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Perspectives in Catalysis

Future directions of catalysis science – Workshop

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Four areas for the future directions of catalysis science were discussed. (1) There is a need for correlation of structure, dynamical rearrangements, transition states and reaction intermediates of enzyme, heterogeneous and homogeneous catalytic systems through investigations of the same reactions under similar experimental conditions. Better understanding of the existing heterogeneous chiral catalytic systems is needed through *in situ* characterization to uncover new chiral systems. (2) New strategies of catalyst synthesis must be developed to establish molecular control over the structure, location and promoter distribution of catalysts. (3) Molecular characterization of the working catalysts, enzyme, heterogeneous and homogeneous, increasingly provides the crucial experimental information on structural details and leads to identification of elementary reaction steps. The frontiers of instrumentation are ever improving time resolution and spatial resolution and application under reaction conditions. (4) Catalytic cycles in soil and minerals and in the oceans must be identified by focussed efforts of collecting data and model studies. Other important directions of catalysis science include methane conversion, electrocatalysis, role of bulk hydrogen atom in catalytic hydrogenation, replacement of homogeneous acids by heterogeneous acid catalysts and further developments of the theory of catalytic processes.

KEY WORDS: future of catalysis science; correlations of enzyme, heterogeneous and homogeneous catalysis; characterization of catalysts; new synthesis of catalysts; global catalytic processes; catalysis in the soil; catalysis in the oceans; theory of catalysis; bulk hydrogen in catalysis; methane conversion

A Workshop on the Future Directions of Catalysis Science, sponsored by the Chemical Sciences, Geo-sciences and Biosciences Divisions of Basic Energy Sciences, the US Department of Energy was held on 28 February through 2 March 2001. The Co-Chairmen of the meeting were Stephen J. Benkovic and Gabor A. Somorjai. The discussions were focussed on four areas:

- Correlations between Enzyme Catalysis, Heterogeneous Catalysis and Homogeneous Catalysis
- New Methods of Catalyst Synthesis
- Characterization of Catalysts under Reaction Conditions
- Global Catalytic Processes

The participants (their list is shown below) were asked to assess the state of their field and point to future directions. Most of the attendees were experimental scientists but contributions from theorists permitted assessments of the state of theory and simulation in the field. Discussions of each subject area are summarized below and the conclusions are highlighted.

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CORRELATIONS BETWEEN ENZYME CATALYSIS, HETEROGENEOUS, AND HOMOGENEOUS CATALYSIS

As we enter the 21st century, the three principal fields of catalysis science, enzymatic, heterogeneous and homogeneous, are in a stage of vigorous development, with our understanding of structure–function–mechanism reaching unprecedented heights in each field. Moreover, it is becoming increasingly evident that these seemingly distinct fields actually share great complementarity, that common tools and approaches are essential to understand and to optimize the catalytic characteristics of each, and that in the future, many currently disparate aspects of the three fields will overlap and merge.

A. Structure

There are clear-cut correlations between enzymatic, homogeneous, and heterogeneous catalysis through the dynamic nature of structure for these processes. The flexibility of structure is necessary in all three cases for the catalytic cycle to operate efficiently, and these dynamic structural changes are complex and may occur either at the active sites or removed from the active site but influencing the bonding or lifetime of reaction intermediates nevertheless.

Enzymes work at the solid–liquid interface and near or at 300 K. It was agreed that their structure is key to their functioning. X-ray crystallography and NMR are the most frequently used structural tools for their study. The use of the kinetic isotope effect and neutron diffraction also provide important information. *The enzyme structure is flexible as its three-dimensional shape is enforced by non-covalent interactions. Flexibility allows the enzymes to adapt to changes of substrate structure and charge configuration as the reaction proceeds which is particularly important for multi-step reactions.* Flexibility also allows enzymes to maximize their interactions with substrate, making contacts on all sides to maximize specificity and catalysis while allowing motion of flaps or domains to let substrates and products into and out of the active site [1–5].

There is evidence that changes in the enzyme's protein sequence at sites that are both distant from the enzyme active site and distant from each other affect the rate of the catalytic steps. This occurs without changes in the protein structure or the binding affinity of reactant molecules. These observations point to the changes in dynamics of the protein molecule itself that are influencing the chemical steps involved in catalysis [6]. The relationship between catalytic activity and protein dynamics is poorly understood [7]. There is evidence from NMR and kinetic studies of the dihydrofolate reductase (DHFR) wild type and mutant enzymes from *Escherichia coli* that catalyzes the reduction of 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate using nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor that the enzyme undergoes a series of conformational changes throughout the catalytic cycle when coupling to the reactant competent species occurs [8]. Calculations suggest that loop motions, as well as discrete domain motions linking all regions of the protein, are important in catalysis [9,10].

Information regarding molecular interactions and the chemical dynamics of enzymes has been derived exclusively from experiments conducted on large ensembles of molecules. Although ensemble-averaged results are essential, they often preclude detailed information because of the lack of *a priori* knowledge of the distributions and fluctuations of molecular properties. A single-molecule experiment directly measures the distribution of a molecular property and its dynamical fluctuation, revealing information hidden in the ensemble average.

For example, *real-time observations were made of enzymatic turnovers of single molecules* of cholesterol oxidase, an enzyme that catalyzes the oxidation of cholesterol by oxygen [11,12]. The active site of the enzyme involves a flavin adenine dinucleotide (FAD), which is naturally fluorescent in its oxidized form but not in its reduced form. The FAD is first reduced by a cholesterol molecule, and is then oxidized by molecular oxygen. The FAD emission blinked on and off, each on–off cycle corresponding to an enzymatic turnover. Statistical analyses of the data revealed a significant and slow fluctuation in the rate of cholesterol oxidation. Also slow conformational fluctuations of the enzyme were independently observed through the fluctuating emission spectrum. The conformational changes caused the rate fluctuation. The rate fluctuation is not described by the fundamental Michaelis–Menten mechanism of enzymology, which works well for describing only the averaged behavior of turnover events. *This illustrates the influence of conformational dynamics on enzyme functions, which can be revealed by the single-molecule experiment*.

