Chapter 1

Quantum Catalysis: The Modeling of Catalytic Transition States

**Michael B. Hall[1], Peter Margl[2], Gabor Náray-Szabó[3], Vern L. Schramm[4],
Donald G. Truhlar[5], Rutger A. van Santen[6], Arieh Warshel[7], and
Jerry L. Whitten[8]**

[1]Department of Chemistry, Texas A&M University, College Station, TX 77843–3255
**[2]Department of Chemistry, University of Calgary, 2500 University Drive N.W.,
Calgary, Alberta T2N 1N4, Canada**
**[3]Department of Theoretical Chemistry, Loránd Eötvös University, Pázmány Péter
st. 2, H-1117 Budapest, Hungary**
**[4]Department of Biochemistry, Albert Einstein College of Medicine, 1300 Morris Park
Avenue, Bronx, NY 10461–1602**
**[5]Department of Chemistry, University of Minnesota, 207 Pleasant Street S.E.,
Minneapolis, MN 55455**
**[6]Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven,
Netherlands**
**[7]Department of Chemistry, University of Southern California,
Los Angeles, CA 90089–1062**
**[8]Physical and Mathematical Sciences, North Carolina State University, Box 8201,
Raleigh, NC 27695–8201**

We present an introduction to the computational modeling of transition states for catalytic reactions. We consider both homogeneous catalysis and heterogeneous catalysis, including organometallic catalysts, enzymes, zeolites and metal oxides, and metal surfaces. We summarize successes, promising approaches, and problems. We attempt to delineate the key issues and summarize the current status of our understanding of these issues. Topics covered include basis sets, classical trajectories, cluster calculations, combined quantum-mechanical/molecular-mechanical (QM/MM) methods, density functional theory, electrostatics, empirical valence bond theory, free energies of activation, frictional effects and nonequilibrium solvation, kinetic isotope effects, localized orbitals at surfaces, the reliability of correlated electronic structure calculations, the role of d orbitals in transition metals, transition state geometries, and tunneling.

Computational chemistry has achieved great strides in recent years, and it has become a strong partner with experimental methods, displacing purely analytic theory almost completely. The essential element in computational chemistry is the use of very general theoretical frameworks that can be applied broadly across a number of fields. Examples are molecular orbital theory, molecular mechanics, transition state theory,

classical trajectories, and the Wentzel-Kramers-Brillouin method. As the techniques of these fields are developed, they can be applied across broad ranges of problems inchemical structure and reactivity. When this pack of techniques is used to attack a herd of problems, it is only natural that attention is first focussed on the easiest ones. As these begin to succumb, computational chemistry sets its sights on more recalcitrant targets. Thus computational chemistry has been very successful for calculating structures and energies of small molecules, structures and energies of large molecules, and properties of simple reactions of these molecules. An emerging competency is the treatment of complex reactions involving catalysts. A critical element in this endeavor is the ability to directly model the transition state.

Systems of interest range from heterogeneous catalysis, through transition metal complexes, both classical and organometallic, to bioinorganic chemistry of enzymes and enzyme mimics. Often a reasonably accurate structure and a semi-quantitative relative energy for possible transition states can be helpful in pointing the way to the correct reaction mechanism. Knowledge of the mechanism is important as it directs the thinking about how to modify the reaction under study or how to create a new reaction. In many cases experimental work will provide an approximate relative free energy for the key or rate-determining transition state, but ascertaining its structure from experimental data is much more difficult. Here, theory can help. In fact conventional quantum chemistry is arguably at its best when determining structures.

Catalysts are molecular devices that are able to perform complicated chemical manipulations on individual molecules. Although they are technologically attractive entities, engineering them for a given task is a challenge that is only slowly coming within reach. Whereas it is possible to efficiently design and build macroscopic machines using classical mechanics, it is quite another matter to do so with individual atoms and molecules, which behave according to the laws of quantum mechanics. Thus quantum mechanical modeling methods play a prominent role in catalyst modeling and computational catalyst design.

An appropriate model of a catalytic system is, in most cases, quite complicated and consists of many atoms. Owing to their relative mathematical simplicity molecular mechanics and classical trajectory studies may be applied with explicit consideration of all components; however full models of practically important systems are beyond the scope of quantum mechanical methods. A more and more popular approach to quantum mechanical modeling is partitioning of the catalytic system (substrate interactions with an enzyme, zeolite pore, solid surface, or solvent) into various regions (1–8). The active site or central machinery (C) is surrounded by a polarizable environment (P) which is embedded in a non-polarizable region (N) and solvent (S). Some regions may overlap and others may be dropped completely from the model, depending on the degree of sophistication of the treatment and their effect on the process. A very great variety of implementations are possible, differing in details, and we will elaborate on some variations at appropriate points in this article.

