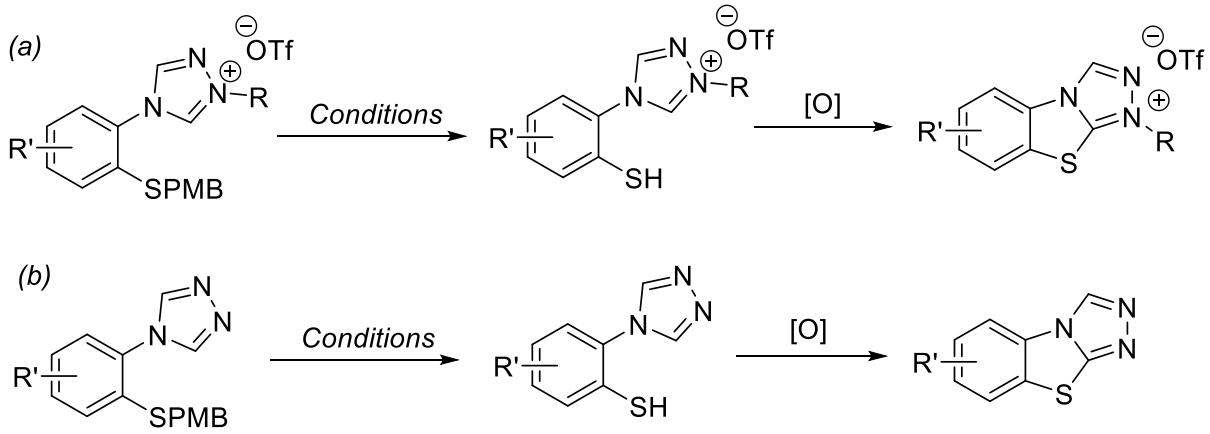

Figure 1. Formation of tricyclic heteroarenes by an oxidative cyclization.

Beyond Strain Release: Delocalisation-Enabled Organic Reactivity

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The principle of 'strain release' dominates reaction design across many areas of chemical synthesis and is a fundamental element of undergraduate chemistry teaching. [1] Strain release is used as a classical tactic to drive organic transformations, with applications in medicinal chemistry, polymer science, and bioconjugation [2] However, strain release alone is an insufficient predictor of reactivity, as seen in the equivalent strain energies, but disparate reactivity of cyclopropane and cyclobutane.[3]

In this contribution, I discuss our team's efforts to elucidate the influence of strain release on reactivity, considering a wide range of examples, from three/four-membered ring openings to azide/cycloalkyne click reactions. We provide a unifying framework that reveals electronic delocalisation (e.g., conjugation and hyperconjugation) as a key factor operating alongside (and even dominating) strain release reactivity.[4,5] We also introduce a 'rule of thumb' that, based on thermodynamic and delocalisation parameters, enables one to quickly estimate reactivity trends. We anticipate that these findings will enhance our understanding of the reactivity of strained molecules and help in the design of 'strain release' tactics for application in organic, medicinal and polymer chemistry.[5]

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Energy Labeling and Read-Out as a Tool to Study Hidden Steps in Mechanisms

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Most experimental methods for the study of reaction mechanisms are directed at the composition and structure of transition states. This includes the determination of rate laws and activation parameters, the observation of substituent effects, solvent effects, and isotope effects, or most simply the consideration of a reaction's stereo- or regioselectivity. In each, the mechanistic probe gauges the nature of a transition state by the rate of passage through that transition state, which must be either a rate-limiting step or one that determines an observable product selectivity. For multistep mechanisms, it is typical for most of the steps to be kinetically hidden, having no experimentally observable effect on the rate or selectivity.

Computational chemistry can often be used to fill in the gaps, but a computational approach may fail for many reasons. Of particular difficulty are mechanisms involving non-adiabatic steps, charge separation and strong solvation effects, non-statistical dynamics, or simply surprising mechanisms that are not considered for exploration in a computational study.

We have found that under certain circumstances the observed selectivity subsequent to an intermediate may vary with the mechanism by which that intermediate was formed. This works because each step in a mechanism initially imbues the resulting intermediate with excess energy. In a designed probe, that energy can be read out from analysis of later selectivity. The energy read out can then be used to characterize the mechanism.

This talk will describe the application of energy read out to the identification of hidden steps in recently developed alcohol-activation reactions. In one case, a proposed hydrogen-atom abstraction mechanism is found to occur instead by a hypobromite chain mechanism. In another, a proposed multi-site proton-coupled electron transfer reaction is found to occur by a previously described but under-appreciated combination of a proton transfer with an adiabatic inner-sphere electron transfer. The implications of the mechanistic probe and the newly identified mechanisms will be discussed.

Dynamic Control of Reactivity and Selectivity in Dirhodium Tetracarboxylate Promoted Reactions

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Recent results of quantum chemical calculations on the reactivity of Rh-bound carbenes will be described, with an emphasis on dynamic models of reactivity and selectivity.

Molecules in a Hurry to Escape Antiaromaticity

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Antiaromatic molecules, unless kinetically trapped or fused to aromatic rings, often are short-lived and difficult to work with—they escape the fate of being called antiaromatic. [4*n*] Rings like cyclobutadiene and cyclooctatetraene can dimerize or adopt nonplanar geometries to avoid antiaromaticity. Benzene is [4*n*+2] antiaromatic in the lowest excited state and isomerizes to fulvene and to the highly strained benzvalene. We recognized that excited-state proton transfer (ESPT) and proton-coupled electron transfer (PCET) reactions can be important pathways for antiaromaticity relief; many examples will be discussed.

Catalysis and Complexity: Adaptive Catalysts for Emergent Function

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Exploiting the power and versatility of catalytic processes requires rigorous interrogation of the constantly changing environment of the catalyst. Detailed understanding of critical events affecting the catalyst, such as activation and deactivation, unproductive off-cycle pathways, and changes in dominant species, is critically important for designing new reactions. However, the seemingly formidable challenge of controlling the reactivity of complex catalytic systems that involve dynamic and rapidly equilibrating mixtures of intermediates may be their advantage: well-defined and therefore non-adaptable catalysts are often inefficient when compatibility with many functional groups and conditions is the goal.

Transition metal-catalyzed reactions of unsaturated species offer an instructive example of weak interactions channeling a complex the process into a particular pathway. Interfaces of two immiscible liquids, such as water and organic compounds, are another example of dynamic catalytic systems that take them to a new level: the catalyst truly does not exist unless a set of reactants is presented. This emergent property of water-organic interfaces profoundly affects many organic reactions by accelerating them or changing their selectivity. Performing reactions “on-water” offers an intriguing opportunity not only to influence chemical reactivity but to peek into the symphony of interactions that are happening at the liquid-liquid interfaces. Case studies of our investigations, illustrated by reactions performed on water/on droplets, teach us that these seemingly simple transformations involve an impressive variety of intermediates and pathways yet often proceed with high selectivity and efficiency.

DNA Cation Radicals: Formation, Action Spectroscopy, and Dissociation Mechanisms

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Radical reactions are at the core of DNA degradation following ionization. We have been developing methods to generate DNA-related cation radicals of nucleobases, nucleosides and oligonucleotides under well-controlled conditions of the rarefied gas phase in an ion trap mass spectrometer. Collision-induced dissociation and electron transfer in precursor ions will be shown to produce cation radicals of different types that are investigated by multistep tandem UV-Vis photodissociation action spectroscopy. Spectra interpretation is aided by DFT calculations of potential energy surfaces, reaction kinetics and dynamics, and vibronic spectra. Mechanisms of cation radical dissociations will be discussed.

Intrinsically Chiral and Multimodal Click Chemistry

Han Zuilhof

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Click chemistry has revolutionized many facets of the molecular sciences, with the realization of reactions that are ‘‘modular, wide in scope, give very high yields, generate only inoffensive byproducts that can be removed by nonchromatographic methods and are stereospecific”.[i] Yet surprisingly little attention has been given to the development of intrinsically chiral click reactions (potentially enantiospecific rather than ‘only’ enantioselective due to chiral auxiliary groups), while the modularity of many click reactions is best compared to one-dimensional LEGO. Of course, much could be done within the constraints – hence forementioned revolution – but it drove attention towards an extension of available click chemistries. The talk will focus on the resulting investigations in the field of S(VI) exchange chemistry.

Excited State Aromaticity and Antiaromaticity: Drivers for Photoreactivity

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Aromaticity and antiaromaticity impact on reactivity in both the electronic ground and excited states, yet the electron counting rules differ in various states. Baird's rule tells that annulenes with 4n pi-electrons are aromatic in their lowest pipi* triplet states (T1) while those with 4n+2 are antiaromatic,[1] a rule which is often extendable to the lowest singlet excited state. Hence, benzene is excited state antiaromatic (ESAA) and its photorearrangement to benzvalene relieves antiaromaticity.[2] Photoreactions of benzene derivatives can also be interpreted in terms of ESAA relief,[3,4] supported by computational studies of cyclopropyl (cPr) ring-openings of various cPr-substituted (hetero)annulenes in their T1 states.[5] The T1 state activation energies for cPr-openings of cPr-substituted [4n+2]annulenes are generally lower than those of cPr-substituted nonaromatic reference compounds while the activation energies are higher when the cPr group is attached to a T1 aromatic [4n]annulene. The strive for excited state aromaticity can also be seen computationally through compounds that can attain T1 homoaromaticity.[6,7]

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Scratching the Surface of Two-Dimensional Polymers

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Synthetic two-dimensional polymers have been synthesized from trigonal-star monomers linked by anthracene dimers. The strategy relies on locking in place the supramolecular order that arises from suitably designed monomers. This strategy, demonstrated in crystals and on surfaces, enables the preparation of large ($> 10^{12}$ repeat units) macromolecules that have a precise molecular structure. The characterization, properties, and potential uses of these 2D polymers will be discussed.

Direct Functionalization of Strained Hydrocarbons

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The chemistry of strained hydrocarbons represented for example by bicyclo[1.1.1]pentanes (BCPs) and cubanes has been experiencing a huge boom in recent years, as clearly demonstrated by numerous articles and reviews. In the case of BCPs, much effort has been directed into the development of modern synthetic techniques that allow incorporation of these cages into complex systems using various cross-coupling reactions on the bridgehead carbon atoms. Such 1,3-disubstituted BCPs thus appeared not only as the biologically active substances, but also became important players in the field of supramolecular chemistry.

In contrast, the reactivity of the methylene bridges on BCPs has been much less explored than the chemical transformations involving bridgehead carbon atoms. The pool of bridge-substituted cages is relatively small, and most of these structures are synthesized stepwise from suitably designed precursors and not from the parent and easily accessible 1,3-disubsituted BCPs.