Dynamical changes of protein conformations can be either fast or slow, ranging from femtoseconds to seconds. While the fast fluctuation can be probed by ultrafast spectroscopic techniques, the slow fluctuation is commonly hidden in ensemble-averaged measurements. A new approach was developed to study conformational dynamics on microsecond to second time scales. The fluorescence quenching of flavin mononucleotide (FMN) by tyrosine *via* photoinduced electron transfer provides a distance-dependent probe for conformational changes. Measurements on single FADH:flavin oxidoreductase (Fre) molecules indicate a broad distribution of conformational states and dynamical fluctuations among them spanning many decades of time scales.

Metal catalysts undergo changes of the surface structure upon adsorption of reactants and during the catalytic cycles [13,14]. Structure sensitive and structure insensitive reactions represent two distinguishable classes of heterogeneous catalytic processes. It appears that for surface structure sensitive reactions adsorbate induced restructuring of the metal surface occurs on the time scale of the catalytic turnover (for example, the CO/NO reaction over rhodium or the N_2/H_2 reaction over iron), or on some crystal surfaces there are multiple reaction channels, some slow and others fast, causing changes of rates (cyclohexene dehydrogenation over platinum). For structure insensitive processes the first monolayer of adsorbates permanently restructures the surface that remains then structurally unchanged over 10^5–10^6 catalytic cycles (ethylene or other light olefin hydrogenation).

There appear to be clear-cut correlations between enzyme and heterogeneous catalysis through the dynamic nature of structure for both processes. The flexibility of structure is necessary in both cases for the catalytic cycle to occur and these dynamic structural changes are complex that may occur at the active sites or removed from the active site but nevertheless influencing the bonding or lifetime of reaction intermediates.

Correlations exist between metalloenzyme and heterogeneous transition metal catalytic processes in the areas of alkane hydroxylation and dehydrogenation, olefin epoxidation, and nitrogen fixation, despite the fact that heterogeneous catalysts typically operate under high temperature and high pressure conditions, while enzymes catalyze similar transformations under ambient conditions. Potentially mediating between these extremes are synthetic metal complexes that mimic the metalloenzyme active sites and catalyze reactions under relatively mild conditions. One example is the enzyme nitrogenase, which carries out the reduction of dinitrogen to ammonia. The active site components are known to be metal–sulfur clusters that contain iron and molybdenum, and their precise structures have been determined from X-ray crystallography; however, a detailed mechanism of action remains elusive despite a significant investment of effort. There have been efforts to model this chemistry with low molecular weight metal complexes; recently low-valent molybdenum complexes have been demonstrated to effect cleavage of the N–N triple bond, but only in a stoichiometric fashion. Thus an important challenge is to develop such catalysts. Examples in the area of hydrocarbon oxidation are nonheme iron enzymes such as methane monooxygenase and the Rieske dioxygenases, which activate oxygen to carry out respectively the hydroxylation of methane and other alkanes and the *cis*-dihydroxylation of arene double bonds. Low molecular weight metal catalysts have recently been identified that can carry out such transformations and in a stereospecific manner. Mechanistic studies of these homogeneous iron catalysts contribute *to a better understanding of enzyme function and raise the possibility of making tractable and tailorable model systems* [15–22].

Correlations between homogeneous and heterogeneous polymerization catalysts have also been studied in the field of olefin polymerization. The structures, thermodynamics, and solution structural dynamics of homogeneous transition metal ion catalyst–cocatalyst systems have been studied and correlated with polymerization rates and selectivities [23–26]. *Refinement of single-site homogeneous and heterogeneous polymerization catalysts has successfully been achieved, leading to polyolefins and polyolefin blends with superior processing, mechanical and recycling properties.* Similarly model heterogeneous catalyst studies identified one or several active sites on the surface of the $MgCl_2/TiCl_x/AlEt_3$ system, depending on modes of fabrication, that can be identified by mesitylene thermal desorption. *The catalyst with single site produced only isotactic polypropylene while the multiple site heterogeneous system produced a mixture of isotactic and atactic polypropylene* [27].

The *synthesis of chiral molecules* can be attained by enzyme, heterogeneous and homogeneous catalysts. Homogeneous Mn or Co ion–ligand systems are being designed for asymmetric oxidation catalysis mimicking the coordination environment of heme-iron-containing monooxygenase proteins. Detailed mechanistic and structural studies of these processes have revealed unexpected and often non-intuitive mechanisms for catalysis and stereoselection in each case. Catalytic asymmetric hydrocyanation of hydrazones was developed to give stable, crystalline acyl hydrazino nitriles in excellent yield. The adducts provide convenient access to a number of useful chiral building blocks [28,29]. Design approaches in heterogeneous chiral catalysis include (1) deposit metal catalysts on chiral supports; (2) immobilization of homogeneous chiral catalysts; and (3) modification of heterogeneous catalysts by chiral modifiers. Deposit metal catalysts on chiral supports was among the early attempts to realize chiral reactions.

An area that has attracted immense efforts is to translate the enormous success in homogeneously-catalyzed chiral reactions into heterogeneous versions via immobilization of high-performance homogeneous catalysts over or in solid supports. Many types of solid supports (polymers, structured solids such as zeolites, and silica) and many clever methodologies have been explored to immobilize a wide range of catalysts for a variety of chiral reactions. The methodologies fall roughly into three categories. The first is to “heterogenize” chiral ligands *via* covalent bonding to solid supports, followed by ligand coordination to the metal center. The second relies on electrostatic interaction between the catalysts and the support. Examples include $Rh(DIPAMP)^+$–PTA–Al_2O_3 and C_2 symmetric *bis*-(oxazoline) Cu(II) in HY zeolite [30–33]. The third involves encapsulation of homogeneous asymmetric catalysts within solid supports such as polymers and zeolitic materials, a “ship-in-a-bottle” approach.

Modification of heterogeneous catalysts by chiral modifiers produced two extraordinarily effective catalytic systems, *i.e.*, the tartaric acid modified Raney Ni for hydrogenation of β-ketoesters [32] and 2-alkanones, and cinchona-modified Pt catalysts for hydrogenation of α-ketoesters [33]. In both cases greater than 90% ee’s can be achieved [34] even under extremely mild conditions [35]. The high enantioselectivities achievable are particularly remarkable considering the structural complexity of heterogeneous systems. On the other hand, the nature of the active asymmetric site, and the mechanisms of the efficient chiral induction remain to be elucidated.