The minimum-size active site model (C) should be composed of those atoms that undergo chemical changes during catalysis, i.e., participate in the bond(s) that will be cleaved or formed during the process. For example, in enzyme catalysis by serine proteases, which hydrolyze peptide bonds, C must contain at least the =N–C=O moiety of the peptide bond, the –OH group of the attacking serine, and the proton acceptor imidazole ring of the nearby histidine. For systems where electronic excitation or electron transfer plays a role (e.g., heme proteins) the minimum-size active site may contain several dozen atoms. Reactions at metal surfaces require considering a large number of metal atoms in order to converge the work function and the tendency to create electron-hole pairs. Reactions in high-dielectric-constant solvents, such as water, require considering a large number of solvent molecules in order to obtain converged electrostatic energies.

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Transition State Theory

The rate constants for reactions in the condensed phase can be written (9)

$$k = \kappa \frac{k_B T}{h} \exp[-\Delta G^{\ddagger,0}(T)/RT] \qquad (1)$$

where $G^{\ddagger,0}$ is the standard-state free energy of activation that reflects the probability of reaching the transition state, R is the molar Boltzmann constant, and κ is the transmission coefficient (10) which contains dynamical effects. $G^{\ddagger,0}(T)$ reflects a compromise of quasiequilibrium energetic and entropic effects; κ reflects the probability of a trajectory recrossing the transition state, and it may include effects variously labeled as dynamic or nonequilibrium effects or friction. The transmission coefficient must also include quantum effects on the reaction coordinate motion, which is otherwise intrinsically classical in transition state theory (11). In conventional transition state theory (12), $G^{\ddagger,0}(T)$ is calculated at the saddle point of the Born-Oppenheimer potential energy surface (PES) for the reaction, whereas in variational transition state theory it is calculated at the maximum of the free energy of activation profile (5,9,12,13), which is the free energy of activation as a function of a reaction coordinate (RC). Models for transition states of catalytic reactions should focus on determining $G^{\ddagger,0}$ and κ.

If barriers are low enough and/or temperatures are high enough, dynamics calculations can be directly used to simulate a reaction in real time and thereby focus on kinetic, thermodynamic, and mechanistic issues. However, this is not feasible if the reaction of interest has a high barrier compared to $k_B T$, where k_B is Boltzmann's constant and T is temperature, unless one employs infrequent event sampling and/or a constraint on the reaction coordinate. In such a case, one can show that it is still possible to obtain statistical information about a given reaction along a reaction coordinate by using umbrella sampling or by enforcing a constrained reaction coordinate and employing generalized normal mode analysis, thermodynamic integration, or free energy perturbation theory where the incremental charge in the reaction coordinate is the perturbation (1–3,14–28). In this approach, one selects (or "distinguishes") a specific RC that most conveniently leads the system through an area of interest, for instance the transition state region. The chemical system is then led slowly along the RC, thereby mapping out the regions adjacent to the RC. This slow mapping yields two types of information. First, the dynamical scanning process can escape from local catchment basins and find reaction pathways unforeseen by the operator (29,30). This is an especially important feature if one is trying to explore as yet uncharted territory. Several recent papers show that this approach works very well for finding lowest-energy pathways in catalytic systems like the Ziegler-Natta metallocene type homogeneous catalysts (29,30). Second, by umbrella sampling, generalized normal mode analysis, integrating the effective forces along the reaction coordinate, or free energy perturbation theory, one arrives at the free energy of activation profile mentioned below Eq. (1), that is, the free energy of activation (5,9,12,13) required to move the system from one cut through the RC to another or from reactants to a particular point along the RC. This technique is a very efficient tool to calculate activation free energies and enthalpies in molecular dynamics.

In order to accelerate the rate of a chemical reaction the catalyst must find a way to interact with the substrate(s) so that the resulting free energy of activation barrier or reaction friction becomes lower than that of the original process in the gas phase or in solution. There is no universal theory of the origin of catalytic rate acceleration; however, in light of the considerations of the previous paragraph, we

may attempt to classify the effects into energetic, entropic, or frictional/dynamical Since energetic stabilization takes place in most cases by non-covalent interactions, it is plausible that electrostatic effects and the participation of ionic and polar species are of utmost importance in catalysis. Electrostatics plays a central role in all of chemistry, and catalytic reactions are no exception. Catalysts may produce a strong electrostatic field around a substrate, and an appropriate model should therefore contain the environment of C, including polar or charged groups and solvent. As mentioned above, aqueous solutions are especially complicated since water is a liquid with a large dielectric constant; thus it has quite a strong influence on molecular transformations of polar species or with polar or charged catalysts. In some cases, transition-metal catalysis may be electrostatic in nature, but in most cases it can be attributed to changing overlap between interacting atomic or molecular orbitals; thus, the effect should typically be described in terms of quantum mechanics. There is evidence that electrostatic catalysis is important for a number of pericyclic reactions (31), and we may speculate that potentially similar effects arise for rearrangements in water or other polar solvents where the initial state of the reaction involves less polar species than the transition state. In such cases metal or other small ions stabilize the transition state by electrostatic interactions. However, for some transition-metal ions, orbital interactions may overweigh electrostatics; thus homogeneous catalysis involving these does not necessarily obey the above rule. For heterogeneous catalysis taking place at interfaces, the arrangement and properties of participating atoms or molecules may differ strongly from the bulk; specific interactions take place here. There are at least two systems, crystal surfaces and zeolite pores, where the electrostatic potential changes extremely rapidly, providing a large electrostatic field difference between the gas phase and the bulk. This may vary in the range of 5 to 20 V/nm and strongly polarize reactant bonds which may result in their fission or enhancement of attack by certain reagents (32). It has been postulated that the catalytic effect of zeolites is mainly due to the strong electrostatic field that may emerge within the pores (33), although this is an incomplete explanation, and one must consider the specific Lewis or Brønsted acid sites that may be present. Electrostatic catalysis in zeolites may be attributed to two main effects. One is the stabilization of cations by the large negative molecular electrostatic potential inside zeolite pores. This effect favors, for example, the formation of protonated species, and thus it may result in stabilization of the corresponding transition states. The other effect is related to the high electrostatic field inside pores that polarizes covalent bonds and promotes them for fission and stabilizes ion pairs.