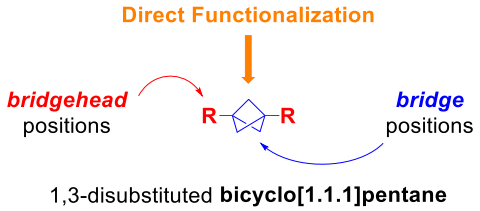

Figure 1. Bridgehead vs. bridge substituted BCPs.

We decided to fill this obvious gap and introduced methodology allowing smooth and chemoselective installation of various functional groups (primarily chlorine atoms, but also chlorocabonyl units) to the structures of such strained species. Each of these unique compounds can be then implemented into numerous systems using very well-established chemistry on the bridgehead carbon atoms. Herein, selective formation of individual isomers will be rationalized and various characteristics of these compounds (relative strain energies, pK_a values of corresponding carboxylic acids, etc.) will be discussed.

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Preparation of Porphyrin Analogs of Graphene

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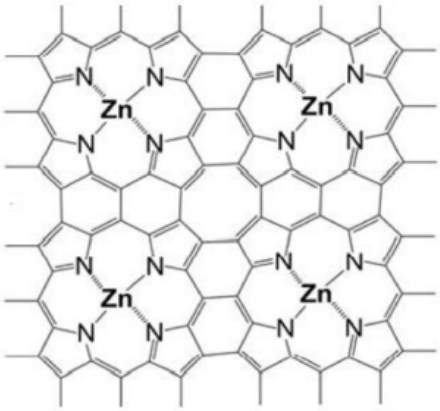
Porphene, $(C_{20}N_4H_2)\infty$, is a regular fully conjugated two-dimensional polymer similar to graphene, composed of fused porphyrin instead of benzene rings, with macrocycle centers 0.84 nm apart. A single sheet of free-base porphene can be prepared by oxidative polymerization of a bilayer of parent Zn(II) porphyrin on the surface of an aqueous subphase containing K2IrCl6 in a Langmuir-Blodgett trough. In contrast, the same treatment converts Pt(II) porphyrin to Ir(III)Cl porphene. The structures of the porphenes were established by several spectroscopic and imaging techniques, both in situ and after transfer to solid surfaces or grids, which produces multilayers (porphite). It appears that porphene has two valence tautomers of similar but unequal energies that interconvert easily at room temperature and in that regard resembles antiaromatic species such as 1,2-d2-cyclobutadiene.

The two protons centered in each macrocyclic ring of free-base porphene can be reversibly exchanged for metal ions, such as Zn(II) and Fe(II), under control of pH and redox conditions. Since the metal ions can carry ligands, metalloporphene properties can be tuned widely without taking any π centers out of conjugation.



Zn(II) porphene

Second Sphere and Solvent Effects on Reactivity

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Solvent linear free energy relationships provide insights into the solvent parameters that are important in controlling reactivity, but use overall descriptors for specific solvents.[1] Hunter has described an electrostatic competition model which is useful for describing binding events in solution through a series of specific localised contacts that reflect specific supramolecular contacts, and is successful for predicting equilibria in mixtures of solvents from the molecular features of the solvents.[2] The model is attractive as it can be implemented simply, and can be applied to mixtures of solvents based on the parameters for local molecular features. We have been applying this model to the analysis of solvent effects on reactivity.

We have also been using the closely related effects of second sphere properties in metal ion complexes to explore how we can create more efficient catalysts for phosphate ester cleavage. We have shown that weak hydrogen bond donors greatly enhance the activity of these Zn complexes,[3] but this has been difficult to improve. Recently, we have introduced new substituents which show remarkable enhancements in activity and investigated how these cooperate with other modes of activation.

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Mechanistic Insight into Silanol Condensation Under Conditions of Rapid Condensate Removal

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The condensation of silanol pre-polymers is an important step in the commercial production of silicone materials. A sometimes undesirable side-reaction accompanying condensation is the formation of cyclic oligomers. In the present studies, we sought greater understanding of the mechanism of the Bronsted acid-catalyzed condensation and attendant cyclics formation in hope of identifying methods that allowed greater control of the condensation product distribution. Computational studies of the condensation mechanism predicted facile proton mobility and privileged structures conducive to condensation in which the proton is preferentially stabilized. Experimental mechanistic studies for silanol condensation were carried out in a modified wiped-film evaporator allowing the mechanism of the reaction to be studied in the irreversible kinetic regime. Under such conditions, the resting state of the Bronsted acid catalyst determines the kinetic order and overall course of the reaction in agreement with computational predictions

Molecular Rotors for the Study of Transition State Stabilization

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The stabilization of transition states by non-covalent interactions have been cited as a key contributor to the catalytic abilities of enzymes and synthetic catalysts. To study the kinetic effect of non-covalent interactions, a series of molecular rotors were synthesized that forms a single non-covalent interaction in the bond rotation transition state (Figure 1a). Thus, the rate of rotation of the rotor provided a direct measure of the transition state stabilization. The rigidity of frameworks and the intramolecular nature of the interactions enabled precise positioning of the interacting functionality. An array of non-covalent interactions were examined including: hydrogen bonding,[1] nà$\pi^*_{C=O}$,[2]nà$\pi_{aromatic}$,[3] nàπ^*_{nitro}, nàπ_{boron} and electrostatic interactions (Figure 1b).

The rotational barriers ($\Delta G^{\ddagger}_{exp}$) were measured using dynamic NMR methods such as EXSY and line-shape analysis. The barriers were compared with control rotors which only formed steric interactions enabling separation of the transition state steric and non-covalent interactions (Figure 1c). Large transition state stabilizations were observed for moderate strength non-covalent interactions. For example, neutral hydrogen bonds and nà$\pi^*_{C=O}$ stabilized the transition states by 4-10 kcal/mol. The transition state structures and the geometries of the non-covalent interactions were studied using molecular modeling, which was able to accurately reproduce the experimental rotational barriers. Energy decomposition analysis provided insight into the origins of the large effect of these normally weak interactions on the transition states.

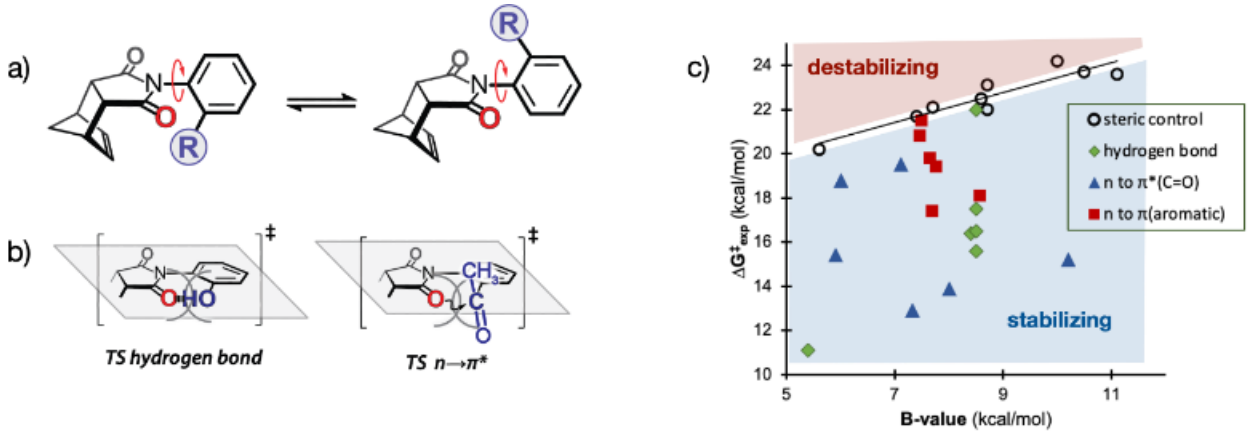

Figure 1. Schematic representation of the a) molecular rotor bond rotation process, b) examples of the intramolecular non-covalent interactions in the bond rotation transition states, and c) comparison of the experimentally measured rotational barriers ($\Delta G^{\ddagger}_{exp}$, kcal/mol) versus the steric parameter (B-value) which provides a measure of the transition state stabilization by the non-covalent interactions.

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Electronically Driven Stereogenesis: Facial Selectivity in the Reduction of Adamantanoness

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In our studies of the phenomenon of face selection in addition and elimination processes, we have made much use of 5-substituted adamantan-2-ones and their derivatives. We have found it possible to account for our observations by assuming that the transition states are stabilized by hyperconjugative donation of electrons into the σ* orbital of the newly forming or breaking bond by the antiperiplanar vicinal bonds. When two of these vicinal bonds are adjacent to an electron-withdrawing substituent, they are rendered electron-poor by it; the two transition states are then unequal in energy, and as a result, syn attack is favored.

We have found that the ratios are larger when the electron demand is greater and that it can approach carbocations where the trigonal carbon carries a positive charge. It, therefore, occurred to us that we might be able to increase the selectivity of ketones by modifying either the carbonyl function or the group X at C-5 so as to make them more electron demanding, and we report here several experiments to assess this idea.

The first of these experiments was based on an observation already in hand, namely, influence diastereoselectivity is the deliberate addition of one of the more traditional Lewis acids. A good example is the complex of 5-Phenyl-2-adamantanone with antimony pentachloride, which has been isolated in pure form and the crystal structure. The increased charge at C-2 is clear both from its deshielding (by 25 ppm relative to the pure ketone) and from the increased C=O bond length (by 0.045 Å). We furthermore found the carbonyl infrared frequency to be reduced by more than 40 cm-1. The reduction of this complex indeed produced the E-alcohol in excess by a margin of 65:35, compared with that of 57:43 for the free ketone. However, the Lewis-acid enhanced reaction also led to side products: a mixture of 2-chloro-5-phenyladamantanes is present as well as two other components that were not identified. Similar results were obtained by adding titanium tri- or tetrachloride; stannic, magnesium, aluminum, or diethylaluminum chloride; nickel bromide; or boron trifluoride etherate; the quantities of side products (but not the E/Z ratio) varied from negligible to serious depending on the counterion, medium, reaction time, and so on, but we did not undertake a systematic investigation. We assume that the similarity of the ratios regardless of the strength of the Lewis acid is due to the more rapid reaction of the complexed ketone, so that the proportion of this species is not important Electron withdrawing substituent at C5 with electron-donating groups (ie.,$SiMe_3$ and $SnMe_3$).

Next, the previously observed preferential syn delivery of hydride anion in the reduction of the carbonyl group of 5-chloro- and 5-fluoroadamantan-2-one are inverted if the identities of all hydrogen and fluorine atoms are reversed. A similar and somewhat smaller alteration is observed in the reduction of 5-chloroperfluoroadamantan-2-one. One plausible interpretation is that the periplanar bonds are then no longer capable of stabilizing the transition state by electron donation, and instead do so by accepting electron density from the incipient bond into the σ* orbitals. The configurations of the reduction products were deduced from their ^{19}F NMR spectra, and GC/MS.

