



Trip Report for
“ACS 20th Rocky Mountain Regional Meeting”
Denver, CO
August 29 - September 1, 2007

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Abstract: *The ACS 20th Rocky Mountain Regional Meeting was held in Denver, CO, on August 29 to September 1, 2007. This was the first joint ACS-AIChE meeting and was hosted by the Rocky Mountain Region of the American Chemical Society (ACS) and the American Institute of Chemical Engineers (AIChE). This was a unique experience of two groups of scientist and engineers combining their ability for a genuine joint meeting. The meeting covered variety of chemistry and engineering topics. This report covers the selected chemistry topics from the meeting.*

Plenary lecture
“Green chemistry and the future”

Terry Collins, Carnegie Mellon University, Pittsburgh, PA

Three R&D areas are important to the technological dimension of a sustainable civilization: safe energy, renewable feedstocks, and non-polluting chemical products and processes. Since William Henry Perkin accidentally synthesized in 1856 the first synthetic dye, more than 80,000 chemicals have been commercialized. In this building of the chemical enterprise, a basic premise has been that useful chemicals cause no harm. Because we had little or no idea of the dangers involved, hazardous chemicals have made their way into the economy often to cause harm for decades until their problems were discovered. But one benefit of our laissez faire building of the chemical enterprise is that we have learned a great deal about chemical hazards. This knowledge can now serve as roadmap for guiding us away from the known hazards. Chemicals can produce three general cellular toxicological endpoints: cell death; DNA-damage/mutagenesis; and epigenetic alteration of gene expression. We can translate this roughly by saying that chemicals can hurt living things by killing them, by giving them cancer, or by impairing their offspring. Green chemistry is the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. In his lecture, Prof. Collins focused on all the above points, but emphasized that getting rid of chemicals that can disrupt cellular development is the greatest challenge to developing a sustainable chemistry.

Professor Collins explored how we might do better to avoid the extremely serious hazards such disruptions represent and focus on structural elements of the chemical enterprise that must be changed if we are to have any hope of success. He also briefly described “TAML Activators,” catalysts that promise new green chemical technologies in many areas, but especially for the purification of water. TAML is a synthetic molecule tetra-amido macrocyclic ligand (**TAML**), which speeds oxidation reactions. One of the promising developments in green catalysis has been the preparation of tetraamido macrocyclic ligand (TAML) iron(III) activators by Carnegie Mellon University chemistry professor Terrence J. Collins. In 1999, Collins received a Presidential Green Chemistry Challenge Award for demonstrating that TAML activators significantly increase the oxidizing ability of hydrogen peroxide and that the TAML/H₂O₂ system can be used in a variety of commercial applications.

According to Collins, TAML activators are water soluble and different examples allow access to a broad pH range -from 1 to 13, the activators are relatively easy to synthesize, and they function well in nanomolar to low-micromolar concentrations. The activators can be readily modified to achieve a desired selectivity, and for most applications minimal capital costs will be needed for their implementation. Initial lab tests indicate that the TAML activators have low toxicity, but complete toxicology studies to check Collins added that his group has most recently used TAML activators for the rapid total destruction of chlorophenols [*Science*, **296**, 270 and 326 (2002)]. Chlorophenols, which are recognized by EPA as persistent environmental pollutants, are commonly used in pesticides, wood preservatives, and personal care products. They are also a by-product of wood pulp bleaching.

“Ionic Liquids: Green Solvents for Reactions and Separations?”