Entropy effects may play an important role for a number of catalytic processes by immobilizing the reacting partners and thus reducing translational, rotational, or, to a lesser extent, vibrational entropy in the transition state. It is an old hypothesis that enzymes should be capable of efficiently catalyzing reactions with unfavorable entropies of activation by acting as "entropy traps;" this means that the binding energy of the enzyme is used to freeze out rotational and translational degrees of freedom by converting them to confined vibrations in the process of forming the activated complex. These effects may be smaller than previously thought since enzyme molecules are quite flexible, e.g., an examination of the entropic contribution to the rate acceleration of serine proteases indicate that this is a small effect (1).

Frictional effects are usually assumed to be less important than equilibrium free energy effects, but are not always negligible (5,34). As discussed elsewhere (35), "friction" and "nonequilibrium solvation" provide two different ways of looking at the effects that decrease the transmission factor. Nonequilibrium solvation may play a significant role in determining the temperature dependence of reaction rates.

Many catalytic processes involve general acid or base catalysis which can provide an alternative reaction path with lower energetic barriers and different free

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energies. The extent of barrier reduction of a proton transfer step is determined by the difference between the proton affinities of the donor and acceptor, which are intrinsic properties of the reactants and catalyst. Catalyst interactions with the reactant may induce changes in its proton affinity or in its state of protonation in the catalyst-substrate precursor complex. In addition, a step of the given reaction that involves proton transfer may be modified by participation of an acidic or basic residue or ligand of the catalyst. In this way the free energy of the proton transfer step is reduced and the reaction is accelerated. On the other hand, fixation of a general acid or base by the catalyst backbone or framework near the active site provides a gross entropy gain as compared to water solution. One common motif is that aqueous solvent may serve as a catalyst by serving as a bridge that both donates and accepts protons (*36,37*).

In addition to these general issues that play a prominent role in all types of catalytic processes, there are many more specific questions to be considered in each kind of catalysis, as discussed in the next section.

Catalytic Systems

Homogeneous catalysis. Transition metal reactions and catalysis have been the subject of several recent reviews (*38–40*). Driven to a large extent by improvements in computer technology and algorithms, high-level quantum chemistry has recently become powerful enough for realistic modeling of homogeneous organometallic catalytic systems on the femto- to picosecond time scale and the sub-nanometer length scale. Molecular orbital calculations employing density functional theory (*41*) (especially with generalized-gradient-approximation density functionals) sometimes allow one to predict chemical activation parameters to within a few kcal/mol. This is already enough to decide whether a catalyst is worthwhile so that expensive synthetic screening experiments can be directed to better use. These powers can also be harnessed to find or explain the actual mechanism of a reaction by investigating the topology of the PES associated with the catalytic system at hand. In the mid-1980s, a novel approach (*42,44*) to *ab initio* PES mapping was conceived by Car and Parrinello (CP). In that approach, the PES is mapped out by simulating the classical dynamics of nuclear motion at finite temperature. Although this in itself is only the time-honored "molecular dynamics" or "classical trajectory" approach that has been used since the 1950s to describe chemical dynamics, the CP method places an emphasis on systematic methods for using atomic forces that are calculated directly from *ab initio* electronic structure calculations on the chemical system at hand. Thus the method is sometimes called a direct dynamics approach. In the CP approach the calculation of forces is fast since the wavefunctions themselves are treated as dynamical variables which are propagated through time in conjunction with their attached nuclei. Nowadays, it is not uncommon to calculate the dynamics of systems with more than 100 atoms over several tens of picoseconds. For the chemist who is interested in predicting activation parameters and reaction pathways, this approach bears several advantages compared to more traditional methods which restrict themselves to locating only a few stationary points on the potential surface.

The application of *ab initio* molecular dynamics to calculate free energy of activation profiles for catalytic reactions is a recent development (*29,30*) and bears much promise, as it does not rely on any analytical approximations to the potential surface. This becomes especially significant when the potential surfaces that one is trying to describe are very complex, so that obtaining an analytical expression for them is difficult. However, the original CP approach suffers from the limitations of using classical mechanics for the nuclear motion, and this can lead to severe quantitative errors in some cases (*45*). Direct dynamics methods that include

quantum effects such as tunneling and zero point energy are also under active development and should see more applicability to catalytic systems in the future (45–48).