Mechanistic Studies on Externally Initiated Suzuki-Miyaura Catalyst Transfer Polymerization

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The field of conjugated polymers (CPs) has recently experienced an impressive upswing toward the development of efficient controlled catalyst-transfer polymerization (CTP) protocols for the preparation of various classes of CPs. Conjugated polymers are materials of choice for a breadth of potential practical applications in electronic, optoelectronic and sensing devices due to tunability of their optical and electronic properties through manipulations of the polymers' chemical structure. In our research program, we focus on developing externally-initiated Pd-catalyzed Suzuki-Miyaura CTP as a functional group tolerant method of choice for precision polymerization capable of furnishing diverse classes of CPs. Suzuki-Miyaura reaction is one of the most important C-C coupling protocols in organic synthesis of small molecules, and its mechanism has been thoroughly studied. However, simple translation of the reagents and conditions developed for small-molecule coupling towards chain-transfer polymerization reaction is unlikely to succeed. Instead, this requires detailed mechanistic studies and improving understanding of the role of various factors on the polymerization process outcome. In this presentation, we will discuss the mechanistic details we uncovered in our studies, specifically the role of two catalytic cycles (boronate and oxo-Pd) and the possibility to control over which catalytic cycle the polymerization proceeds. We will also show how better mechanistic understanding of this process enabled improving the effectiveness and controlled nature of the polymerization.

Mechanisms of Molecular Weight Growth for Polycyclic Aromatic Hydrocarbons

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Today's world faces a grand dual challenge of providing affordable and reliable energy while reducing emissions. Meeting that dual challenge requires a multifaceted approach: not only the clean or renewable primary energy sources to avoid carbon emissions but also the storage and conversion of secondary energies (e.g., electricity, hydrogen, and ammonia) for the energy mix. Additionally, CO_2 capture and sequestration will also play important roles in reducing emissions. The role of petroleum hydrocarbons during the energy transition is yet to be defined. This talk will discuss an emerging new area on converting petroleum hydrocarbons to carbon materials to meet society's materials demand enabled by the structural characterization of petroleum molecules.

A brief update on recent advances in applying non-contact AFM to studying petroleum hydrocarbons will be summarized by the first direct imaging of petroleum hydrocarbons in real space.[1] Numerous novel polycyclic aromatic hydrocarbons (PAHs) have been discovered. Aromaticity and bonding characters were studied to identify the structural patterns and predict their reactivities. The aromatic pathways in porphyrins and PAHs were imaged to understand their chemical reactivities, [2] and the force required to break a single bond was measured to understand the nature of a chemical bond and the contrast of AFM structures. [3] Finally, these studies on chemical reactivities are crucial for growing hydrocarbon molecules from small to large to make functional carbon materials.[4-5] Some puzzling reaction mechanisms will be presented, [6] and the challenges for future research will be discussed.

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Cation-Coupled Redox Processes in Soluble Nanoporous Cages

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Nanporous materials such as MOFs, COFs, and nanocages are increasingly targeted as tunable supports for molecular electrocatalysts, especially those for producing and using fuels. In these materials, the confined catalytic sites are influenced by the local pore environment, providing opportunities for tuning catalytic activity but also creating a complex mechanistic picture since the pores must be altered from their as-synthesized state by the movement of protons and electrons during electrocatalysis. To better understand how nanoconfined environments influence and respond to proton-coupled electron transfer and other cation-coupled redox processes, porphyrin-walled nanocages were employed as soluble model structures for examining such processes. The reduction of the porphyrin cages was found to induce the uptake of organometallic cations, illustrating one way that a porous structure can respond to redox changes. Cation uptake was observed even when the cages retain a substantial positive charge (9+) after reduction, and anions bound inside the cages appear to be important for supporting this unexpected behavior. The role of anions in mediating cation uptake was extended to studying proton-coupled electron transfer processes that are especially relevant to electrocatalysis. The basicity of confined carboxylate groups was increased dramatically by the reduction of cobalt sites hosted in the walls of the cages, providing lessons for how the redox state of a pore might influence the chemistry of proton relays and key intermediates (e.g., M-CO2- species) involved in electrocatalytic transformations. Implications of these findings for the design of extended porous electrocatalysts will be discussed.

Aryloxenium Cations

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Aryloxenium cations containing a formally positively charged, monovalent oxygen atom with an incomplete electron shell are key reaction intermediates in many important organic reactions. However, their chemical properties are difficult to study in solution due to challenges in generating them cleanly as well as due to their short lifetimes in solution. In this study, several quinoline-based oxenium cations were generated in the gas phase in a linear quadrupole ion trap mass spectrometer in order to examine their gas-phase reactions. No diagnostic radical reactions, i.e., SCH_3 radical abstraction from dimethyl disulfide, iodine atom abstraction from allyl iodide, or hydrogen atom abstraction from cyclohexane, were observed, in agreement with quantum chemical calculations that predict the closed-shell singlet ground states to be favored by 21 – 26 kcal mol^{-1} (CASPT2/CASSCF(12,12)/cc-pVTZ//CASSCF(12,12)/cc-pVTZ level of theory). Instead, highly exothermic electrophilic addition reactions (50 - 60 kcal mol^{-1} for dimethyl disulfide) were found to dominate, followed by fragmentation of some of the adducts. Examination of the collision-activated dissociation (CAD) of some of the isolated adducts suggested that the adducts contain an intact neutral reagent. Their CAD behavior supports the hypothesis that most products formed upon the ion-molecule reactions arise from fragmentation of the initially generated adducts. Based on several pieces of evidence, addition is concluded to predominantly occur at the least negatively charged carbon atom (based on calculated electrostatic charges) in the benzene ring instead of the pyridine ring. Addition reactions to these sites are so exothermic that no or very little more energy is needed for fragmentation to follow. The likely mechanisms of several fragmentation reactions were identified using quantum chemical calculations.

Poster Presentations

Periselectivity of Competing Sigmatropic Shifts: Designing an Orbital Symmetry Forbidden [3s,5s] Sigmatropic Shift through Palladium(II) Promoted Transition State Complexation and Stereoelectronic Effects

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Body of abstract: The [3s,5s] sigmatropic shift is an example of an orbital-symmetry forbidden reaction that is outcompeted by the allowed [3s,3s] sigmatropic shift. Density functional theory calculations are used to show Pd(II)-promoted systems with strategically placed substituents participating in stereoelectronic effects select for the [3s,5s] process.

Development of Methodologies for 10/11B KIE Measurements at Natural Abundance

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Kinetic isotope effect (KIE) measurements made at natural abundance using quantitative 13C NMR spectra have proven valuable in the mechanistic investigation of many reactions and have played a central role in identifying cases where transition state theory fails to account for observed selectivity and reactivity patterns. These NMR-based methodologies are advantageous because they avoid the often time-consuming and expensive synthesis of an isotopically labeled substrate. Organoboron chemistry has enjoyed extensive and increasing focus in both academic and industrial settings due to the ease of forming and breaking B–C bonds. Yet, it is often difficult to experimentally probe the key steps in the mechanisms of these reactions. The direct measurement of boron KIEs by NMR is infeasible due to the quadrupole moments of the 10B and 11B nuclei (I=3 and 3/2, respectively). Herein, we describe a methodology for obtaining 10/11B KIEs at natural abundance using the 19F NMR spectra of BF4 salts. The methods are straightforward, quantitative, and involve relatively easy isolations of the minor component of reaction mixtures. Furthermore, collection of spectra for quantitative integrations is fast due to the favorable nuclear properties of 19F (I=1/2, ω=2.5×108 Hz/T) as well as its monoisotopic composition. As an example, samples regularly give over 1,000 S/N in a single scan. These methods have been applied to the Suzuki-Miyaura coupling and hydroboration reactions with both BBN and BH3·SMe2. The experimental values can be interpreted quantitatively using KIE predictions for key transition structures.

Investigation into the Rearrangement Pathways of Alkylidene Carbenes to Strained Heterocyclic Alkynes by 13C Isotope Labelling

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Small-ring strained cycloalkynes pose valuable synthetic targets from both a theoretical and a practical standpoint, due to the considerable distortion imparted upon the two sp-hybridized carbons in the ring and the high degree of reactivity that results from this distortion. Exocyclic alkylidene carbenes are useful precursors to cycloalkynes due to their ease of generation by photolysis of cyclopropanated phenanthrene derivatives. Once formed, alkylidene carbenes undergo 1,2 carbon shifts, resulting in formation of cyclic alkynes [(1)]. In the case of unsymmetrical heterocyclic alkylidene carbenes, the 1,2 shift can involve migration of either of the two allylic atoms, both of which lead to the same alkyne [(2)]. The pathways of rearrangement were elucidated for two heterocyclic alkylidene carbenes through the synthesis of 13C-labelled substrates. Computational studies were also conducted on the heterocyclic alkylidene carbenes, the results of which were found to be in agreement with the experimental data.

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Programmed Polyene Cyclization Enabled by Chromophore Disruption

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Diterpenes harboring [6-6-6] fused ring system comprise a very broad and divergent family of natural products. One of the most general and biomimetic approaches to their total synthesis is polyene cyclization. This strategy was utilized for the synthesis of numerous diterpenoids via both cationic and radical pathways. However, substrates deviating from the common biomimetic polyene precursors have proven challenging: poor regioselectivity control, incomplete cyclization for heterocyclic derivatives, and hard initiation for electron-deficient alkenes.

In this work, a new programmatic polyene cyclization was developed utilizing β-ionyl derivatives. Unlike the biomimetic approach, the current method relies on photoinduced deconjugation of extended π-system of chromophores to form a contrathermodynamic diene followed by tandem Heck bicyclization to afford [4.4.1]-propellanes. Such an approach was shown to overcome the limitations of canonical polyene cyclization. Moreover, the utility of the chromophore disruption approach was demonstrated by the total synthesis of taxodione and salviasperanol – compounds that were never shown to have common synthetic pathways.

A Novel method for C–H functionalisation of Aryl-Alkyl Ethers

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Aryl alkyl ethers are ubiquitous in both natural products and pharmaceutical compounds. From the top 200 small molecule pharmaceuticals by retail sales in 2020 the aryl alkyl ether moiety is present in compounds such as: Aripiprazole, Empagliflozin, Fluoxetine Metoprolol and Tamsulosin. Additionally, in nature, lignin is a key reservoir of biomass and mono-lignans are connected via aryl alkyl ether linkages. Previously it has been shown that aryl alkyl ethers can be difficult to functionalise, although hydrogen atom transfer and proton-coupled electron transfer have been found to be successful. We now highlight a new approach for the functionalisation of aryl-alkyl ethers via direct single-electron oxidation of the substrate and subsequent deprotonation. The mechanism of this reaction has been extensively studied and applied to the formation of 50 examples. Several heterocyclic compounds were successfully synthesised and thus this reaction has potential use in the pharmaceutical sector in making APIs. Additionally, this new method of aryl alkyl functionalisation complements the previous methodology and, through competition experiments, high levels of selectivity have been observed in a reaction mixture containing multiple substrates.