Heterogeneous chiral catalytic systems have been applied to a wide a range of reactions such as hydrogenation, epoxidation, *cis* dihydroxylation, hydrosilylation, C–C bond formation, aziridination, cyclopropanation, and ring opening reactions of epoxides, with the number of immobilized homogeneous systems dominating. The challenges associated with the immobilization approach include metal leaching and selectivities that are often observed to fall below those of their homogeneous counterparts.

Future directions

There is a need for the correlation of structure, dynamical rearrangements and reaction mechanisms of enzyme, heterogeneous and homogeneous catalytic systems through investigations of the same reactions under similar experimental conditions. There is a need for studies of a broader range of enzyme systems with focus on transition state structure, on the molecular basis of the role of flexibility, inhibitor design and restructuring of the catalysts. These structural and mechanistic insights would then be incorporated into catalyst design [36–38]. Better understanding of the existing, highly efficient heterogeneous chiral catalytic systems is needed to uncover new chiral catalytic systems. The emerging efforts in *in situ* characterization of the chiral surface and chiral surface processes can potentially advance our understanding of the fundamental aspects of this unique and technologically important class of reactions. Establishment of virtual centers aimed at understanding catalysis by enzymes and heterogeneous surfaces and the application of this understanding to the design of new catalysts, is strongly recommended. The interdisciplinary training of new researchers is essential.

B. Transition states

The understanding and control of transition states is a central theme of enzyme, heterogeneous and homogeneous catalysis. *Enzymatic transition states* have been experimentally established for only a small number of enzymes [39–44]. Rate enhancement for most enzymes is thought to be achieved by: (1) the binding of reactants to the catalytic site; (2) the mechanical closing of loops or domains over the catalytic site to exclude solvent which can sometimes also be important in preventing reactant escape; (3) ground state destabilization by electrostatic destabilization, distortional binding, and pre-alignment of the groups that accomplish chemistry and, preferentially, bind to the transition state charge and shape. In the closed complex of the enzyme-trapped reactants, a dynamic search occurs to achieve the low energy pathway through an arrangement of the substrates to approximate the transition state configuration [45–47]. Product formation at the catalytic site is followed by loop or domain opening and product release. As in other fields of chemistry, the lifetime of the transition state is thought to be related to the conversion of a vibrational to a translational mode of the reacting atoms. In some enzymes transition state transit occurs more rapidly than the loop opening step that allows substrate or product release, resulting in many forward and reverse transits of the transition state prior to product release. This observation emphasizes the role of the catalytic site loops and domains that isolate reactants from bulk solvent, gate the entry and release of reagents to the catalytic site, and for a finite time, make the release of reactants impossible. This state corresponds to the tight-binding achieved by analogues of the transition state. Reorganization of the active site from the ground state enzyme (the Michaelis complex) is necessary for the binding of transition state analogues. Transition state analogues cause catalytic site loops to close and the enzyme and analogue to achieve contacts similar to the transition state. In the closed state, with optimized contacts, the binding energy approaches that of the $\Delta\Delta G^{\ddagger}$ relative to substrate binding, *i.e.*, 10^{10}–10^{15} fold greater affinity than that of the enzyme·substrate complexes. Efficient design of transition state inhibitors requires knowledge of the enzymatic transition states. These have been experimentally established for only a small number of enzymes. In several of these cases, transition state inhibitors have been designed and synthesized, and are the most powerful inhibitors known for these targets. It is now apparent that transition state inhibitors have the potential to act as biologically active agents in a large number of health-related disorders. The frontier in this field is to develop theory and methods to permit facile determination of transition state structure and its extrapolation to the design of transition state inhibitors [39–44].

Challenges for the future of enzymatic transition state structure and inhibitor design

The future of transition state analysis and inhibitor design lies in developing new technologies to permit accurate experimental knowledge of enzymatic transition states that are not yet experimentally accessible. Enzymatic reactions that have the chemical steps obscured by slow product release, irreversible collisions of reactant and the catalytic site, and rapid and reversible chemical equilibrium on the enzyme prior to reactant release offer experimental challenges that have not yet been completely overcome. Synthesis of labeled reactants for kinetic isotope effect measurement is an additional barrier that can, in principle, be circumvented by natural abundance ^{2}H, ^{13}C, ^{15}N and ^{18}O measurements. High accuracy measurement of these isotope effects with small amounts of reactants remains a challenge that may soon succumb to the rapid developments in mass spectrometry and NMR.

Despite the challenges, enzymatic transition state analysis in 2001 is analogous to the early development of protein crystallography. The extensive experimental data collection, the nontrivial computational challenge and the synthesis of novel compounds with numerous stereochemical centers all contribute to the challenge. The rewards of transition state information and powerful transition state inhibitors far outweigh these barriers. We foresee a future where all enzymes of significance for inhibitor design will be characterized by: (1) kinetic studies to identify rates of catalytic steps, (2) structural analysis using X-ray crystallography, and (3) enzymatic transition state analysis to give the geometry and a quantum chemical description of the transition state. These descriptions, when combined with molecular dynamic simulations of E·S and E·TS, will permit an understanding of the enzymatic bonding of substrate and transition state and will permit the logical design of transition state inhibitors.

Intermediates and activated states in heterogeneous catalysis

In heterogeneous catalysis the formation of spectroscopically characterizable concentrations of reaction intermediates can often be obtained by photon or electron impact. Electron irradiation produces methyl groups from methane, phenyl groups from benzene, and a 3-carbon metallacycle from cyclopropane on different metal crystal surfaces. Heteroatom intermediates can also be obtained by electron impact [48–50].

Using photons, hydrocarbon intermediates have been obtained by low temperature photolysis of adsorbed monohalides of the target intermediate. Once synthesized, spectroscopic characterization (vibrational, electronic, structural) can proceed using optical and electron probes [48–50].

Selectivity is the key issue in heterogeneous catalysis science. Thus, the study of reaction intermediates in multipath reactions is a major direction of catalysis research. Catalytic reforming studies of n-hexane or n-heptane on metal surfaces indicate that β-hydride elimination is critical on bifunctional catalysts where most skeletal rearrangements of olefins are promoted by acidic sites on the oxide support, while it plays only a minor role on pure metal surfaces [51–55]. The relative rates of α- *versus* γ-hydride elimination are significantly different on platinum and nickel surfaces. This difference is the likely reason for the predominance of hydrogenolysis on nickel versus the unique reforming activity of platinum.