Calculations on large catalyst systems have been dramatically speeded up by the use of quantum-mechanical/molecular-mechanical (QM/MM) partitioning (1,3,8,49) of the catalyst system in CP simulations. This is an example of the general C/P/N/S partitioning techniques mentioned above. Here, parts of the simulated system that do not involve any bond making or breaking processes are described by a molecular mechanics force field, whereas the chemically active catalyst site is still described by high-level density functional theory. QM and MM parts of the system interact through van der Waals and Coulomb forces. Enormous time savings are achieved when these techniques are compared to a pure QM dynamics calculation because MM calculations are typically 10,000 times faster than analogous QM calculations. This workable and very efficient model has recently been demonstrated for the Brookhart ethylene polymerization catalyst (50).

Further developments in dynamical reaction modeling will undoubtedly arise soon. For example one will see QM and QM/MM CP simulations that account not only for the immediate reactants, but also for a whole reaction ensemble, including solvent and "spectator" species. Other approaches to treating the solvent quantum mechanically are also under investigation (51,52). Dual-level techniques involving high-order and low-order quantum mechanical methods (53–56), rather than mixing quantum mechanics and molecular mechanics, may also be useful.

The above emphasis on the *interface* of electronic structure (the ultimate source of the PES) and dynamics does not mean that the problems with the electronic structure *per se* are fully solved for transition metal catalysis. *Au contraire*, as anyone who has done calculations knows, there seem to be more pitfalls and pathological problems with transition metals than one encounters with lighter elements. When one uses effective core potentials to avoid explicit inclusion of core-electron basis functions, one finds the counter-intuitive result that the heavier third-transition-row metals can be treated more accurately than the first-transition-row metals. The reason for this unexpected behavior is the larger relative spatial extent of the $5d$ orbitals compared to the $3d$. Thus, third-transition-row metals form stronger, more covalent bonds with most ligands due to the large overlap provided by the $5d$ orbitals. Thus, for geometry optimizations of third-transition-row systems with monovalent (H, R, Cl) and coordinate covalent (NR_3, PR_3, CO) ligands, hybrid density functional methods such as B3LYP (57) and the standard second-order Møller-Plesset perturbation method (58) (MP2) for treating electron correlation usually yield similar and reasonable geometries (59). Even Hartree-Fock-Roothaan single-determinant self-consistent field methods (58) (HFR) can be adequate for geometries of many systems.

The choice of basis set provides an especially difficult problem for modeling catalytic reactions involving transition metals. Many of the standard basis sets in both commercial and public domain codes have serious inadequacies. Sometimes the d space is missing an essential diffuse d function, or the outer $(n + 1)s$ and $(n + 1)p$ functions are treated inadequately (60,61). This is a dangerous situation for new practitioners in the field as they may have some understanding of standard light-atom basis sets but be unaware that the transition-metal basis set, which is coupled to a reasonable ligand basis set, may have serious deficiencies. Thus, if one calculates unsystematic behavior, such as in a survey of structural trends in electronically similar molecules, and is unaware of the basis set inadequacy, one can attribute the observed behavior to faults in methodology or—even worse—to new and unexpected chemistry.

Although the relative energies one calculates are often not as accurate as the structures, they may be accurate enough for trends. Higher-order electron-

correlation methods (*62*) such as MP4, QCISD, CCSD, and especially CCSD(T), can provide more reliable energies. When one moves from monovalent ligands to divalent ligands such as O, additional problems arise because of the stronger near-degeneracy situations one encounters. In such cases, HFR geometries may no longer be adequate and one must use at least the B3LYP or MP2 methods. Although the calculated structures may be realistic, the energies may be unreliable, especially if these divalent ligands participate in the reaction under study. Second-transition-row metals with monovalent and coordinate covalent ligands fall into the same category. When second-transition-row metals are bonded to multivalent ligands, MP2 energies are inadequate even for trends, and HFR makes unacceptably large errors in the geometry (*63*). The situation for first-transition-row metals is dramatically worse. Here, even for monovalent and coordinate covalent ligands, MP2 may have unexpected pathological problems in determining the structure, and higher-order electron-correlation methods such as MP3 and MP4 may oscillate strongly and provide unacceptably large errors in relative energy. Geometries from B3LYP and relative energies from QCISD, CCSD, and CCSD(T) are usually adequate and more consistent than those from MP2, MP3, or MP4 (*64*). The most unsatisfactory situation occurs for first-transition-row elements with multivalent ligands such as found in metal oxo or nitrosyl complexes (65). Here the near-degeneracy problem is so great that MP2 is totally inadequate even for the geometry; thus one usually resorts to B3LYP or similar methods for the geometry in such cases and to CCSD or CCSD(T) for energies, although even these methods can fail. Thus, as in so many other branches of computational chemistry, the treatment of systems with near-degeneracy effects remains an impediment to progress. All these problems become much worse for transition states than for reactants, and they may become even more critical when one considers metal clusters.