Electron and Hole catalysis via Reductant and Oxidant Upconversion: The Case of 1,2-Disila-3,5-cyclohexadiene

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The phenomenon of reductant upconversion describes a seeming chemical paradox in which an exergonic reaction converts a weak reductant into a stronger reductant. A similar concept has also been developed for oxidant (hole) upconversion. Such redox upconversion processes provide the key to using electrons and holes as true catalysts for chemical transformations because they allow for chain propagation through electron transfer. Reductant upconversion has been reported for organic compounds containing N – O, O – O, C – N, S – N, and even C – C bonds. This work explores the possibility of redox upconversion in electrocatalytic transformations of 1,2-disila-3,5-cyclohexadiene. We show that, even though both oxidative and reductive reactions involve Si-Si bond scission, as long as these processes rely on electron and hole upconversion, they have to proceed via different mechanisms.

Mechanistic Study of Enantioselective Pd-catalyzed C(sp^3)-H Activation of Thioethers Involving Two Distinct Stereomodels

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Asymmetric Pd-catalyzed C(sp3)-H activation directed by native functional groups has seen major development over the recent years. Ligand design has been instrumental in achieving enantioselective C(sp3)-H functionalization directed by weakly binding directing groups. Thioethers have been extensively employed in organic synthesis as expedient entry points into multiple carbon oxidation states via transformations of the C−S bond. We have developed a protocol utilizing MPAA and a new class of chiral MPAAn ligands, enabling α- and β-desymmetrizing aryl thioether-directed C(sp3)–H arylation, respectively. Quantitative structure-selectivity relationship (QSSR) analysis revealed extreme variation in sensitivity of substrates to substituent effects of ligands and directing groups: whereas 3-pentylsulfides (α-desymmetrization) responded positively to substitution on ligands and directing groups, isobutyl sulfides (β-desymmetrization) were entirely insensitive. These unexpected results required extensive theoretical studies for stereomodel development. High-throughput DFT computational studies4 with meta-dynamics sampling of the flexible chiral ligand scaffolds allowed to locate over 570 unique enantio- determining C(sp3)−H cleavage transition states. Statistical thermodynamics analysis identified the dominant TS ensembles, and NCI analysis revealed key interactions responsible for enantioinduction. In both systems, enantioselectivity is achieved through a ligand-through substrate stereoinduction relay via dispersion interactions with transiently chiral S-Ar group, however the role of these components are different in the two systems. Two new stereomodels were proposed, accurately predicting enantioselectivity and highlighting the different approaches to achieving stereocontrol in the two types of substrates. This study will assist in improving ligand design and complementing mechanistic understanding necessary for the development of new catalytic systems for enantioselective C(sp3)-H activation.

A Unified Approach to Decarboxylative Halogenation of (Hetero)aryl Carboxylic Acids

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Aryl halides are a fundamental motif in synthetic chemistry, playing a critical role in metal-mediated cross-coupling reactions and serving as important scaffolds in drug discovery. Although thermal decarboxylative functionalization of aryl carboxylic acids has been extensively explored, the scope of existing halodecarboxylation methods remains limited, and there currently exists no unified strategy that provides access to any type of aryl halide from an aryl carboxylic acid precursor. We report a general catalytic method for direct decarboxylative halogenation of (hetero)aryl carboxylic acids via ligand-to-metal charge transfer. This strategy accommodates an exceptionally broad scope of substrates. We leverage an aryl radical intermediate toward divergent functionalization pathways (1) atom transfer to access bromo- or iodo(hetero)arenes or (2) radical capture by copper and subsequent reductive elimination to generate chloro- or fluoro(hetero)arenes. The proposed ligand-to-metal charge transfer mechanism is supported through an array of spectroscopic studies.

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The BHAS Reaction as a Convenient and Predictive Assay for Aryl Radicals

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The base-induced homolytic aromatic substitution (BHAS) reaction is a well-defined and significantly investigated radical process[(1)]**.** Reacting KOtBu with the designed substrate, 2-iodo-m-xylene, in benzene as solvent in the presence of an appropriate electron donor, leads to formation of xylyl radicals which in turn lead to the formation of a mixture of two simple biaryl products, biphenyl and dimethylbiphenyl in a predictable ratio[(2)]. This property potentially allows this system to be used to detect xylyl radicals that are formed in other ways in other reaction types. We propose that the predictable outcome of the BHAS reaction with 2-iodo-m-xylene, along with the ease of analysis, make it a convenient test for the intermediacy of aryl radicals in reactions. This presentation reports the application of this assay to cases of interest.

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Synthesis and Evaluation of 6-Alkoxy-3-hydroxypyridine Quinone Methide Precursors for Resurrection of Organophosphorus-Aged AChE

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Acetylcholinesterase (AChE), an enzyme responsible for hydrolysis of the neurotransmitter acetylcholine, is inhibited by organophosphorus (OP) nerve agents and pesticides via phosphylation of the active site serine residue. The inhibition is reversible with the FDA-approved therapeutic pralidoxime (2-PAM). If not treated timely, there is a subsequent aging process where the phosphylated serine residue undergoes a dealkylation reaction, leading to an oxyanion in the active site. At present, there are no FDA-approved therapeutics to recover the activity of OP-aged AChE, a process called resurrection where the inactive (dead) aged enzyme is brought back to the native (alive) form. Our team reported a 3-hydroxypyridine quinone methide precursor (QMP) which was able to in vitro resurrect an OP-aged form of AChE and was improved to a more active 6-methyl-3-hydroxypyridine core. This study focuses on further modifications to the 6-position where we sought to evaluate stereoelectronic effects by varying 6-alkoxy substituents. A multi-step synthetic route was developed to synthesize a library of 50 novel QMPs, using 10 different alkoxy groups and 5 unique amine leaving groups. Preliminary screening of this 50-QMP library with various OP-aged AChE forms has shown an improved resurrection ability with multiple amine leaving groups and an increased tolerance for steric bulk at the 6-position versus 6-methyl-3-hydroxypyridine QMPs. Further investigation is underway to rationalize this effect and to guide additional studies to maximize resurrection ability, leading to improved drug-like compounds for in vivo verifications of efficacy and safety.

Synthesis and Screening of Pyrazolyl-peptide Organometallic Complexes

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Often overshadowed by their azido congener, diazo compounds—and their reactivity in 1,3-dipolar cycloadditions—provide unique opportunities in the molecular sciences. Afforded pyrazoles can act as either a H-bond donor or acceptor, rendering them compelling ligands to make organometallic complexes. We have employed modular strategies to synthesize pyrazole-containing peptide ligands, where metal complexation imparts unique properties, we seek to harness for various applications.

Real-Time Polymer Viscosity–Catalytic Activity Relationships on the Microscale

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Polymer growth induces physical changes to catalyst microenvironments. Here, these physical changes are quantified in real time and found to influence microscale chemical catalysis and polymerization rate. By developing a method to "peer into" optically transparent living-polymer particles, simultaneous imaging of both viscosity changes and chemical activity was achieved for the first time with high spatiotemporal resolution, through a combination of fluorescence intensity microscopy and fluorescence lifetime imaging microscopy (FLIM) techniques (Figure 1). Specifically, an increase in microenvironment viscosity led to a corresponding local decrease in catalytic molecular ruthenium ring-opening metathesis polymerization rate, plausibly by restricting diffusional access to active catalytic centers. Consistent with this diffusional-access model, these viscosity changes were found to be monomer-dependent, showing larger changes in microenvironment viscosity in crosslinked polydicyclopentadiene compared to non-crosslinked polynorbornene. The sensitivity and high spatial resolution of the imaging technique revealed significant variations in microviscosities between different particles and subparticle regions. These revealed spatial heterogeneities would not be observable through alternative ensemble analytical techniques that provide sample-averaged measurements. The observed spatial heterogeneities provide a physical mechanism for variation in catalytic chemical activity on the microscale that may accumulate and lead to nonhomogeneous polymer properties on the bulk scale.

Testing the Limits of Radical-Anionic CH-Amination: a 10-Million-Fold Decrease in Basicity Opens a New Path to Hydroxyisoindolin

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An intramolecular C(sp3)-H amidation proceeds in the presence of t-BuOK, molecular oxygen, and DMF. This transformation is initiated by the deprotonation of an acidic N-H bond and selective radical activation of a benzylic C-H bond towards hydrogen atom transfer (HAT). Cyclization of this radical-anion intermediate en route to a two-centered/three-electron (2c,3e) C-N bond removes electron density from nitrogen. As this electronegative element resists such an "oxidation", making nitrogen more electron rich is key to overcoming this problem. This work dramatically expands the range of N-anions that can participate in this process by using amides instead of anilines. The resulting 107-fold decrease in the N-component basicity (and nucleophilicity) doubles the activation barrier for C-N bond formation and makes this process nearly thermoneutral. Remarkably, this reaction also converts a weak reductant into much a stronger reductant. Such "reductant upconversion" allows mild oxidants like molecular oxygen to complete the first part of the cascade. In contrast, the second stage of NH/CH activation forms a highly stabilized radical-anion intermediate incapable of undergoing electron transfer to oxygen. Because the oxidation is unfavored, an alternative reaction path opens via coupling between the radical anion intermediate and either superoxide or hydroperoxide radical. The hydroperoxide intermediate transforms into the final hydroxyisoindoline products under basic conditions. The use of TEMPO as an additive was found to activate less reactive amides. The combination of experimental and computational data outlines a conceptually new mechanism for conversion of unprotected amides into hydroxyisoindolines proceeding as a sequence of C-H amidation and C-H oxidation.

From the Bulk to the Interface: Controlling Chemoselectivity of Cycloadditions

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The old tenet corpora non agunt nisi soluta (substances do not react unless dissolved) has been with us since the early days of chemical synthesis. Unsurprisingly, organic reactions are usually performed in homogeneous solutions in organic solvents. In addition, many organic reactants are not only insoluble in water but are also incompatible with it. The immiscibility of many organic substances with water has been widely exploited for product separation using extraction. In contrast, Nature relies on water to create unique molecules, large and small, with exquisite chemoselectivity. Water-assisted transformations have gained more attention in the recent years. Herein, we report on our investigations of the mechanism and selectivity of dipolar cycloaddition performed on water. We recently described reactions of azides with bromoethane sulfonyl fluoride (BrESF) on microdroplets of water leading to the formation of 4-bromo substituted triazoles. Yet, the alternative pathway, the formation of 4-fuorosulfonyl triazoles, can take place in polar organic solvents. Investigation of this reaction led us to development of a synthetic methodology to produce bromo-triazoles in preparative yields and up to 100:1 selectivity using aqueous emulsions. Importantly, we have discovered that detergents poison the water interface, and chemoselectivity could be inversed to 4-fuorosulfonyl triazoles again. We have probed the reaction mechanism both experimentally and computationally. Our studies shed light on the origin of chemoselectivity in the explicit stabilization of transition states with solvent molecules. The details of the reaction investigation and mechanistic studies will be presented and discussed.