In catalytic oxidation processes the oxygen coverage strongly influences partial oxidation pathways as compared to total oxidation of 2-propyl groups. It appears that OH groups on the metal surface may play an important role in altering reaction paths [51–55].

The role of modifiers that can make hydrogenation catalysts enantioselective is beginning to be explored. Transition state studies in chiral synthesis over platinum that is modified by cinchona to selectively hydrogenate α-ketoesters such as ethyl pyruvate to produce the optically pure (R)- or (S)-α-hydroxoesters (ethyl lactate) could reveal the structural ingredients for chiral catalysis. This information can then be correlated with results obtained by enzyme catalysis of similar reactions [51–55].

A unique area of heterogeneous catalysis is *ultrahigh temperature* ($\geqslant$1300 K), *short residence time* ($\sim 10^{-3}$ s) *processes*. Catalytic combustion and pyrolysis are these types of reactions. Spectroscopic evidence indicates the surface *catalyzed formation of free radicals* such as methyl

(CH_3) and hydroxyl (OH) which then undergo secondary hydrogen abstraction and coupling reactions on the surface and in the gas phase to yield the reaction products. Mass spectroscopy, electron spin resonance, infrared spectroscopy and other optical spectroscopies are utilized in these studies [56,57]. Studies of the elementary reactions in this circumstance permit the development of catalytic combustion at lower combustion temperatures while maintaining high turnover. This would drastically reduce NO_x formation in this circumstance. Controlled pyrolysis that can be surface catalyzed could lead to methane conversion strategies and those of light alkanes that would produce desirable products ranging from olefins to cyclic aromatics [58,59].

Studies of reaction intermediates during surface catalyzed reactions, under reaction conditions, became possible by the use of sum frequency generation (SFG)-surface vibrational spectroscopy. The technique can distinguish between surface species that turn over and those that remain stagnant on the surface during the catalytic cycle. *During the hydrogenation of light olefins, π-bonded species that are weakly bound to the metal surface hydrogenate while other σ-bounded or alkylidyne species are spectators* [60,61]. During the dehydrogenation and hydrogenation of cyclohexene 1,3-cyclohexadiene and 1,4-cyclohexadiene reaction intermediates were detected. During CO oxidation over platinum the presence of platinum carbonyl species were detected that induce CO dissociation to C and CO_2 at the ignition temperature where there is a rapid temperature rise and the combustion reaction becomes self-sustaining. It appears that the onset of the second exothermic reaction, carbon oxidation to CO_2 in addition to the oxidation of molecular CO, is the reason for ignition [62–64].

Future directions

Studies of reaction intermediates and transition states, that are carried out at low pressures using model systems, should be correlated with studies of reaction intermediates during catalytic reactions. Transition states and reaction intermediates detected during enzyme catalyzed reactions should be correlated with similar reaction studies, but using heterogeneous and homogeneous catalysts. Fertile areas for investigations are the catalytic conversion of chiral molecules and high temperature, short residence time processes involving free radicals that include pyrolysis and catalytic combustion.

NEW METHODS OF CATALYST SYNTHESIS

Most high surface area oxide catalysts are synthesized by sol–gel techniques. When transition metals are dispersed on the high surface area oxides they are usually deposited from solution, oxidized, then reduced. Since selectivity is the major concern for catalysis science for the future, precise control of the size, structure and location of the catalysts is necessary. This cannot be readily achieved by present catalyst synthesis techniques. Therefore, new methods of catalyst fabrication are at the frontier of catalysis science. In order to achieve molecular level control, several new strategies for catalyst synthesis are tried. “Single source” molecular precursors such as $OV(O^tBu)_3$ and $Zr(OCMe_2Et)_4$ in non-polar solvents are used to produce well-dispersed mixed oxides with high surface area. Using molecular precursors in the presence of block copolymer templates, mesoporous, multicomponent oxides have been prepared [65–68]. Titania–silica materials are prepared from $Ti[OSi(O^tBu)_3]_4$ molecular precursors and have been found to be highly active for the epoxidation of cyclohexene. Micro- and mesoporous materials are prepared by using spherically-shaped dendrimers that are assembled into porous networks, the structures and porosities of which depend on the dimensions of the dendrimeric building block.

Recent breakthroughs in nanofabrication technology on the one hand, and in the molecular directed 3D assembly of inorganic porous media on virtually all length scales, now make it possible to design and create catalytic surfaces with atomically defined functionality [69–81]. Highly ordered, 3D porous surfaces that are mechanically, thermally and hydrothermally stable are being developed that have surface areas to 1500 m^2/g or greater. The surfaces can be structured during the assembly to have bi- or polymodal channel access with each channel being effectively monodispersed in pore size from 1 to 50 nm. The 3D surface architecture can be designed in a variety of configurations, for example homogeneous arrays of channels, bicontinuous channel arrays with right and left handed helicity; single cage arrays or arrays of two different cages with different pore-size accessibility to each cage. The composition of these 3D high surfaces area supports is being varied over a wide range from main group (silica, alumina, carbon) to transition metal (titania, zirconia, zinc oxide, copper oxide, platinum metal, copper metal) and binary or ternary phases ($SiO_2 \cdot TiO_2$, $TiO_2 \cdot Al_2O_3$, $ZrO_2 \cdot TiO_2$). The versatility of these 3D surfaces is also enhanced by the fact that they can be readily functionalized either by coassembly with the desired organic group during the initial assembly of the inorganic phase or by subsequent grafting.

The use of block copolymers to direct the assembly of these materials is proving to be a particularly efficacious approach for the design of these 3D surfaces. The molecular hydrophobic/hydrophilic domains of simple, inexpensive block copolymers can be easily transferred to template the wall structure (hydrophilic) and pore structure (hydrophobic) domains of the 3D inorganic surface. Furthermore, the block copolymers can be recovered at ~80–90% efficiency and used for additional support synthesis. The synthesis chemistry can be combined with processing to give in a simple procedure, powders of specified particulate shape, fibers, films, porous “hard” spheres, hollow spheres with highly patterned porous wall structure, or hierarchical structures with selected porosities at the nano, meso and micro length scales.