Zeolites. Transition states of elementary reaction steps in zeolite catalysis pose yet another set of specialized problems. The discovery that carbenium (*66*) and carbonium (*67*) ions in zeolite catalysis are usually transition states and not stable ions, as proposed in homogeneous acids, is due to applied quantum chemical research on protonation by zeolites. Early work, especially by Kazansky (*68,69*), showed that the low dielectric constant of zeolites makes charge separation difficult. Charge separation occurs when protons are generated by dissociation from their bound state in the zeolite. Protonated species become stabilized by the strong electrostatic attraction between their positive charge and the negativity charged zeolite wall. This has found early confirmation in quantum chemical studies of ammonium formation by protonation of ammonia (*70*). Proton transfer can only occur when ammonium binds back to the zeolite by directing two or three of its positively charged hydrogen atoms to the negatively charged oxygen atoms. The relatively high activation energies for proton-induced reactions stem essentially from the high zeolite deprotonation energies (~ 300 kcal/mol).

A major issue in quantum chemical calculations on zeolites is the validity of cluster models that are commonly used. Of course there is also the question of the level and kind of quantum chemical method that is adequate. Models and methods should be of about the same sophistication. For a model that is too small even the most precise *ab initio* quantum mechanical calculations may lead to erroneous results. On the other hand, low-level calculations on appropriately large models may provide artifacts as well. A minimum requirement that cluster models have to satisfy is that they are neutral. Because the deprotonation energy of a cluster tends to oscillate and slowly converges with size, the question of which cluster size is adequate to obtain representative results for the zeolite situation becomes paramount. As cluster models evolve, various C/P/N/S partitionings (in the classification introduced above) may be identified as particularly appropriate.

Geometry relaxation of cluster geometries in reactants as well as transition states is usually essential. A main effect of embedding of a cluster in the zeolite lattice is to reduce full relaxation of the cluster slightly (71) and to affect transition state energies by the non-equivalence of the oxygen atoms around the protonation site (72). Long-range electrostatic effects appear to be minor for geometry relaxation in embedded clusters. A shortcoming of the cluster approach is the absence of any steric constraints on the size of reaction intermediates or transition states due to limitations induced by the size of the zeolite micropores. Preliminary results (73) indicate that such special constraints can be incorporated by suitable embedding approaches and, dependent on the size of reaction systems, they can induce dramatic changes compared to results obtained with non-embedded clusters.

A major issue with lattice approaches such as CP techniques (42–44) when used to analyze the effects of zeolite cavity size is the non-reliability of current density functional techniques (41) to properly compute van der Waals interactions. Despite these and other limitations, the impact of quantum chemistry on the fundamental understanding of zeolite catalysis has been significant. As mentioned above, the proper formulation of reaction energy diagrams was first accomplished theoretically and is now gradually being confirmed by experimental studies (74). One reason for the success of computational methods applied to this kind of catalysis is the compensation of the forces controlling the covalent hydroxyl bond strength and the counteracting stabilization of the electrostatic attraction between protonated species and zeolite wall. Embedding techniques have reached the stage where quantitative agreement between measured and experimental protonation energy of ammonia has become possible (75). Because of the well understood geometry of zeolites and their accessibility to detailed spectroscopic probing, theoretical study of catalysis in these materials will remain very fruitful to deepen our understanding of catalysis as well as theoretical approaches.

Metal and metal oxide surfaces. Electronic structure methods aimed at a molecular-level description of the chemisorption and reaction of adsorbates on metal surface pose yet another set of problems. Some of these problems are also relevant to catalysis on metal oxide surfaces. Applications of these methods are relevant to transition metal heterogeneous catalysis (76). Questions of interest include:

- chemisorption energetics of molecules and molecular fragments
- adsorbate structure and spectra as a function of surface site
- interaction of coadsorbed species
- dissociative chemisorption
- surface reactions (heats of reaction and activation energies)
- nonequilibrium geometries, mechanistic issues, and potential energy surfaces
- electronic and geometric effects on trapping and activation

First-principles theory is needed to unravel complexities associated with such surface phenomena and to provide a framework for the interpretation of experiments.

The difficulty in treating metal and oxide surfaces using first-principles theory is that there are conflicting demands on the theory. At the solid surface, the treatment must be accurate enough to describe surface-adsorbate bonds and energy changes accompanying chemical reactions (generally, this is most readily achieved if the system is small), while for metals and oxides a large number of atoms is required to describe either conduction and charge transfer processes or the Madelung potential (in this case methods for treating large symmetric systems are most appropriate). Embedding methods (another example of the C/P/N/S approach discussed above) seek to balance the accuracy versus size aspects of the problem.