Unique Yet Typical Oxyanion Holes in Aspartic Proteases

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Proteases do much more than cleave peptide bonds—these enzymes depict fundamental concepts of enzyme catalysis, and provide drug targets for the treatment of hypertension, Alzheimer's disease, HIV/AIDS, COVID-19, and other pathogens. We have revealed a stereoelectronic link between the "most obscure of all the proteases" —aspartic proteases—and the textbook depiction of nature's catalytic strategy of transition state stabilization within serine proteases—the "oxyanion hole". Unique to aspartic proteases, n→π* donation from the forming carboxy-terminus into an active-site glycine is facilitated by H-bonds that are strikingly similar to those within typical oxyanion holes. This previously unrecognized mode of catalysis expands the understanding of bioorganic reactivity and provides a new strategy for rational drug design—the ability to target a glycine carbonyl contained within the active site of all aspartic proteases.

Dynamic Effects on Migratory Aptitudes in Carbocation Reactions

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Carbocation rearrangement reactions are of great significance to synthetic and biosynthetic chemistry. In pursuit of a scale of inherent migratory aptitude that takes into account dynamic effects, both uphill and downhill ab initio molecular dynamics (AIMD) simulations were used to examine competing migration events in a model system designed to remove steric and electronic biases. The results of these simulations were combined with detailed investigations of potential energy surface topography and variational transition state theory calculations to reveal the importance of nonstatistical dynamic effects on migratory aptitude

Predicting UV-Vis-NIR Absorbance Spectra of Novel Long-Wavelength Azo Dyes

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A decade ago Aprahamian and coworkers reported their accidental discovery (Yang, *JACS* **2012**) of a BF_2-coordinated azo dye which photoisomerizes at much longer wavelengths than conventional azo dyes. They then used electron donors on the phenyl moiety to tune spectroscopic properties of these dyes (Yang, *JACS* **2014**) before returning to their intended hydrazone chemistry.

A failed attempt in our group to incorporate these dyes into photoresponsive polymeric materials yielded improved synthetic methods, the ability to functionalize the quinoline moiety of the dye, and preliminary evidence that these changes impact the dyes' spectra at least as much as substituents on the phenyl moiety. With ACS PRF funding, we have turned our attention to exploring the ability to tune the dye and/or introduce synthetic handles via the quinoline moiety. In order to focus efforts on dyes of particular interest, we proposed to use TD-DFT computations to predict the absorbance spectra of the dyes.

Unfortunately, the lone computational prediction of their parent dye reported by Aprahamian & Hughes was a fluke: their TD-DFT method is unsuccessful even for any of their own derivatives. After extensive attempts to vary functionals, basis sets, solvent models, and other parameters to achieve quantitatively accurate TD-DFT spectra, we have found success using TD-DFT computations of known dyes correlated to experimental data to afford a fit that allows us to use a precise but inaccurate combination of functional, basis set, and solvent model to accurately predict the long wavelength absorbance maxima of both known and novel dyes.

Synthetic Tools for Multi-Stage Diversification

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Modularity enables diversity. Since its inception two decades ago, "click chemistry" has both embodied this idea and driven innovation throughout the molecular sciences. The key to this strategy's success lies in its simplicity: molecular building blocks are clicked together using "near-perfect" reactions. We continually seek to harness fundamental principles of chemical structure and reactivity in the pursuit of modular synthetic tools. Recent progress will be discussed.

Transition State-to-Intermediate Continuum: Mechanistic Contrast of a Dry vs Wet Perepoxide in the Singlet Oxygen 'Ene' Reaction

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A mechanistic study is described for the reactions of singlet oxygen with alkene surfactants of tunable properties. Singlet oxygen was generated either top-down (photochemically) by delivery as a gas to an air−water interface or bottom-up (chemically) by transport to the air−water interface as a solvated species. In both cases, reactions were carried out in the presence of 7-carbon (7C), 9-carbon (9C), or 11-carbon (11C) prenylsurfactants [(CH3)2C=CH(CH2)nSO3− Na+ (n = 4, 6, 8)]. Higher 'ene' hydroperoxide regioselectivities (secondary ROOH 2 to tertiary ROOH 3) were reached in delivering 1O2 top-down through-air as compared to bottom-up via aqueous solution. In the photochemical reaction, ratios of peroxides 2:3 increased from 2.5:1 for 7C, to 2.8:1 for 9C, and to 3.2:1 for 11C. In contrast, in the bubbling system that generated 1O2 chemically, the selectivity was all but lost, ranging from 1.3:1 to 1:1. The phase-dependent regioselectivities appear to be correlated with the 'ene' reaction with photochemically generated, drier 1O2 at the air−water interface vs those with wetter 1O2 from the bubbling reactor. Density functional theory-calculated reaction potential energy surfaces were used to help rationalize the reaction phase dependence. The reactions in the gas phase are mediated by perepoxide transition states with 9 kcal/mol binding energy for C=C(π)···1O2. The perepoxide species, convert to defined stationary structures in the aqueous phase, with covalent C–O bonds and 21 kcal/mol binding energy. The combined experimental and computational evidence points to a mechanism for 1O2 'ene' tunability in a perepoxide continuum from a transition state to intermediate.

Computational Evidence for Tunneling and a Hidden Intermediate in the Biosynthesis of Tetrahydrocannabinol (THC)

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Multidimensional tunneling is computed for four biosynthetic steps leading to tetrahydrocannabinol (THC). The steps are a Diels-Alder reaction of a quinone methide, an acid catalyzed keto-enol tautomerization, rotamerization about a C-O bond in a carboxylic acid, and decarboxylation. Tunneling contributions to the rates of these steps varied from 19% to 61%. The computational procedure, though focused on tunneling, also revealed large changes in the zero point energy (ZPE) along the reaction path that create a hidden intermediate – one that is not a minimum on the potential energy surface but is only detectable by including ZPE corrections along the path.

Regioselective Asymmetric Dearomatization of Pyridiniums

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The piperidine ring is the most common nitrogenous heterocycle amongst marketed drugs. As a result, new strategies for the asymmetric construction of substituted congeners of this important heterocycle are of utmost importance in the synthetic pursuit of complex and medicinally relevant molecular targets. Recently, our research group became interested in the redox-economic synthesis of biologically active alkaloids through the simple dearomatization of pyridine starting materials. While the nucleophilic dearomatization of pyridines has been investigated for several decades, there is no known method to achieve controllable and regiodivergent asymmetric additions starting from the same starting material. Establishing such a method would be crucial towards accessing broad molecular space from simple aromatic precursors in a practical and efficient manner.

This presentation concerns our work addressing this synthetic conundrum in a target-oriented fashion. Through the use of a chelation effect, we have been able to orchestrate the regioselective asymmetric addition of both akynyl and aryl organomagnesium reagents to substituted N-alkyl pyridinium electrophiles. The former transformation allowed for a concise synthesis of the quiniiolizine alkaloid (+)-Lupinine. The latter, being regiodivergent in nature, has enabled the synthesis of the monoterpenoid indole alkaloid (+)-N-methylaspidospermimdine and the antidepression treatment Paroxetine.

Origins and Implications of Post-transition State Bifurcations in Rh-promoted C-H Insertion Reactions

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C-H insertion reactions catalyzed by dirhodium catalyst have been derived and utilized as a powerful strategy in synthetic chemistry. Interestingly, we discovered that a class of reported Rh-catalyzed β-lactonization reactions suffers from post-transition state bifurcation (PTSB) feature, forming beta-lactones (P1) and ketene+ketone fragmentations (P2) with the same transition state structure (TSS). In PTSB cases, a single "ambimodal" TSS leads directly to two products without any minima intervals. Under this circumstance, traditional transition state theory (TST) cannot explain the preference between two products because there is only one barrier for them to share. Herein, we implemented both density functional theory (DFT) calculation and ab initio molecular dynamics (AIMD) simulation to estimate the yield and selectivity of β-lactones. The weak interaction between the catalyst and substrate was studied by energy decomposition analysis (EDA) and non-covalent interaction (NCI) plot to unmask the specific role of the 2-bromophenyl substituent. This pair of beneficial interactions facilitate reactions by decreasing the activation energy barrier. While in terms of dynamics, our study on potential energy surface (PES) implies that the slope of vectors towards P1 and P2 controls the preference between P1 and P2, hinting at the long-lasting impact of conformational effects post-TS. Besides, we tried to rationalize the high yield of beta-lactone given by chiral D2-symmetric catalyst Rh2(s-TCPTTL)4. Surprisingly, PTSB still exists with a strong favorite to fragmentations. But with a "cage" effect support by bulky ligands on Rh2(s-TCPTTL)4, beta-lactone can be formed with a following [2+2]-cyclization under room temperature.

Electronically Activated Cycloalkynes

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Strained molecules harbor a unique ability to pique the interests of both the synthetically and theoretically inclined. Cycloalkynes—and their use in strain-promoted pericyclic annulations (e.g., 1,3-dipolar cycloadditions)—offer synthetic tools that have emboldened practitioners within the molecular sciences to reach new levels of innovation. Those well-versed in reaction mechanisms (i.e., physical organic chemists) have risen to the challenge of providing reagents and strategies for high chemoselectivity while avoiding instability. Among the most successful strategies are those that integrate increased strain (reactant destabilization) with electronic activation (transition state stabilization).

We have developed a tunable framework to consolidate the unique electronic features of various cycloalkyne classes within a single scaffold. Our design strategy incorporates both direct and remote electronic activation strategies to tune cycloalkyne stability and reactivity. We are currently optimizing the modulation strain and stabilization through computational and experimental methods with the overall goal of providing designer cycloalkynes tailored for desired applications.