Electron beam lithography has been employed to fabricate ordered arrays of metal nanoparticles (Pt, Ag) on oxide substrates (SiO_x, AlO_x, TiO_x). These show high activity for isomerization, dehydrogenation, and hydrogenation reactions. Although their surface area is small, these model catalyst studies permit the systematic variation of particle size, distances between particles and oxide–metal interfaces to explore changes of selectivity as a function of these variables [82,83]. Three-dimensional nanostructures instead of two-dimensional must be assembled in order to obtain surface areas that can be used in the technology.

Focus on selectivity in catalysis science makes it necessary to develop metal oxide catalysts with uniform active sites [84–86]. However, there are important questions we must answer to explore the possibility of successful fabrication of such catalysts. Where does the local view of surface reactivity become inadequate? What is the chemistry of surface defects? How do we connect the sites and reactions in surface science studies with those that are present under catalytic reaction conditions? Oxide surface characterization under reaction conditions is necessary to develop the structure–reactivity relations.

Future directions

To establish molecular control over the structure, location and promoter distribution of catalysts to achieve high selectivity new strategies of catalyst synthesis must be developed. These include single molecular precursors, synthesis of microporous framework around nanoparticles of uniform particle size and electron and photolithography techniques that are under investigation.

The combination of precisely designed and uniform nanoparticle catalysts with the highly ordered supports described above to give the optimum combination of activity, selectivity and throughput is achievable. There is good evidence that nano/mesoscale patterned silica structures make excellent templates for other non-oxide compositions including carbon and metals, further extending the compositional possibilities of 3D surface materials. The electrochemical synthesis of highly ordered 3D mesoporous surfaces made up of either metals or oxides with preferred pore orientation is evolving as an alternative approach for micron size thin film or membrane synthesis. The functionality and size of the 3D surfaces opens the door for supported biocatalysis, as well as for enantio- or stereo-selective catalytic synthesis of pharmaceuticals or polymers. The monodispersed sizes of the pores of these materials can be used for introducing large molecule reactant, transition state and product selectivity and in the case of polymer synthesis with supported catalysts, defining polymer crystallinity, orientation and morphology by confined extrusion of the product.

CHARACTERIZATION OF CATALYSTS UNDER REACTION CONDITIONS

Catalyst characterization, structure, composition, surface area and oxidation state have been the responsibility of analytical groups in the past and it has usually been performed on the fresh and spent catalysts before use and after deactivation. In the past ten years atomic level studies using electron microscopy [87,88] and scanning tunneling microscopy revealed that the adsorption of reactants and the formation of reaction intermediates and products dramatically change the structure of catalysts. While some of these changes remain after the reaction, the working catalysts are likely to have different structures, compositions and oxidation states than what can be detected “pre-natal” or “post-mortem.” Thus, molecular level analysis during the catalytic reactions is necessary to identify the state of the active catalysts that can then be correlated with reaction rates, selectivities and deactivation. A large number of techniques have been developed that provide molecular level analysis of the working catalyst surface under reaction conditions, although model systems (*i.e.*, flat surfaces) have to be used in some cases. These are optical, vibrational spectroscopy techniques, Fourier transform infrared (FTIR) [89–92], sum frequency generation (SFG)-vibrational spectroscopy [93,94] and UV-Raman spectroscopy [95]. Reflection–absorption infrared spectroscopy can be made more surface sensitive in the presence of gas-phase species (a) by exploiting surface selection rules by using polarization modulation; (b) if the gas phase molecules do not adsorb infrared radiation; and (c) the vibrational frequencies of adsorbed molecules are different from those of the gas phase. Polarization modulated infrared reflection absorption spectroscopy (PM-IRAS) and SFG have proved to be extremely useful techniques for atmospheric pressure experiments [90,96–99]. Because it has to satisfy both dipole (IR) and polarizability (Raman) selection rules SFG can only be obtained from media that lack inversion symmetry. Thus SFG-vibrational spectroscopy is uniquely surface monolayer sensitive. Using excitation by UV-light will separate the Raman transitions from fluoroscence making the UV-Raman signal much easier to resolve. Nuclear magnetic resonance (NMR) studies can also be performed under reaction conditions. Synchrotron radiation that provides high intensity and tuneable photons from X-ray to far infrared is being used increasingly in catalysis research [100–102]. Grazing angle X-ray diffraction provides surface structure [103–108] and X-ray diffraction at high intensities that can be performed at high temperatures during reactions can provide time-resolved changes of catalyst structure. Extended X-ray absorption fine structure (EXAFS) provides nearest neighbor distances and number of nearest neighbors and their variations as a function of time and reaction conditions. Most studies under reaction conditions demanded the use of photon-in–photon-out scattering techniques. Recent innovations permit the application of X-ray photoelectron spectroscopy at high reactant pressures by clever use of geometry and differential pumping [109]. Some of the new non-optical techniques are scanning probes, scanning tunneling microscopy (STM) and atomic force microscopy (AFM). Both can readily be used at high pressures or at the solid–liquid interface [110–112].

Inelastic neutron scattering spectroscopy (INS) is a powerful technique for studying adsorbed species and monitoring chemical rearrangements in the adsorbed layer under reaction conditions.