Joan F. Brennecke, University of Notre Dame, Notre Dame, IN

There has been an explosion of interest in the use of ionic liquids for a variety of reaction and separation processes. They are particularly attractive for homogeneously catalyzed reactions since many catalysts are essentially immobilized in the Ionic Liquid. Large selectivities, especially of carbon dioxide over other gases, make them attractive for gas separations. A major driving force in the use of Ionic Liquids is their low volatility and, therefore, potential for reducing air emissions. However, all Ionic Liquids are soluble to some extent in water so toxicity and biodegradation are extremely important. She presented that most of the long chain alkyl Ionic Liquids are toxic. Since these are soluble in water, they can kill fishes and microorganism in water. The toxicity of shorter alkyl chain Ionic Liquids are less compare to longer chain Ionic Liquids. But based on studies, Ionic Liquids are not mutagenic. Also, most of the Ionic Liquids are not biodegradable. Long chain alkyl Ionic Liquids are biodegradable compare to short chain alkyl Ionic Liquids.

“Green Synthesis of Ionic Liquids”

Jay C. Schleicher, Sylvia Nwosu & Aaron M. Scurto, University of Kansas, Lawrence, KS

Ionic liquids have been touted as the next great class of environmentally-friendly solvents due to their lack of vapor-pressure and molecularly “tunable” properties. However, reports of their synthesis often include the very solvents that they will purportedly replace. Moreover, ionic liquids are often too costly as industrial-scale replacements solvents. As kinetic and thermodynamic data of their synthesis is nearly non-existent in the literature, little to no emphasis has been placed on reactor engineering and process intensification to reduce the cost of the ILs. For ionic liquids to be truly sustainable and to be used ubiquitously, they themselves must be made in a correspondingly benign manner in potentially large quantities and for low cost. The kinetic constants are both sensitive to the solvent and concentration of the reactants. Solvatochromic probes and linear solvation energy relationships (LSER) have been used to connect measures of “polarity” with kinetic rate for these reactions. Solvent selection in light of principles of green chemistry and engineering is discussed. Compressed CO₂ has been shown to be an attractive tunable reaction/separation medium. Phase behavior with CO₂ has a large implication on both the reaction and separations scheme and can be used to optimize the entire process of this environmentally-benign medium.

“Super Critical Carbon Dioxide; Competitive Green Catalytic Oxidation Systems Featuring Selective Use of Media, Phase Relationships, Catalysts and Oxidants”

Daryle H. Busch and Bala Subramaniam, University of Kansas, Lawrence, KS

Carbon dioxide expanded liquids, CXLs, provide transport and safety advantages for catalytic oxidation reactions using the green oxidants, oxygen and hydrogen peroxide. These benefits have been explored for the oxidation of various substrates, including alternatives for important reactions: p-xylene to terephthalic acid, cyclohexane to adipic acid, p-nitrotoluene to p-toluic acid, olefins to epoxides, phenols to quinones, and replacement of chromium (VI) oxidants for benzylic alcohols and alkyl benzenes. Catalysts range from transition metal salens and porphyrins, and, for hydrogen peroxide, lewis acids based on high valent early transition metals,

to the catalyst for the venerable mid-Century process, cobalt/manganese acetate/bromide, the more recent Shell/Eastman catalyst, cobalt and zirconium acetates, and cobalt acetate catalysts with organic radical sources such as N-hydroxy imides, aldehydes and ketones. Hydrogen peroxide, runner-up to oxygen as a green oxidant, is disadvantaged for CXLs by the immiscibility of water and carbon dioxide. When achieved, monophasic hydrogen peroxide oxidations show substantial improvements over their phase transfer counterparts. Gas/liquid biphasic propylene to propylene oxide catalytic oxidation can be pressure intensified by appropriate inert gases.

“Coupling Chiral Homogeneous Biocatalysis with Benign Heterogeneous Separation”

Elizabeth M. Hill, James M. Broering, Jason P. Hallett, Charles L. Liotta, Charles A. Eckert and Andreas Bommarius, Georgia Institute of Technology, Atlanta, GA