Synthesis of nucleotide phosphates as efficient inhibitors of PNPase

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Nucleotides can function as effective drugs and can have an impact on various biochemical pathways[1]. Polynucleotide Phosphorylase (PNPase) is an exoribonuclease with important biological functions and has been proposed to be a promising druggable target [2]. In this work, various nucleotide methyl phosphates were synthesized and tested as PNPase inhibitors. These models were chosen due to their potential to inhibit this ribonuclease. C2'-, C3-' and C5'- methyl phosphate derivatives of uridine, adenosine, guanosine, cytidine, 8-oxo-7,8-dihydroguanosine (8-oxoG), and 8-oxo-7,8-dihydroadenosine (8-oxoA), along with their corresponding nucleoside analogs were synthesized using standard methodology. A general route started with selective silylation at the 5' and 2' positions using DMAP and TBDMS-Cl. Phosphorylation was accomplished via their corresponding phosphoramidites, followed by substitution with MeOH in the presence of ethylthiotetrazole, and subsequent oxidation using t-butylhydroperoxide. Deprotection was achieved via treatment with NH4OH, followed by fluoride which led to the desired final nucleotide phosphate. These targets were obtained in overall yields of 5-25% (after 4-9 steps). Electrophoretic analyses (20% denaturing PAGE) showed that the pyrimidine derivatives are effective inhibitors and that placing the phosphate at C2' position leads to increased activity of PNPase. We envision that this selective inhibition will enable the development of effective inhibitors of PNPase. [3]

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The Synthesis of Spirocyclic Ether via Silver-Catalyzed Cyclization of ortho-Alkynylarylketones

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ortho-Alkynylarylketones are useful substrates for the preparation of valuable compounds. Spirocyclic ether is one of the most important scaffolds which showed a wide ranges of biological activities. In this work, we have developed a novel synthetic methodology for diastereoselective synthesis of spirocyclic ether derivatives employing ortho-alkynylarylketone substrates. Under our optimal protocol, substrates would be activated by silver catalyst to generate 1,5-diketone as the key intermediate which underwent cyclization via intramolecular nucleophilic addition of enol towards oxonium ion intermediate to furnish the desired spirocyclic ethers. In addition, our method could be applied to substrates with various substituent groups to provide the corresponding spirocyclic ethers in moderate to good yields.

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Understanding Heteroatom Doping Effects in Extended Pentalenes

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Polycyclic [4n] antiaromatic hydrocarbons (PAAHs) exhibit favorable optoelectronic properties (e.g. small singlet-triplet gaps) for applications in organic electronics, such as organic field-effect transistors, organic solar cells, and organic batteries [1]. A powerful synthetic strategy to modulate the properties of these PAAHs is by fusion to conjugated heterocycles (e.g., furan, pyrrole, thiophene). Depending on the position of the heteroatom, isomers of heterocycle fused PAAHs can display disparate energetic, antiaromaticity, and charge transport properties [2,3]. But the positional effects of heteroatom-doping in PAAHs are largely underexplored. We carried out DFT calculations to study the positional effects of heteroatom doping for a series of heterocycle fused [4n] pentalenes. By relating the structure of pentalene to pentafulvene, we uncovered a simple approach to understand and predict the effects of heteroatom doping on the optoelectronic properties of extended pentalenes. This work has relevance for understanding the properties of many recently prepared extended pentalenes for charge transport applications [4,5].

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Molecules in a Hurry to Get Rid of Antiaromaticity

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In this presentation, I will show that the drive for molecules to get rid of excited-state antiaromaticity triggers all sorts of photochemical reactions that are relevant for processes such as photosynthesis, photocatalysis, and energy conversion. This work was inspired by Baird's 1972 work[1] showing that the Hückel π-electron-counting rule for aromaticity [4n+2] and antiaromaticity [4n] reverse in the first triplet excited states. This means that aromatic compounds can become excited-state antiaromatic upon photoexcitation. Benzene, for example, is ground state aromatic and can stay trapped in a bottle for years, but becomes antiaromatic and highly reactive upon photoexcitation, rearranging to the strained and explosive benzvalene among other interesting structures[2]. I will present the importance and the mechanistic implications of excited-state antiaromaticity on photochemical reactions of proton[3], electron[4], and proton-coupled electron transfer[5].

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Forbidden Electrocyclizations of Cethrene and Biphenalenylidene: Calculations on the Contribution of Heavy-Atom Tunneling

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Dimethylcethrene (DMC) and biphenalenylidene (BP) are biradicaloid polycyclic conjugated hydrocarbons that undergo thermally forbidden six-electron conrotatory cyclization via helical geometries.[1,2] The occurrence of thermal electrocyclic ring closures that violate the Woodward–Hoffmann rules harkens back to one reported by Josef Michl for dimethylpleiadene.[3] The significant discrepancy between measured activation energies and computed barrier heights suggests that carbon tunneling may contribute to the reactions of DMC and BP, though it may not be the only factor. As part of our broader effort to explore the scope of heavy-atom tunneling in organic reactions, we report density functional calculations on the electrocyclic ring closures of cethrene and (Z)-biphenalenylidene, as well as multidimensional tunneling calculations to predict rate constants with and without tunneling. Computed tunneling-inclusive rate constants suggest that carbon tunneling dominates both cyclizations below 300 K.Results of calculations to evaluate other factors will also be presented.

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Late-Stage Modification of Pharmaceuticals via SuFEx Click

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Click chemistry – a nature inspired approach for rapid synthesis of useful compounds – since its dawn has dominated organic synthesis. Modern development of ‘near-perfect” reactions enables modular manipulation of building blocks. Our group has recently reported a mild route to SuFExable pyrazoles. We are now poised to rapidly explore unknown chemical space via controllable diversification of these densely functionalized heterocycles. Recent progress in late-stage modification of FDA-approved pharmaceuticals to unlock new properties will be presented.

Carboxylate as a Non-innocent L-ligand – Computational and Experimental Search for Metal-bound Carboxylate Radicals

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Metals have the ability to stabilize a variety of transient species through coordination, i.e. radicals. Carboxylate radicals are well known organic compounds; on their own they are reactive, electrophilic, O-centered radicals with the tendency to undergo fast decarboxylation. However, as metal-coordinated ligands, they generally behave as one-electron X-ligands that form a covalent M-O bond with the loss of radical character and oxidation of the metal. Is it possible for a carboxylate ligand to remain a radical while coordinated to a metal-center? In theory the radical character could be preserved if carboxylate were to act as a two-electron L-ligand, using a lone pair from oxygen to form a dative bond with the metal. Such non-innocent behavior of a carboxylate ligand has not been reported, to our knowledge. Through the computational exploration of spin density, thermodynamics, and natural charge on a variety of first-row transition metal carboxylate-complexes we determine that carboxylate will bind to the transition metal as an L-ligand if the high spin state is accessible. Additionally, the ideal metal for this reaction needs to satisfy two requirements: 1. Be oxidizing enough to form the carboxylate radical 2. Not be so oxidizing that a full-fledged 2e- bond forms between the metal and carboxylate. The computational predictions are in agreement with the experimental yields for the tested first-row transition metals. Finally, we explore the mechanism of H-abstraction by the carboxylate radical and find that the non-innocent carboxylate radical is more reactive than a free carboxylate radical in a similar system.

Transition-Metal-Free Synthesis of C3-Chlorinated Benzothiophene Derivatives using NaOCl · 5H2O

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Benzothiophene and benzofuran are common scaffolds for drug development[1]; thus, processes that facilitate regioselective functionalization can be a valuable addition to current methodology. Reactions utilizing sodium hypochlorite (NaOCl) are well studied; however, its reactivity is yet to be fully explored in the context of these heterocycles. In this work, sodium hypochlorite pentahydrate was used to halogenate the C3-position of nine substituted and unsubstituted heterocyclic structures. A general procedure to achieve this transformation involved stirring the derivatives in aqueous acetonitrile solutions in the presence of NaOCl · 5H2O. It was found that results varied as a function of temperature and time, where reactions carried out at room temperature favored oxidation at the sulfur atom, whereas increased temperatures led to the desired C3-chlorinated compounds. Furthermore, the use of benzothiophene structures resulted in higher yields, whereas the benzofuran analogues displayed low overall yields, presumably from the formation of a peroxide intermediate. The presence of electron withdrawing or electron donating groups at the C2-position did not influence the outcome of the reaction. To gain a better understanding on the mechanism, modeling (via density functional theory) showed that the chlorination reaction is mediated by a heteroatom-hypochlorite bond, that enables chlorination at the C3 position via a pseudo electrophilic aromatic substitution. Overall, this is an attractive strategy because it can be carried out under mild and metal-free conditions in yields that vary from 10-70%.

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Geometrically Flexible 3D Nanocarbon

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Nanocarbons, which are nanometer-sized carbon materials, exhibit unique optical, electric, magnetic, thermal, mechanical, and host-guest properties, that are determined by the geometric arrangement of their aromatic subunits. The development of nanocarbons with ubiquitous architectural attributes is of great importance to expand the scope of applications of carbon materials and to stimulate new technologies in materials science. Herein we present the design and bottom-up synthesis of a geometrically flexible 3D nanocarbon (GFN-1) featuring a rigid triptycene backbone equipped with three curved π-panels that can flip freely in solution at room temperature. GFN-1 is capable of co-assembling with C60 or C70 through convex-concave π-π interactions into pseudo-2D lattices where fullerenes are organized into 1D arrays. Cocrystallization of GFN-1, C60 and C70 in the ratio of 2:1:2 yielded a 2D supramolecular hexagonal tessellation where 2D layers are held together by strong π-π contacts and fullerenes are fully isolated. This work paves the way for the utilization of shape and electronically complementary nanocarbons to construct functional supramolecular assemblies for electronic and sensing applications.

Solvent Effects on the Temperature Dependence of Hydride Kinetic Isotope Effects of NADH/NAD+ Model Reactions

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Solvent effects on the kinetics and temperature dependence of kinetic isotope effects (KIEs) (characterized by ΔEa = EaD - EaH) of a hydride transfer reaction of NADH/NAD+ analogues were determined. The solvents are acetonitrile (dielectric constant = 37.5), isobutyronitrile (21.0), chloroform (4.8), and the mixtures of acetonitrile and chloroform. Both the reaction rate and ΔEa (1.0 – 1.8 kcal/mol) increased with decreasing solvent polarity. The ΔEa values are outside of the semiclassical range suggesting a hydride tunneling mechanism. Both the reaction rate and ΔEa did not change appreciably as chloroform was gradually added to the acetonitrile until the mixed solvents reached 80%chloroform/20%acetonitrile (v/v) when the rate started to increase rapidly. This suggests two relatively separated solvation shells around the positively charged tunneling ready state (TRS), with acetonitrile solvation shell inside to well solvate the TRS and chloroform outside. When the acetonitrile shell becomes thin to an extent when the de-solvation of TRS by chloroform starts to function, the rate and ΔEa increase drastically. Computations suggest that the hydride donor-acceptor charge-transfer complexation vibrations in the TRS are likely more rigid in acetonitrile than in chloroform. Therefore, a smaller ΔEa corresponds with a more rigid TRS complex, consistent with the recently proposed vibration-assisted activated H-tunneling model. This TRS rigidity – ΔEa relationship replicates the observations in enzymes (more rigid TRS complex and smaller ΔEa) vs. variants (looser and larger ΔEa) and supports the proposal that enzyme active site compressive effects are coupled to the chemical reaction coordinate.