Many theoretical studies and calculations, varying considerably in quality, have been reported for adsorbate/metal systems (76). Most of these have been

performed on a portion of an ideal metal lattice, and only a few allow local reconstruction of the substrate. In cluster studies of metals, one of the fundamental questions is the convergence of the adsorption energy and other properties with respect to cluster size. Many calculations have shown that even very small clusters of fewer than ten atoms allow strong bonds to develop with adsorbates. Highly ionic adsorbates are more problematic since charge transfer should occur from a much larger number of metal atoms than for covalent or slightly ionic bonds for which the screening length for charge transfer is much shorter. Erratic behavior has been observed for calculated adsorption energies on small clusters. Although energies are sometimes seriously in error, other properties such as bond length or vibrational frequencies are often in rather good agreement with experiment. On the question of convergence with respect to cluster size, it was expected that gradually enlarging the cluster would lead to convergence of the adsorption energy. This goal has proved to be elusive. There are different interpretations of the convergence situation: (1) a realistic approximation of the metal band structure and assurance that orbitals of the correct symmetry in the appropriate energy range are available to interact with an adsorbate requires *a priori* a large cluster, and (2) a cluster boundary near the adsorption site can obviously distort the adsorbate-surface bonding.

Although embedding and periodic methods may be required for *high* accuracy in the treatment of metals, there are many examples in which small cluster models have provided *useful* accurate descriptions of adsorbate energetics, vibrations, and core level shifts. When clusters reach a certain size, there apparently are compensating effects that allow many such problems to be treated, and the use of different references states of a cluster has provided a practical way to improve the accuracy of adsorption energy calculations. Slab calculations, which traditionally have provided the most powerful way of treating adsorbate overlayers and photoemission, have now been extended to surface and interstitial impurities. Clearly, in order to describe coadsorbed species and surface reactions, the theoretical model must include a sufficient number of surface atoms so as to eliminate artifacts associated with the boundary.

It has been possible, for quite a few years, to perform high-quality quantum chemistry calculations on the electronic structure of molecules. More recently, the capability of performing band calculations for metallic systems has also advanced. Early attempts at understanding adsorbate bonding to metal surfaces focused on the metal work function, the local density of states of the metal, orbital hybridization in the molecular fragments, and, for transition metals, the interaction of s, p, and d bands with the adsorbate. Although the electrons in the metal are delocalized, one of the early observations was that the strong interactions, typically on the order of 30–100 kcal/mol, between nonmetal adsorbates and the surface split out a set of orbitals that could be regarded as localized in the vicinity of the adsorption site.

Early calculations on copper and nickel revealed that the main contribution to bonding between adsorbates such as oxygen and hydrogen and the metal surface comes from the metal s and p orbitals, which have overlap interactions with the adsorbate that are much larger than those of the d orbitals. There is now little doubt that the s and p electrons provide the main contribution to the energetics when species with unsaturated valence are bonded to transition metal surfaces (*76*). For this reason, one can often replace the d electrons of atoms by effective core potentials and still obtain good energetics (*77,78*). Although the s and p contributions dominate in the first-row transition metals, this does not mean that d electron contributions are unimportant, since, quite to the contrary, they are responsible for the interesting differences in transition metal behavior. One of the reasons the d electron participation in bonding is sometimes obscure is because d orbitals bond indirectly in most instances by mixing with the metal s and p orbitals and with the adsorbate, analogous to atomic orbital hybridization, but with more extensive s, p

delocalization. The explicit participation of d electrons in bonding modulates the s and p interactions and gives rise to the special properties of transition metal systems (*76*). A simple hybridization picture that describes the reactivity of transition metals such as Ni, Pt, Cu, and Au has been reported (*79*). The adsorbate orbitals are viewed as first interacting with the metal s band to produce a bonding state. Such interactions do not vary much for different transition metals. The resulting bonding state then interacts with the metal d states to produce bonding and antibonding states; the net interaction depends on the coupling matrix elements with the renormalized state and the extent to which the d band is filled. The authors explain the variation in transition metal reactivity in terms of the location of the latter antibonding state (*79*).

Other issues concerning the role of d electrons in transition metals lie in their differential participation in transition states for adsorbate reactions on surfaces (*76,80*). Evidence from studies of methane dissociation on nickel points to the importance of Ni $3d$ electron contributions in enabling the C-H bond stretch. Likewise, when adsorbates move across transition metal surfaces, the d contributions to the bonding are found to differ significantly between atop sites and sites where there is bonding with multiple surface atoms. For higher-series transition metals such as Pd and Pt, there is an entirely new dimension to the participation of d electrons that derives from the reduced spacing between the $d^n s^1$ and the $d^{n+1} s^0$ atomic states. Studies reported in this volume of the reaction of adsorbed ethyl on Pt(100) to product ethylene coadsorbed with hydrogen reveal closely spaced electronic states that differ in d occupancy and overall electron spin. The complexities of processes with competing reactant states are just beginning to be appreciated.

Another class of transition states for catalysis at metal surfaces is that associated with photochemical reactions. A study describing the photoinduced dissociation of methane physisorbed on Pt(111) has been reported in which the key feature of the process is the formation of an electronically excited state characterized as a CH_4^- electron attachment complex that interacts with a positive image charge localized near the metal surface (*81*). The reaction takes place by movement on the electronically-excited-state PES to produce a distorted methane geometry followed by decay to the ground state and methane dissociation.