Recent advances in optical microscopy have allowed high sensitivity, high spatial resolution, high time resolution, and high spectral selectivity. These advances make possible new observations and new insights into catalysis: from enzymology to surface analyses. (a) *Coherent anti-stokes Raman scattering (CARS) microscopy*. Confocal and multiphoton fluorescence microscopy are powerful tools for three-dimensional imaging of chemical and biological samples, especially for living cells. For chemical species or cellular components that either do not fluoresce or cannot tolerate fluorescence labeling, Raman microscopy provides a contrast mechanism based on molecular vibrations. However, the intrinsically weak Raman signal necessitates high laser powers and is often overwhelmed by the fluorescence background of the sample. To overcome the problems, a new technique, coherent anti-Stokes Raman scattering (CARS) microscopy, has been developed to image living cells in a noninvasive manner [113,114]. CARS microscopy does not rely on the presence of fluorophores, but retains the resolution and three-dimensional sectioning capability of confocal and multiphoton fluorescence microscopy. Complementary to these techniques, CARS microscopy provides a contrast mechanism based on vibrational spectroscopy. The vibrational contrast mechanism, combined with an unprecedented high sensitivity at a biologically tolerable laser power level, provides new possibilities for microscopic investigations of living cells. (b) *High resolution near-field optical microscopy.* Recent advances in aperture-less near-field microscopy [115] make it possible to obtain spectroscopic mapping of photosynthetic membranes with better than 20 nm resolution. The key behind this technique is a sharp metal tip, illuminated with light of a proper polarization. The highly enhanced and localized field around the tip results in two-photon excitation (TPE) of the sample fluorescence. 3D electromagnetism simulation based on the finite difference time domain method (FDTD) has been used to design new tip shapes and coupled with a dual beam focused ion beam (FIB) instrument to fabricate the tips. These new tips have high field enhancement and provide unprecedented spatial resolution ($\sim$10 nm), comparable to the size of individual protein molecules. With this resolution different regions in the thylakoid membrane fragments extracted intact from Spinach chloroplasts have been spectroscopically identified. This methodology can also be applied to surface characterization. Microcalorimeters have been developed that can be used to detect the heat of adsorption of a fraction of a monolayer of adsorbed atoms or molecules studies on single crystal model catalysts [116–118]. This technique opens up surface thermodynamics to molecular level studies. It permits monitoring the heat of adsorption of irreversibly adsorbed species that could not be determined by thermal desorption techniques. Studies can be carried out to directly determine binding energies of carbon, hydrogen, and nitrogen to permit validation of theoretical calculations performed on these systems. There are opportunities to adapt the microcalorimeter to studies of the solid–liquid interface to measure heats of adsorption during enzyme catalyzed reactions.

Future directions

Molecular studies of the working catalysts, enzyme, heterogeneous and homogeneous, increasingly provide the crucial experimental information that will provide structural details and lead to identification of elementary reaction steps and transition states so necessary to establish molecular reaction mechanisms. *The frontiers of instrumentation is ever improving time resolution and spatial resolution and applications under reaction conditions*. Just as time-dependent NMR studies elucidate enzyme catalyzed elementary reaction sequences, SFG and PM-IRAS reveal time dependent changes of reaction intermediate concentrations on heterogeneous catalysts, while time resolved X-ray diffraction monitors structural changes. These *in situ* studies are likely to reveal the molecular ingredients that control reaction selectivity. We should achieve time resolution that is shorter than turnover times. Time resolution on the scale of molecular motion would yield powerful information on molecular dynamics during the catalytic cycle. Since the catalytically active surface is “flexible” its rearrangement should be correlated with catalytic activity and selectivity. Spatial resolution of surface probes is most important to monitor surface structural heterogenities under reaction conditions. Perhaps near-field optical techniques will provide the opportunity of much improved spatial resolution for several of the optical probes.

Isotope labeling, coupled with time resolved spectroscopic monitoring of isotope concentrations is one of the most powerful techniques to monitor the kinetics of elementary reaction steps in catalytic reaction over enzymes, surfaces or in homogeneous systems.

Other challenges and opportunities in catalysis science

Methane conversion

The methane molecule has the highest hydrogen to carbon ratio of all hydrocarbons and thus it produces the most energy per CO_2 formed when burned. *Catalytic combustion* is the reasonable method to produce clean energy from methane because it produces much less than 1 ppm of NO_x due to the lower combustion temperatures [119,120]. There are many challenges involved in understanding this technology including the proper measurement of the rates of reaction. *High temperature, short contact time reactions* could convert methane to higher molecular weight chemicals and fuels. Understanding the control of free radical formation and reactions could make methane conversion more selective by this route [58,59].

Methane is plentiful in the form of *solid methane hydrate* [121], under the ocean at the continental shelves at depths of 2–3 km. Its genesis and its recovery are important fields for catalysis science.

Electrocatalysis

The use of external potential to aid catalytic conversion at solid–liquid interfaces is an important area of catalysis science [122]. Proton conducting membrane reactors can perform oxidative dehydrogenation of alcohols [123]. Air can be used as a source of oxygen. Nafion (DuPont) can be used at low temperatures ($<150\,^{\circ}$C) as a polymer membrane. Acid–base polymer blend membranes can be used for dehydrogenation or partial oxidation of alkanes and olefins [124]. A better understanding of the electrocatalytic reaction mechanisms is needed to optimize the rate and selectivity [123,125].

The role of bulk H atom in catalytic hydrogenation

There is evidence from low pressure studies that hydrogen atoms emerging from the bulk of Ni metal to the surface are the reactive species in the hydrogenation of adsorbed methyl radical [126], ethylene [127] and acetylene [128] to gas phase products. Surface bound H atoms are either unreactive or less reactive. For example, hydrogen stored in bulk palladium is more reactive during the hydrodechlorination of chlorofluorocarbons (C_2F_3Cl) than surface bound hydrogen [129]. In the case of hydrogenation of acetylene on Ni, surface bound hydrogen atoms react to form a sole product, adsorbed ethylidyne [128]. They do not hydrogenate acetylene to ethylene or ethane. Only bulk hydrogen atoms are observed to hydrogenate acetylene to the gas phase products ethylene and ethane. The distinctive chemistry of a bulk hydrogen atom is believed to arise largely from its significantly higher energy as compared to a surface bound hydrogen atom [127,128,130–132]. Exploring the role of other atomic species that reside in the bulk of catalysts such as oxygen and carbon is an important frontier area of catalysis science.

Replacement of homogeneous acids with heterogeneous acid catalysts

In fine chemical synthesis the replacement of homogeneous acids with heterogeneous acids has met only with limited success on a practical scale even though solid acids greatly decrease costs and reduce high levels of waste [133–136]. In addition to poor activity one frequently observes poor selectivity to the desired products or poor stability of the catalyst due to coking or strong adsorption of one of the reactants or products.

Solution-phase descriptions of acidity are not adequate to describe solid acids because proton transfer reactions are very different in the two media. A better understanding of the role of solvent effects in acid catalysis is clearly needed.

THEORY

A. Electronic structure calculations of structure and reactivity: opportunities and challenges

While electronic structure theory is a 70 year old field, it is only over the past 10–20 years that it has become central to chemistry as a whole. This has resulted from two critical developments. First, is the sustained exponential growth in computer power (doubling every two years or so), as embodied in Moore's Law. This means that the scope of applicability of all simulation methods is continually increasing. With development of massively parallel computing, this now seems likely to continue into the future, beyond the ten-year time frame on which physical device limits will be approached.