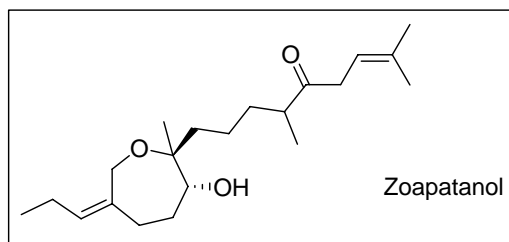
There is a broadly recognized need for the development of environmentally benign processing techniques and the use of alternative solvents. Bommarius group described a method for sustainable biocatalysis in an Organic Aqueous Tunable Solvent (OATS) system in which a hydrophobic substrate is transformed with a homogeneous enzymatic catalyst in a single liquid phase. Subsequent CO₂ addition produces a biphasic mixture where the hydrophobic product partitions preferentially into the organic rich phase for separation while the hydrophilic enzyme catalyst partitions into the aqueous rich phase, where it is recyclable. Greater than 99% enantiomeric excess (ee) is shown for catalyzed hydrolysis of styrallyl acetate with *Candida Antarctica* lipase B (CAL B) both before and after CO₂-induced separation. This system combines homogeneous enzymatic reactions with a built-in heterogeneous separation for enantiomerically pure products.

“Chiral ligands, auxiliaries and fictionalized material from carbohydrates”.

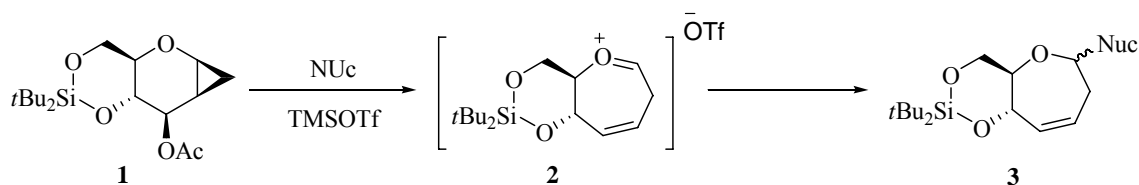
Jamie Singleton, Krishna Shteli and John O. Hoberg, University of Wyoming.

Seven numbered oxacycles are central nuclei of numerous natural products. The simple zoapatanol to complex polyether cytotoxins brevetoxins and ciguotoxins are the examples. The unusual biological properties of these compounds make it more interesting and numerous studies towards their synthesis have appeared. Hoberg, *et al* introduced cyclopropanated carbohydrates as substrates for their formation. They proposed that the reaction involves loss of acetate to give oxonium ion which is intercepted by a nucleophile to give the ring expanded oxepane. This methodology thus incorporates the optical activity and multiple functionality inherent in carbohydrates.

Figure 1



Scheme 1



Nucleophile	% Yield	Diastereoselectivity
TMSsallyl	91%	80:1
TMSSPh	85%	6:1
TMSN ₃	69%	2.5:1
TMSOallyl	0%	0
	 77%	80:1
	 68%	3:1
	 68%	7:1

“D-Chiro Inositol as Chiral Ligand in AAA Reaction”

Jamie A. Singleton and John Hoberg, University of Wyoming, Laramie, WY

Inositols (cyclohexanehexols) are a carbocyclic class of the carbohydrate family consisting of nine stereoisomers, including a pair of enantiomers (D-chiro and L-chiro), with the formula C₆H₁₂O₆. Because all of the ring atoms are carbon, their chemistry is very different from ‘normal’ carbohydrates, not only due to the absence of anomeric reactions, but also because all of the hydroxyl groups are secondary and differ only in spatial orientation. The previous is advantageous for their use as chiral ligands and auxiliaries (lack of complications due to mixtures of diastereomers and relative inertness), but the latter introduces some difficulties when functionalizing these compounds. Ozaki¹ has demonstrated the utility of Di-O cyclohexylidene protected derivatives of the L-chiro isomer in various cycloaddition reactions and reductions of

α -keto esters. Hoberg's group have shown that the C2 symmetric Di-O-isopropylidene derivatives of both D and L-chiro inositol gave ee's >95% in 1,4-conjugate addition of lithium thiolates. Because of the wide variety of topologically diverse ligands that can potentially be synthesized from the inositol scaffold, this group have developed a new class of C2 symmetric diphosphine ligands that have better control the regio and stereoselectivity of carbon-carbon bond forming allylations over a broader range of allylic substrates than is currently possible in Pd(0) catalyzed asymmetric alkylations.