Cobalt Photocatalytic Activation of Alcohols to Carbon Centered Radicals using Cobalt Complexes

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Using readily available cheap alcohol starting materials, a strategy for using cobalt to access acyl radicals or carbon radicals using unactivated alcohols has been developed. Most traditional methods for alcohol activation require pre-activation of the alcohol, for example creating acyl selenides or xanthate esters, which generates stoichiometric waste in both the activation step and radical forming step. Employing a catalytic strategy with predictable reactivity to reach these same carbon radicals would be a powerful synthetic tool with reduced environmental impact. Drawing inspiration from vitamin B12, a strategy to create these same acyl or alkyl radicals has been developed using simple starting materials. Simple and cheap alcohols can be easily carbonylated in the presence of carbon monoxide onto cobalt porphyrins to yield stable alkoxycarbonyl complexes in excellent yields. These cobalt complexes have been irradiated with light to form styrene or ethyl benzene in high yields as well as form lactones.

Utilizing DFT to Gain Mechanistic Insight into Nickel sp^2-sp^3 Catalysis and [4+1] Cycloadditions

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Mechanisms for the (i) formal Rh- catalyzed [4+1] cycloaddition of vinyl isocyanates and vinyl ketenes to afford spirooxindole cyclopentenones and (ii) Ni- catalyzed 1,4-addition of trialkylboranes to α, β-unsaturated esters have been investigated computationally. A collaborative effort between the Wiest and Ashfeld groups studies the formal Rh- [4+1] cycloaddition to rationalize the retention of stereochemistry through a concerted polar mechanism. Hammett studies have been conducted for the ketene and isocyanate at the para position of the phenyl group and 6- position of the oxindole moiety. The ketene and isocyanate Hammett plots suggest that the effects of para-substitution are due to electron donating stabilization rather than radical stabilization. The closed-shell σ+ plot for both show strong agreement with the experimental σ+ plots, which suggests that the vinylcyclopropane-cyclopentene rearrangement is concerted and polar. Initial insights into the proposed mechanism for the Ni- conjugate addition yielded a calculated transmetallation barrier of 52.3 kcal/mol. The 7- membered transition state for this pathway features an unfavorable geometry where the B – C – Ni angle is 95.3° and the C – B distance is 2.6 Å rendering this pathway unfeasible. New investigations study a base-mediated pathway where that carbonate coordinates to both the trialkylborane and the Ni-π complex which allows for a 6- membered transition state that facilitates the transmetallation of the alkyl group. This pathway allows for a more favorable geometry than the previously calculated 7- membered transition state. Open-shell pathways cannot be ruled out and will be studied further when a favorable transmetallation geometry is discovered.

Olefin Functionalization/Isomerization Enables Stereoselective Alkene Synthesis

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Olefin functionalization and synthesis (particularly of highly-substituted olefins) have been longstanding problems in the organic chemistry community. Recently, nickel has emerged as a powerful catalyst in, inter alia, functionalization and synthesis of olefins. Despite these recent successes, the understanding of the mechanisms for olefin functionalizations tends to be limited, and the factors that control the reactivity and selectivity of reactions with Ni(I) species in particular are not well understood. Here, we demonstrate that catalytic amounts of a nonprecious N-heterocyclic carbene−Ni(I) dimer complex in conjunction with a sterically hindered base promote site and trans-selective coupling of monosubstituted olefins with a wide range of electrophiles to deliver tri- and tetrasubstituted alkenes in up to 92% yield and >98% regio- and stereoselectivity. The protocol can be used to prepare both carbon- and heteroatom substituted C=C bonds, which provides distinct advantages over existing transformations of alkenes. Mechanistic and DFT studies were carried to shed light on the regio- and stereochemical outcome of these catalytic processes. These computational results unearthed a non-radical isomerization mechanism by an odd-electron Ni(I) species and demonstrated the vital role played by the interactions between the sterically hindered base and ligand in inducing stereoselectivity.

Reaction Mechanisms Revisited with the Help of Computational NMR

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It is impossible to come up with a sensible mechanistic rationale based on misassigned structures of reaction products. While NMR – the most informative analytical tool for solution structure elucidation – has advanced significantly in novel pulse sequences and multi-dimensional experiments, the interpretation of experimental data remains challenging and every so often leads to misassignment. In this work, we discuss the important role of our machine learning-augmented DFT method for computational NMR, DU8ML, in helping to avoid incorrect mechanistic inferences based on an erroneous interpretation of the product structure. DU8ML-based analysis of unusual reaction products recently reported in the literature helped to identify several flawed reaction mechanisms proposed because of the problematic NMR structure elucidation work. In this presentation, we will discuss several recent cases and propose alternative mechanistic rationales for these reactions based on the corrected structures of the intermediates and products.

Probing Free Energy Landscape of Organophotoredox Catalyzed Intermolecular Anti-Markovnikov Hydofunctionalization of Alkenes

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Organophotoredox catalysis is emerging as a more efficient way for synthesizing organic molecules. These approaches depend on the capacity of the organic dyes to convert visible light into chemical energy by engaging in single-electron transfer with organic substrates, thereby generating reactive intermediates responsible for photoredox hydrofunctionalization reactions. Despite rapid advances in synthetic methodology, there is a dearth of mechanistic studies detailing the underpinnings of these reactions. A rational approach to understanding the mechanistic landscape of these reactions is key towards making methodological advances towards enantioselective photocatalysis. Herein we present a combination of 13C kinetic isotopes effects (KIEs) and density functional theory (DFT) calculations to decipher the free energy landscape of organophotoredox catalyzed intermolecular anti-Markovnikov hydrofunctionalization of olefins

Clicking Carbon-Rich Materials

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Heteroatom placement controls the properties of both cycloadditions reactions and carbon-rich materials (graphene). We are harnessing the modularity of highly efficient cycloaddition reactions to control heteroatom placement within polycyclic aromatic hydrocarbons with tunable properties.

Selective Formation of *N,N'*-2,5-Diketopiperazines via Conformationally Controlled Intramolecular Amidation

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Amide conformations can be described as either *cis* or *trans* relative to the a-carbon of the carbonyl group. Secondary amide conformations in peptides are typically *trans* at room temperature, favoring the lowest energy conformation as a result of rapid interconversion; however, the tertiary amide conformations in peptoids interconvert less readily and thus experience increased preferences for specific amide conformations. This work highlights an improved synthesis of diketopiperazines with regiocontrol by using an innovative intramolecular amidation-cyclization methodology for the formation of *N,N'*-2,5-diketopiperazines deploying steric hindrance and tertiary amide conformational control to provide the amine nucleophile with highly specific reaction trajectory preference for a specific intramolecular electrophile.

Reductive Cleavage of Ester-based Plastics with Electrogenerated Organic Electron Donor

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Poly(ethylene terephthalate) - PET - is among the most widely produced ester-based thermoplastics. Due to its high mechanical strength, it is used in a variety of applications, including food and beverage packaging such as the ubiquitous plastic water bottle. While mechanical methods for polymer recycling are commonly utilized on industrial scale, the chemical decomposition of these wastes to their monomeric building blocks is considered the only sustainable recycling method. The general chemical recycling methods for PET are solvolysis and hydrogenolysis, which often requires the use of highly corrosive basic reagents or high hydrogen pressures at high temperatures. To address the challenge, we develop new redox strategies for the recovery of valuable building blocks from ester-based plastics via reductive chemical and electrochemical methods. The benzimidazole-based organic electron donor 4,4'-(1,1',3,3'-tetramethyl-1,1',3,3'-tetrahydro-2H,2'H-[2,2'-bibenzo[d]imidazole]-2,2'-diyl)bis(N,N-dimethylaniline), termed (N-DMBI)2 dimer, is used for the reductive breakdown of PET plastics. The effective reducing strength of (N-DMBI)2 is estimated to be –1.94 V (vs. FeCp2+/FeCp2), which is thermodynamically capable of reducing various substances, including polyester model compounds. In this study, we use electrochemistry for the reductive generation of (N-DMBI)2 dimer from the stable [N-DMBI]+PF6– precursor. The electrogenerated (N-DMBI)2 dimer is a promising mediator for the cleavage of PET models through (i) reductive generation of reactive basic intermediates or by (ii) direct electron transfer to the ester moieties. The utilization of electro-generated organic electron donors for reductive chemistries, both chemically and electrochemically, is targeted as green synthetic methodology that circumvents harsh reaction conditions or corrosive energetic reagents.

The Staudinger Reduction of Aryl Azides: An NMR Study of Phosphazide Chemistry

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The Staudinger reduction is a well-established method for the preparation of aryl amines from their respective azides. The reaction is believed to proceed via the formation of phosphazides, with subsequent loss of nitrogen to form the iminophosphoranes (aza-Wittig chemistry). The amine is formed by hydrolysis of the aza-Wittig intermediate. An 1-H and 31-P NMR study, performed as part of our attempts to generate aminopyridine and quinoline N-oxides from their respective azides, indicates that under certain conditions the amines may be generated directly from the phosphazide in competition with, rather than following, nitrogen expulsion. The structure-reactivity behavior of this alternative mechanistic pathway is discussed.

The Roads Not Taken: Mechanism and Origins of Regio- and Chemoselectivity of Directed CoIII-catalyzed Alkenylation of N-Pyridyl

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The regioselectivity, chemoselectivity, and mechanism of a Co-catalyzed alkenylation of N-pyridyl-2-pyridone with terminal alkynes (Ravikumar et al. J. Org. Chem. 2021, 86, 14, 9444–9454) was probed and rationalized using density functional theory calculations. A mechanistic understanding of the reaction is important as many details remain unclear and resolution of these questions could facilitate the improvement of its substrate scope and the refinement of catalytic conditions. The mechanism is predicted to involve three steps: C–H activation ortho to the pyridine directing group affording a six-membered cobaltacycle intermediate, insertion of the alkyne into the CoIII–aryl bond resulting in a seven-membered cobaltacycle intermediate, and a proto-demetalation step. Results indicate that the bulkier group on the alkyne distal to the pyridone is more favorable for the overall catalytic cycle. Our results demonstrate that attractive dispersion interactions modulate both ligand binding energies, thereby affecting reaction barriers, and the magnitude of reaction feasibility. Further, we show that temperature plays a key role in controlling the chemoselectivity of the reaction. The computed mechanism of the full catalytic cycle is consistent with the experimental data. Our detailed mechanistic survey provides important insights for regio- and chemoselective alkenylation reactions of 2-pyridones.