The second equally important factor is the development of electronic structure methods themselves to the stage where they are both accurate enough and practical enough to be useful in an extremely broad range of applications [137]. The development of reliable exchange–correlation functionals for density functional theory in the late 1980's and early 1990's was critically important [138]. Also of importance has been the development of wavefunction-based methods that are capable of meeting or exceeding the target of chemical accuracy in reaction energies: a precision of 1 kcal/mol or better [139]. This is approximately five times more accurate than DFT. Together with efficient algorithms to implement these methods within large-scale commercial and public domain program packages, electron structure methods are now very widely applied.

Reported electronic structure calculations have been strongly focused on predictions of the structure (minima and saddle points) and relative energies of isolated molecules. Within much of organic chemistry, this permits a description of reaction mechanisms. The precision of structure prediction for minima is typically better than 0.01 Å in bond lengths and 1° in bond angles. Density functional calculations, which are most widely used because of their relative economy, are typically quite robust for relative energies of different minima, but can perform more erratically for barriers. All widely used methods are weakest for situations where different electronic states are close in energy. They are also typically limited to systems of a few tens of first-row atoms at present (or heavier atoms with the use of pseudopotentials). In addition to locating and characterizing stationary points, the growing use of Car–Parrinello dynamics [140] to generate relative short picosecond trajectories is yielding many useful insights.

At the same time, there has been growing use of electronic structure methods for the description of surface chemistry in general and heterogeneous catalysis, in particular over the last decade. The adsorbate–surface system is often treated as a finite isolated cluster, as appropriate for examining local chemistry, defect sites, and disoredered systems. Alternatively for ordered systems or relatively high coverages, the use of periodic slab models for electronic structure calculations is quite commonplace. Either of these models is an additional approximation above and beyond what is required to study isolated molecules. Cluster models neglect long-range forces that contribute to surface binding in some cases. Slab models may not describe important defect sites. For reasons such as these it is important to validate the chosen model on a careful case-by-case fashion in close collaboration with experiment.

If a given model is successfully validated, it may then be used to address a broad spectrum of issues that lie at the heart of improved understanding of catalytic function, and then, by implication, improved catalysis design. Observable properties that can be calculated include stable chemisorbed structures, both intact and dissociated. The spectroscopy (either involving vibrations or core or valence electronic levels) of surface species can be calculated. Other observables that are not easily observed experimentally may then be calculated, such as transition structures (saddle points) and the associated reaction barriers. All of the input necessary to calculate rate constants by simple statistical mechanical methods such as absolute rate constants can be obtained. Finally, electronic factors that may account for the calculated mechanism can be examined, such as frontier orbitals, electrostatic potential maps, *etc*. This range of central quantities is why electronic structure calculations are already widely adopted as an additional analysis tool by experimental groups.

While recent applications are too numerous to even count it is perhaps worthwhile to mention three representative examples that illustrate aspects of present capabilities. First, Neurock and van Santen [141,142] have applied DFT calculations on both slab and cluster models to study the catalytic hydrogenation of ethylene on Pd(111). The clusters ranged in size between Pd(7) and Pd(19), while the slab was used to study ordered overlayers. Stable structures and plausible intermediates were characterized, as well as transition structures, permitting them to conclude that the mechanism likely proceeds through the di-σ bonded species. Second, the IBM Zurich group used slab DFT calculations to study the chemisorption of thiols, thiolates and disulfides on Au(111), which has relevance for self-assembled structures on this surface. Unfortunately, the calculations showed a strong sensitivity to the choice of density functional, so that no firm conclusions could be drawn on strength of binding of thiols and thiolates. However, it was clear that disulfides energetically prefer to dissociate to thiolates. Third, Ryder *et al.* [143] have recently reported a study of the nature of proton migration at the acid site of the zeolite catalyst ZSM-5, using cluster models (see, for example [144,145]). The calculations indicated a substantial barrier to proton hopping from oxygen to oxygen of about 28 kcal/mol, which was not highly sensitive to the choice of the cluster model. It was highly sensitive to the presence of adsorbed water, which can reduce the barrier to almost zero, and substantially affect the overall rate even when present in trace amounts.

These examples show that electronic structure calculations can already be an effective adjunct to experiment for understanding surface chemistry and catalysis. On-going and future developments of electronic structure algorithms will only make them more attractive. There is a need to develop robust reduced scaling algorithms (if possible linear scaling) for existing methods [144,145]. New theories are also needed for problems where there are near-degeneracies such as bond-breaking. Better integration is needed between the methods used for isolated molecules and solid state methods. Together with the relentless pace of computer hardware development, progress on these fronts will make electronic structure calculations ubiquitous in the future as a window into the nature of heterogeneous catalysis, that will be primarily used by the experimentalists themselves.

B. How statistical mechanics helps characterization, synthesis, and experiment design in heterogeneous catalysis and enzyme evolution

Among the most exciting developments in statistical mechanics over the past decade have been powerful methods for the computer simulation of materials. In many instances, extensions appear possible that will allow investigation of the increasingly-tailored microscopic properties of new materials. Moreover, new field-theoretic techniques in statistical mechanics allow computation of meso- and macroscopic material properties from such atomistic simulations. Four notable examples of the use of statistical mechanics for energy-related applications are discussed below.

Zeolite stucture determination

Zeolites continue to be synthesized at a furious pace. Crucial to the development of the field of zeolite science is the ability to determine the structure of newly-synthesized materials. Roughly 150 framework structures have been reported, yet another several dozen distinct synthetic zeolites remain unsolved in the patent literature. The derivation of an atomic-scale model of the framework crystal structure of a newly-synthesized zeolite is a non-trivial task. The difficulty stems primarily from the polycrystalline nature of most zeolite samples, with crystallite sizes typically below 5 μm. Notable improvements in single-crystal diffraction techniques have been made, primarily through the use of synchrotron X-rays, but fundamental limitations still exist.

There is a direct, real-space method for zeolite structure solution from powder diffraction data [146]. The advantage of this method is that it requires only easily available powder data, and it incorporates little preconceived bias of the investigator in the structure solution scheme. All publically known zeolites can be solved with this approach, and roughly ten new structures have been solved with this method. The method is freely available to anyone on the web (www.mwdeem.chemeng.ucla.edu/zefsaII).