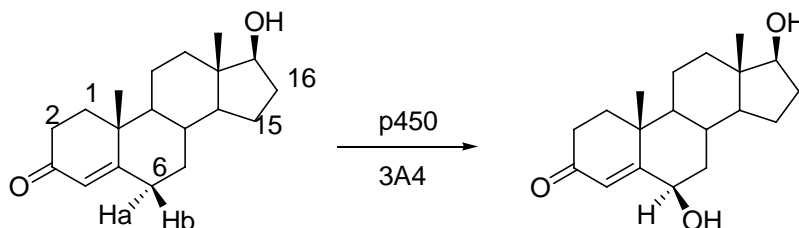
Reference: Akiyama, T.; Yasusa, T.; Ishikawa, K; Ozaki, S. *Tetrahedron Lett.* 1994, 35, 8401-8404.

“Hydrogen abstraction of testosterone by cytochrome P450 3A4: A computational approach.”

Yan Zhang and Hai Lin, *University of Colorado at Denver and Health Sciences Center, Denver, CO*

A member of the ubiquitous iron-hemo-proteins P450 super-family, the human P450 3A4 enzyme plays a critical role in drug metabolism. Lin's group reported a computational study of testosterone hydroxylation, a prototype reaction catalyzed by this enzyme. Density functional calculations at the B3LYP level of theory are carried out to investigate the hydrogen abstractions at the 1H, 2H, 6H, and 15H positions by the oxidant species in the catalytic cycle. The hydrogen abstraction is generally considered to be the rate limiting step in the abstraction-rebound mechanism. The calculated reaction barrier increases from 13 kcal/mol for the 6H-abstraction to 19 kcal/mol or even higher for the 1H, 2H, and 15H abstractions, as measured from the reactive complex. For hydroxylation at a given position, the barriers in both the low-spin and high-spin states are rather similar, with differences typically within 1 kcal/mol, which is in line with the two-state reactivity mechanism. The significantly low barrier for the 6H-abstraction is due to the resonance stabilization offered by the C4-C5 double bond. The theoretical findings are consistent with the experimental observation that 6H hydroxytestosterone is the most prominent metabolite for this reaction. Docking testosterone in the active site of cytochrome P450 3A4: Simulations suggest protein conformational changes are critical to substrate binding

Scheme 2



“Non-enzymatic digestion of proteins by microwave assisted acid hydrolysis”

Nicolas J. Hauser, *University of Wyoming, Laramie, WY*

Mass spectrometry has become a powerful tool in protein identification because of advances in mass analyzer designs and the advent of new ionization techniques. Proteins can be identified by performing a database search on MS/MS data that is generated from a peptide sequence tag,

which comes from the protein itself. Proteins are cleaved at a specific amino acid residue which creates a mixture of smaller peptides. These peptides contain all of the sequence information of the protein which can be found by performing MS/MS on the peptides. These proteomic measurements can be applied to mixtures of proteins. The most popular method of digestion is that of using an enzyme to specifically cleave a protein at designated amino acids. However, in alternative methods, in cases where enzymes do not have the right specificity or are not wanted otherwise. Also, for rapid field portable instrumentation enzymes are not suitable because the conditions required for enzyme activity and storage are difficult to accomplish in the field. Recently, the rapid chemical digestion of proteins by using a mild acid to cleave at aspartyl residues has been shown to be an effective digestion technique. The use of microwave irradiation was explored as a technique to rapidly increase the rate of acid hydrolysis of proteins to produce peptides that could be used to identify the proteins. Also, the use of microwave irradiation to increase the rate of disulfide bond breaking using dithiothreitol. Several test proteins were successfully cleaved specifically at aspartic acid residues and identified by performing a database search of the resulting MS/MS data.