Fe-Cajudy talyzed Multicomponent Cross-Coupling of [1.1.1]propellane with Grignard Reagents and Alkyl Halides

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Bicyclo[1.1.1]pentanes (BCPs) are of great interest to the agrochemical, materials and especially in medicinal chemistry since that improve the pharmacokinetic profile of drug candidates, and typically increases metabolic stability, aqueous solubility, and membrane permeability.[1]Despite the growing number of synthetic methods for accessing functionalized BCPs, reports of MCR are rare[2] and the use of iron in this type of process is practically unexplored.[3] In this context, we have developed an iron-catalyzed reaction that utilize [1.1.1]propellane to form 1,3-difunctionalized bicyclopentane. We demonstrated that this protocol forms two carbon-carbon bonds or carbon-halogen, one on each side of the BCP in a one-pot reaction under mild reaction conditions in good to moderate yields (up to 91%).
Additionally, DFT calculations were performed to describe the reaction mechanisms involved.

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Cesium Effect: Novel Mechanistic Concepts and Synthetic Applications

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The use of cesium salts in a large variety of synthetic conversions has received increasing interest in the last two decades and today has reached industrial acceptance. Numerous prominent examples for the benefits of cesium salts in organic synthesis have been reported, however, also straightforward nucleophilic substitution reactions can be improved by substituting standard bases with cesium salts. The unique effect of cesium salts in many reactions emerged empirically and stems from the special properties of the cesium cation: it has a very large ionic radius, a low charge density, and high polarizability. In practice, the use of cesium increases product yields, offers shorter reaction times, uses smaller amounts of reagents, and requires, mild reaction conditions and easier work-up procedures. The "cesium effect" is a term widely spread in scientific publications to describe the advantages concerning yield and reaction conditions of cesium-assisted reaction protocols as compared to conventional routes. The effect is based on observations, it is empirical and quite difficult to pin down and clarify. Currently, we are investigating this effect via multinuclear NMR. We will report herein a plethora of carbon-heteroatom bond formation strategies discovered in our laboratories (ie., C-N, C-P, C-O, C-S, C-Se, C-Ge, C-Te, C-C, C-Si), cesium salts in organic synthesis, and ring-closure/macrocyclization reactions.

Assembled Triphenylamine Bis-urea Macrocycles and Linear Analogues

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Triphenylamine radical cations stabilized by substitution on the para-position hold promise as spin-containing building blocks for polymer magnets. Self-assembly potentially affords an alternative strategy for stabilizing organic radicals. Herein, we examine the effect of assembly on the stability of photogenerated radicals of urea tethered triphenylamines (TPAs). TPA containing bis-urea macrocycles and urea tethered linear analogues were synthesized and their crystal structures determined. These crystalline materials control the distinct microenvironment around the photoactive groups. Upon excitation in solution, TPAs with unsubstituted para-positions form radical cations that rapidly degrade. Upon UV-irradiation of the supramolecular assemblies, both linear and macrocyclic systems display remarkably persistent and regenerable radicals. Advantageously, the TPA bis-urea macrocycles assemble into columnar structures affording porous organic materials. Upon activation these crystals undergo guest exchange in single-crystal-to-single-crystal transformations generating a series of isoskeletal host-guest complexes that can be directly compared. Our recent focus is on loading guests that show favorable reduction potentials with respect to the TPA as well as guest monomers that can undergo polymerizations. We are investigating the factors that influence the electron transfer process, probing the quantity of radicals formed and evaluating their stability.

High-Throughput Synthesis and Modification of Peptides

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Expanding chemical space beyond the genetically encoded amino acids endows biomolecules with unique properties. As nature harnesses chemical (post-translational) modifications, we seek to incorporate synthetic modifications into peptide scaffolds. We are currently utilizing high-throughput techniques (i.e., phage display) to fabricate modified peptides to understand the role of peptide structure on employed techniques and synthesize biomaterials with utility in various applications.

Aromaticity gain as a driving force for the photocleavage of bonds: A Case Study on Barton Esters

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Barton esters can be a source of radicals and have been used to synthesize different classes of compounds such as terpenoids, amino acids, and vitamins.[1] The proposed reaction mechanism in the literature involves homolytic cleavage of the N–O bond under light or heat to form the radical products.[2] Using pyrithione as a model, we suggest that the N–O bond in Barton esters breaks heterolytically instead. The bond breaking mechanism occurs through a state crossing from the first $1\pi\pi^*$ excited state to a repulsive $1\pi\sigma^*$ state in which the antibonding orbital is located on the oxygen. From there, the N–O breaks heterolytically to give homolytic products. Our calculations reveal that this is a low-barrier state crossing (ca. 12 kcal/mol). We hypothesize that the aromaticity gain obtained from the N-O bond cleavage is the driving force. These findings coincide with recent works from our group showing that O–H photolysis in phenol proceeds through heterolytic bond cleavage rather than an assumed homolytic cleavage as a result of excited-state antiaromaticity relief.[3] Many other photocleavage reactions may be explained by a similar mechanism.

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Mechanistic Complexity in the Diphenylprolinol Silyl Ether Catalyzed Michael Addition

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The diphenylprolinol silyl ether catalyzed Michael addition of aldehydes and β-nitrostyrene has been subject to intense mechanistic scrutiny. Conflicting theories have emerged regarding the origin of stereocontrol in this reaction. The reaction is accelerated by acidic additives such as acetic acid and p-nitrophenol. By measuring 13C kinetic isotope effects on β-nitrostyrene, we probe the mechanism of this reaction under a variety of conditions. Our results suggest that the key carbon-carbon bond-forming step between the enamine and β-nitrostyrene is irreversible and stereo determining when the reaction is performed in the presence of acidic additives. However, in the absence of these additives or when deuterated aldehyde/acetic acid is used, a step following C–C bond-formation exerts partial rate-limiting influence and contributes to the stereochemical outcome of the reaction. This delicately balanced free energy profile provides a new framework for interpretation of the vast body of prior mechanistic studies of this landmark reaction.

Twisted Alkenes–A New Entry into Four Membered Rings?

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Twisting a double bond can be a strategy to activate alkenes for thermal [2+2] cycloadditions, and generating four-membered rings. Computations suggest that anti-Bredt alkenes[1] (i.e., bicyclic systems with a double bond at the bridgehead position) can undergo stepwise [2+2] cycloadditions with alkenes (ethylene, tetrafluoroethylene, and cyclopentene) and alkynes (acetylene and cyclooctyne) through reaction barriers ranging from 4.3–37.8 kcal/mol. Anti-Bredt alkenes with highly twisted double bonds can mimic the triplet state geometry of ethylene (D2d, 90° HCCH dihedral angle)[2], and have low to near barrierless energies for C–C bond formation at the bridgehead position. These findings open possible new routes to making cyclobutanes, cyclobutenes, and to generate other heterocyclic four-membered rings, relevant for drug precursors and natural products.

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Investigation of the Mechanism of Indophenol Formation in the Photolysis of p-Azidophenoxide

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Upon photolysis, p-azidophenoxide undergoes a condensation reaction to form a dark colored, blue indophenol product.[1]The mechanism for this reaction is unclear, to say the least. Although it is tempting to suggest the photolysis step is the dissociation of the azidophenoxide to form the quinonimide, mass spec analysis shows that the quinonimide is present in solution in the dark and is not a short lived intermediate. The reaction requires polar protic solvent, and therefore likely involves quinonimine as a reactant. In this work, we have used real-time reaction monitoring by mass spectrometry to investigate the mechanism of the reaction. Formation of the product is enhanced with appropriate SET sensitizers, but is inhibited by strong SET inhibitors. The role of oxygen is instructive, and the reaction has been carried out in oxygen saturated and deoxygenated solutions. Ultimately, the mechanism of the reaction is compared to the mechanisms for the photochemical SNAr reactions of haloanilines and for the Gibbs reaction.

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SuFEx-able Pyrazoles as a Versatile Scaffold

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Click chemistry has transformed the field of molecular design. Dipolar cycloadditions and sulfur fluoride exchange (SuFEx) reactions have diversified the landscape of molecular assembly. Synthetic strategies enabled by click reactions allow access to novel modular scaffolds. Diverse reactivity of recently reported SuFEx-able HN-pyrazoles opens a wide molecular space to explore new molecules and their properties for drug discovery, medicinal chemistry, chemical biology, material design, and related fields. Recent progress will be discussed.

Rational Design and Development of Fe-Catalyzed Multicomponent Radical Cascades/Cross Couplings

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Transition metal–catalyzed cross-coupling reactions are some of the most widely used methods in chemical synthesis. Notable advantages of iron as a potentially cheaper, more abundant, and a less toxic transition metal catalyst have drawn the interest of our lab, in particular to explore the mechanism of action in two- and three-component radical cross-couplings.[1] In this vein, we have designed the first asymmetric Fe-catalyzed intra- and intermolecular difunctionalization of vinyl cyclopropanes with alkyl halides and aryl Grignard reagents, supported by mechanistic studies.[2] Next, we explored the difunctionalization of unactivated olefins with alkyl halides and Grignard reagents. The reaction tolerates a wide range of sp2 hybridized nucleophiles, alkyl halides, and unactivated olefins bearing a diverse range of functional groups.[3] Our most recent work highlights iron's practical application in more elaborate multicomponent cross-couplings including formation and trapping of α-boryl radicals and allyl alkyl halides for practical synthesis of cyclic fluorous compounds.[4] In this conference, I will present my work on a unique iron catalytic manifold for the coupling of allyl radicals and organoiron species.

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Molecularly Imprinted Nanoparticles as Synthetic Enzymes for Glycan and Ester Hydrolysis

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Although chemists rightfully argue that enzymes are "not different, just better" than synthetic catalysts, artificial enzymes created on purely synthetic or semi-natural platforms generally do not match their natural counterparts in performance. The deficiency of artificial enzymes has many reasons. Apart from a detailed understanding of enzymatic activity, a large roadblock is the lack of suitable synthetic strategies to construct multifunctional active sites with accurately positioned catalytic groups for substrates with complex structures and shapes. In recent years, we have developed a method to molecularly imprint surfactant micelles [1]. The nanoconfinement of the polymerization and cross-linking yield an extraordinary templating effect, with the imprint/nonimprint ratio in binding frequently reaching hundreds and sometimes 10,000. Installation of catalytic groups through postmodification turn the water-soluble nanoparticles into enzyme-like catalysts [2,3], with biomimetic or "unnatural" catalytic motifs. Our synthetic cellulases outperform some natural enzymes in cellobiose hydrolysis, with a 10-to-the-10th power of rate acceleration. Our synthetic esterase could hydrolyze nonactivated alkyl esters at room temperature and neutral pH, while more reactive aryl esters stay intact in the same solution. The catalytic designs and mechanistic studies of these catalysts will be presented.

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