Metal oxide surfaces pose special difficulties in treating the strong electrostatic effects and are not as well understood as metal surfaces.

Enzymes. Enzymes, like other catalysts, usually work by stabilizing the corresponding transition states (*1*). Nevertheless, enzymatic reactions, like other types of catalysis, have their unique features. A reliable modeling of enzymatic reactions must capture the energetics and dynamics of the relevant transition states. This should allow one to determine which factors are crucial for efficient catalysis. Modeling enzyme transition states is especially challenging because of the large size and complexity of proteins. It is certainly not enough to obtain an accurate quantum mechanical description of the isolated substrate. In principle, one can model enzymatic reactions by QM/MM approaches using *ab initio* or semiempirical Hamiltonians, including the empirical valence bond (EVB) Hamiltonian (*1*). The EVB method is also called molecular-mechanics/valence-bond (MMVB); it involves creating a $n \times n$ configuration interaction matrix (where n is the number of configurations, typically 2 to 6, but in some cases as large as 14) with MM diabatic energies on the diagonal and a semiempirical expression for the nonzero couplings. Enzyme transition states can be modeled by reasonable potential surfaces, and more refined treatments will emerge in the future. At this stage, it is already possible to explore key issues about the nature of the enzyme-substrate transition states. Such exploratory studies indicate that the transition states of enzymes are similar to the

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corresponding transition states in solution except that the enzyme is a "better" solvent since it has to undergo a smaller reorganization in order to reach its transition state configuration (*1*). For example, one may hypothesize that in enzymatic mechanisms where the polarity of the transition state is greater than that of the reactant, the major source of catalytic rate acceleration is electrostatic stabilization of the transition state by protein dipoles (*6,82*). At present, however, most methods do not allow one to sort out dynamical effects and non-equilibrium free energy contributions. Here we will examine what can be deduced from current simulation methods with the EVB approach about these effects and the nature of transition states of enzymes.

Before proceeding, though, it is important to define the relevant questions in a clear way. In particular, it is important to emphasize that the catalytic effect of an enzyme is defined as the ratio between the reaction rate in the presence of enzyme and the rate of a reference reaction, where the reference reaction is most conveniently taken as the same reaction in solution (*1*). The corresponding *difference* in activation free energies is easier to evaluate than are the absolute free energies of activation (*1,2*). Usually, electrostatic stabilization of the transition state charges provides the largest catalytic effect. This electrostatic effect is exerted by preoriented polar groups of the active site. Thus very often the most important feature of an enzymatic transition state is the arrangement of the surrounding environment and not the actual nature of the reacting fragments. This point should be explored further by *ab initio* quantum mechanical approaches and also correlated with experimental studies. Despite the obvious importance of the reduction of activation free energies it is also important to be able to explore other factors such as dynamical effects, non-equilibrium effects, and nuclear tunneling effects. Since the importance of such factors cannot be determined uniquely by experiments, it is essential to use simulation studies in analyzing those factors and in relating them to the observed rate constant.

The importance of frictional effects has sometimes been invoked for enzyme catalysis (*83*). In order for such effects to be catalytic, one must have a different frictional correction (or different κ) for the rate constant in the presence of the enzyme and in water. The transmission factor can be related to the time-dependent autocorrelation $C(t)$ of the difference between diabatic EVB or MMVB potential energy surfaces of the reactant and product or to the autocorrelation of the corresponding reactant and product environmental reaction fields (*1*). Thus, under the assumptions where this relation holds, comparing $C(t)$ for the enzymatic and solution reactions should tell us whether dynamical effects are important in enzyme catalysis. An EVB study of this issue (*1*) indicates that $C(t)$ is similar in enzymes and in solutions, and therefore frictional effects are not likely to provide a substantial catalytic contribution. In other words, the fluctuations of the environment at the transition state are not so different in enzymes and in solution. Frictional effects are inseparable from nonequilibrium solvation. Preliminary EVB studies have shown that nonequilibrium solvation effects are quite similar in enzymes and in the corresponding reaction in solution. The main difference is the reduction of the reorganization energy in enzyme active sites, which is not a dynamical effect but rather a factor that contributes to $G^{\ddagger,0}(T)$

A related issue is associated with quantum mechanical nuclear tunneling. This issue has been explored by path integral centroid calculations using EVB potential surfaces, which indicate that tunneling effects are similar in the enzyme and solution (*48*), but more complete studies are required. In particular multidimensional semiclassical tunneling methods show that nuclear tunneling can be a very sensitive function of small differences in effective potentials or tunneling path lengths (*34,47,84*). Experimental kinetic isotope effects (KIEs), which are discussed below, should provide a way to verify whether tunneling is important.