Study of the zeolite nucleation mechanism

A key current limitation in the discovery of new zeolites with optimized properties is our lack of fundamental understanding of the zeolite nucleation and crystallization process. Important correlations between structure-directing templates and the resulting zeolite material have been made. And experimentally-motivated hypotheses about the fundamental nucleation events have been put forward. A complete understanding of the crystallization pathway, however, has not yet been achieved.

The confluence of recent experimental results and increased computational capabilities suggests that now is the time for a serious theoretical investigation of zeolite synthesis. Preliminary simulation results indicate the feasibility of the approach. Understanding zeolite nucleation is important not only scientifically for the discovery and synthesis of new materials, but also in an engineering sense for improving the performance of existing materials that are not performing as well as they could due to poor “crystallinity.”

Protocols for heterogeneous catalyst materials discovery based upon Monte Carlo [147]

The goal of combinatorial materials discovery is to find compositions of matter that maximize a specific material property, such as catalytic activity or selectivity. This problem can be reformulated as one of searching a multidimensional space, with the material composition, impurity levels, and synthesis conditions as variables. The property to be optimized, the figure of merit, is generally an unknown function of the variables and can be measured only experimentally.

Present approaches to combinatorial library design and screening invariably perform a grid search in composition space, followed by a “steepest-ascent” maximization of the figure of merit. This procedure becomes inefficient in high-dimensional spaces or when the figure of merit is not a smooth function of the variables, and its use has limited most combinatorial chemistry experiments to ternary or quaternary compounds.

The experimental challenges in combinatorial chemistry appear to lie mainly in the screening methods and in the technology and chemistry for the creation of the libraries. The theoretical challenges, on the other hand, appear to lie mainly in the library design and redesign strategies. This was addressed by exploiting an analogy between combinatorial materials discovery and Monte Carlo computer modeling methods. The multiple-round, Monte Carlo protocols are especially effective on the more difficult systems with larger numbers of composition and non-composition variables.

Protein molecular evolution – enzyme evolution [148]

The space to be searched in protein combinatorial chemistry experiments is extremely large. Consider, for example, that a relatively short 100 amino acid enzyme were to be evolved. The number of possible amino acid sequences of this length is 20^{100}–10^{130}, since there are 20 naturally occurring amino acid residues. Clearly, all of these sequences cannot be synthesized and then screened for figure of merit in the laboratory. Some means must be found for searching this space with the 10ˆ4 or so proteins that can be screened per day experimentally.

A hierarchical decomposition of the protein space can provide an effective searching procedure. It is known from protein structural biology that proteins are encoded by DNA sequences, DNA sequences code for amino acids, amino acids arrange into secondary structures, secondary structures arrange into domains, domains group to form protein monomers, and protein monomers aggregate to form multi-protein complexes. By sampling on each level of this hierarchy, one is able to search the sequence space much more effectively. Search strategies making use of the DNA, amino acid, and secondary structure hierarchy can be described. With this approach, functional protein space has a large, yet manageable, number of dimensions. That is, in a 100 amino acid protein domain there are approximate 10 secondary structures of 5 types (helices, loops, strands, turns, and others) roughly yielding the potential for $\sim 10^7$ basic protein folds. Organization into secondary structural classes represents a dramatic reduction in the complexity of sequence space, since there are $\sim 10^{170}$ different DNA sequences and $\sim 10^{130}$ different amino acid sequences in this space.

Statistical mechanics, in many forms, is an extremely useful tool in the field of catalytic science. Direct applications can be found in heterogeneous catalysis, and two applications to zeolites are given here. Less direct is the idea of using statistical mechanics as an inspiration for experiment design. Example applications include library design and redesign in hetero- and homogeneous catalysis. A final example is the design of protocols for *ab initio* enzyme evolution, that is, the evolution or discovery of completely new enzymes.

GLOBAL CATALYTIC PROCESSES

There are natural catalytic processes that occur in the atmosphere, in soil, by minerals and in the ocean. Photosynthesis and catalytic ozone destruction by NO_x and fluorocarbons are examples of these processes. There is intensive research going on to identify and study catalytic processes in the atmosphere. There is very little research in soils and minerals although the nitrogenase enzyme is well recognized for its ability to fix atmospheric nitrogen and provide it to plants. Even less research is performed to study catalytic cycles in the oceans although data is being collected at various depths and latitudes. The CO_2/carbonate cycle, the genesis of methane hydrate found at depths of 2–3 km (200–300 atm), factors affecting the basic pH and ocean floor chemistry all need to be investigated.

The only aspect of atmospheric catalytic chemistry that was discussed at the Workshop involved the role of chemical and biochemical catalysis in the global sulfur cycle [149–151]. The fast catalytic oxidation of sulfur compounds in the atmosphere causes air pollution and acid rain, while the slow oxidation of carbonyl sulfide, the most abundant sulfur species in the lower stratosphere, into sulfate aerosol may affect the Earth's radiative balance and contribute to warming. The global sulfur cycle involves the transformation of reduced sulfur species to highly oxidized species such as sulfuric acid. In the same time the sulfate reducing bacteria under anaerobic conditions reduces sulfates to H_2S. Heterogeneous iron and manganese species in clouds, fogs and aquated aerosols catalyze the oxidation of sulfur species. Sulfur containing free radicals and the presence of OH radicals provide additional reaction pathways. It was found that TiO_2, Fe_2O_3 and various silicates also catalyze the photooxidation of SO_2 and the hydrolysis of sulfur-containing organic molecules such as thiophosphoric acid esters (*e.g.*, parathion).

There is much less work in the field of mineral catalysis [152–155]. Mineral surfaces are known to catalyse organic tranformations (isomerization, dehydrogenation, hydrolysis, *etc*.). Because of the complexities of natural mineral systems research is focusing on (1) characterization of natural materials and (2) model studies. Iron oxides and manganese oxides, the most abundant materials in the soil, should be the attention of future surface studies. Chromium and arsenic ions have catalytic redox cycles that occur on these surfaces which involve the elimination of the toxic species associated with one of their oxidation states (Cr^{6+} and As^{3+}).

Future directions

Catalytic cycles in soil and minerals and in the oceans must be identified by focused efforts of collecting data and model studies. This knowledge is essential to understand how our planet functions. These catalytic processes are just as important to our survival and global management of resources as is photosynthesis.

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