The relationship between transition state structure and KIEs is implicit in transition state theory (*11*), and it was presented in beautiful detail by Biegeleisen and Wolfsberg in a landmark paper in 1958 (*85*). It was clear from this work that direct information about transition state structure could be obtained from isotopic reaction rates in chemical systems. Systematic determination of kinetic isotope effects combined with bond energy/bond order vibrational analysis (BEBOVA) led to semiempirical transition state structures of several non-enzymatic reactions by the early 1970s. A Steenbock Symposium was held in 1976 on the use of kinetic isotope effects in enzymology, and a book of biological transition state applications was published in 1978 (*86,87*). A computer program, BEBOVIB, was written in 1977 to facilitate BEBOVA calculations for matching transition state structures to intrinsic kinetic isotope effects (*88*). These developments for understanding isotope effects for chemical reactions set the stage for applications to enzymes early in the 1980s.

Major problems in the application of KIEs to enzymology arise from the ability of enzymes to partition the progress along the reaction coordinate into several energetically discrete steps. The chemical step rarely provides the major energetic barrier in the conversion of substrates to products. Thus the kinetic isotope effects can be partially or completely obscured by slow steps associated with substrate binding, product dissociation, or protein conformation changes. In recent years, these problems have been euphemistically termed "kinetic complexity," and, when present, they cause the expression of fractional intrinsic isotope effects. The intrinsic KIEs require quantitation of each complicating step and correction to give the isotope effects associated with the chemical step. These problems were summarized by Northrup in 1981, and they have been systematically investigated and solved in the past 15 years (*89–91*). In 1998, practical solutions are available for the problems caused by almost any form of kinetic complexity, and a growing list of enzymes is available where complete families of intrinsic KIEs have been measured. In these cases, the isotope effects can be used to test models of enzymatic transition states. Recent efforts in transition state analysis have included complex reactions in which the substrate is also a protein undergoing covalent modification by the enzymatic protein catalyst (*92*).

Using the conventional transition state formalism of Beigeleisen and Wolfsberg, enzymatic transition state structures can be constructed systematically from the intrinsic KIEs. One possible procedure is as follows. First one constructs a truncated structure that includes at least all atoms within two bonds of the reaction center. Normal vibrational modes are generated for the reactant and transition state structures, and from these the isotopic partition functions are determined to yield the KIEs for each isotopically labeled position. From the truncated structure, a full transition state molecule is created by adding back the cutoff atoms and re-optimizing the structure while holding fixed the geometry defined by the KIEs (*93*). The analysis provides a full molecular model of the transition state, constrained by the experimental values of the isotope effects. Single-point calculations using GAUSSIAN94 (*94*) lead to the electronic wave function for the transition state. Wave functions for the substrate and transition state are compared to identify the characteristics of the transition state. It should be kept in mind that the accuracy of this procedure is limited by the accuracy of conventional transition state theory, which assumes that the transition state structure and force constants are independent of isotopic substitution and which neglects tunneling. In many cases the structures and force constants of the variational transition states are expected to be different for different isotopic versions of the reaction (*95*). The critical configurations along tunneling paths may also be isotope dependent (*96*), and if tunneling is important, it is essential to include reliable multidimensional tunneling approximations when calculating the KIEs (*97,98*). Light-atom transfers, such as proton and hydride

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transfer are especially susceptible to isotope-dependent transition state locations, recrossing effects, and tunneling corrections (99).

What are we learning about enzymatic transition states? The most revealing studies compare the transition states for the uncatalyzed solution reactions to the same reactions catalyzed by enzymes. In most cases, the transition states for the enzymatic reactions occur earlier along the reaction coordinate and demonstrate bond distortions remote from the reaction center. The presence of enzymatic activators which increase the reaction rate are also capable of changing the transition state structure. Substrates that undergo attack by nucleophiles show earlier transition states when better nucleophiles are participating. When kinetic complexity has obscured the intrinsic chemical KIEs, appropriate mutations have been made to slow the reaction rate and make the intrinsic KIEs observable. In some cases mutational changes have been demonstrated to alter the transition state structure. Finally, enzymatic transition state structure is sufficiently specific to provide information that guides the synthesis of transition state inhibitor analogues. These powerful inhibitors have now been synthesized for at least four enzymes which have been analyzed by transition state methods. Much of this work has been summarized in recent reviews (*91,100*).

The conjunction of methods for measurement of enzymatic kinetic isotope effects, determination of their intrinsic values, and the use of this information to constrain the limits of computationally determined transition states has opened a new era of understanding enzymatic catalysis. The approach requires no information about the structure of the catalyst and can provide both comparative and direct information about the transition state. It is anticipated that this approach will have an active future in understanding enzymatic catalysis and in the design of transition state inhibitors.

Outlook

What does the future hold for computational modeling of catalytic transition states? First, we need more reliable, affordable electronic structure methods for predicting saddle point structures, not only in the gas phase, but at gas-solid interfaces, in zeolites, and in solution. Furthermore experience with more accurate dynamical methods (*17,101*) shows that there are often important corrections to treatment based on classical dynamics and conventional transition state theory, so we will often need to apply more complete dynamical theories. The transition state concept will be broadened and stretched in the process, but it is safe to assume that it will continue to be the most fruitful theoretical concept in the currently emerging field of computation-driven catalyst design.

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