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Computational Catalysis—Past, Present, and Future

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Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

biocatalysis · electronic structure · enantioselectivity · multiscale modeling · quantum chemistry

1. Introduction

On the occasion of the centennial of the Max-Planck-Institut für Kohlenforschung, this Essay first reviews the historical development of computational quantum chemistry, in the context of catalysis and research at the Institute. Thereafter it illustrates the current status of computational catalysis, using examples from recent work at the Institute. It concludes with some comments on the future perspectives of the field. The Essay does not attempt a comprehensive coverage of the literature but rather presents a subjective selection of past and present research, as well as subjective views on future directions.

2. Historical Overview

The Max-Planck-Institut für Kohlenforschung (KOFO) was inaugurated in July 1914 (then still as Kaiser-Wilhelm-Institut). From the very beginning, its mission was catalysis. This was clearly expressed in a visionary talk[1] by Emil Fischer in 1912 that strongly supported the concept of investigating the chemical use of coal through catalysis. Some of his key statements (translated into English): "… *chemistry … has entered a new epoch in recent years, the age of catalysis. With the use of catalysts we succeed in the most surprising transformations … at temperatures that are many hundred degrees lower than those required previously. The chapter of catalysis is virtually unlimited, and thorough research in this area promises rewarding success.*" Evidently, already a century ago, experimentalists were fully aware of the great importance and potential of catalysis, which is not surprising in view of breakthroughs such as the development of the Haber–Bosch process in the early 1900s.

2.1 Early Experimental Discoveries

The first three directors of the Institute were Franz Fischer (1914–1943), Karl Ziegler (1943–1969), and Günther Wilke (1969–1993). Early catalysis research at KOFO was entirely experimental and was conducted in a completely empirical manner. The first great success (in 1925) was the development of the Fischer–Tropsch process of coal liquefaction, the conversion of coal via syngas to synthetic petroleum (gasoline) using heterogeneous transition metal catalysts.[2] This process found large-scale industrial application, and contemporary gas-to-liquid conversion plants in the oil industry are still based on Fischer–Tropsch chemistry. Even greater was the impact of the discovery (in 1953) of the Ziegler catalysts for the low-pressure polymerization of olefins, in particular ethylene and propylene, using organometallic "Mischkatalysatoren".[3,4] The Ziegler catalysts were adopted worldwide by the chemical industry, and variants are still used today to produce annually around 100 million tons of polymers. This research was recognized with the Nobel Prize in Chemistry awarded to Karl Ziegler and Guilio Natta in 1963.[5,6]

2.2. Theory in the Early Days

Theory and computation did not play any role in the great achievements outlined above—they were lagging far behind. To put things into perspective, we note that the Institute was inaugurated in 1914 just one year after the Bohr model was proposed as the first attempt towards a quantum description of the atom,[7] and two years before Lewis structures were introduced as an elegant, yet very simplified representation of molecules and their electronic structures.[8] The Fischer–Tropsch process was discovered in 1925, roughly at the time when the foundations of quantum mechanics were formulated, for example by Schrödinger[9,10] and Heisenberg,[11] and two years before the first quantum-mechanical treatment of chemical bonding in the hydrogen molecule.[12] The following years witnessed a number of significant theoretical advances such as the derivation of the Hartree–Fock equations,[13,14] but actual computations were restricted to problems that could be solved by hand or with available mechanical calculators, such as the systematic work by Hartree on various atoms[13] and the accurate calculations by Hylleraas on helium.[15] Theoretical notions in chemistry were mostly qualitative, for instance making use of the simple one-electron Hückel model for π-electron systems[16] and valence bond concepts.[17] While quantum mechanics was acknowledged to be the correct theory for chemistry,[18] quantitative computational work was simply not feasible before the development of electronic computers that started in the 1940s.

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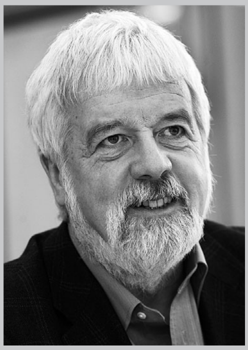
2.3. Computations in the Early Days

Computational chemistry was still in its infancy when the Ziegler catalysts were discovered in 1953. The Roothaan equations had just been derived[19] for the variational calculation of molecular orbitals (MOs) in a suitably chosen basis set, the first ab initio MO calculations on diatomic molecules began to appear, and chemical applications for larger π-electron systems became possible at the semiempirical level, for example using the Pariser–Parr–Pople method.[20,21] In the 1960s, there were methodological advances in correlated ab initio calculations, the Kohn–Sham approach to density functional theory (DFT) resolved many of the fundamental problems associated with the DFT treatment of the kinetic energy,[22] and a systematic hierarchy of semiempirical valence-electron MO methods was introduced.[23] In spite of these and other advances, serious computations on the mechanisms of catalytic reactions were still out of reach, because the quantum-chemical methods were still too inaccurate and the computers even at the end of the 1960s were still much too slow. At that time, chemical thinking was influenced more strongly by novel qualitative concepts of reactivity such as the Woodward–Hoffmann rules[24] and frontier orbital interactions.[25]

2.4. Advances in Computational Methods

During the Wilke era (1969–1993) computational chemistry matured with significant methodological progress on all fronts. A variety of ever more accurate correlated ab initio treatments were developed including multireference configuration interaction, many-body perturbation theory, and coupled cluster theory, with the CCSD(T) variant emerging as the "gold standard" for ground-state calculations.[26,27] DFT methods became much more attractive for chemists with the advent of generalized-gradient-approximation functionals[28–30] and hybrid functionals,[31] which are computationally efficient, generally applicable, and fairly reliable. Improved semiempirical methods of the MNDO type[32–34] allowed fast explorations of potential energy surfaces, especially for organic and bioorganic molecules. Hybrid quantum mechanics/molecular mechanics (QM/MM) approaches were introduced for the study of enzymatic reactions.[35] The combination of molecular dynamics (MD) and DFT calculations paved the way to on-the-fly first-principles simulations of nuclear motion and chemical reactions on the ps scale.[36]



Walter Thiel studied chemistry at the University of Marburg where he completed his doctoral degree in 1973 (with A. Schweig). Following a postdoctoral stay at the University of Texas at Austin (with M. J. S. Dewar) he earned his Habilitation at Marburg in 1981. He became Professor of Theoretical Chemistry at the University of Wuppertal in 1983 and Professor of Chemistry at the University of Zürich in 1992. He has been Director at the Max-Planck-Institut für Kohlenforschung since 1999 and Honorary Professor at the University of Düsseldorf since 2001. His scientific interests cover many topics in theoretical and computational chemistry, with emphasis on large molecules, spectroscopy, dynamics, and catalysis.

2.5. From a Feeble Start in Computational Catalysis to Exponential Growth

During the 1970s and 1980s, an increasing number of reactions (mostly from organic chemistry) were studied at the semiempirical and ab initio MO levels in the framework of transition-state theory, but calculations on catalytic processes were still very rare because of limitations in the available methodology and in hardware performance. Transition-metal-catalyzed reactions often involve electronically demanding species in the catalytic cycle, which are normally not described well by semiempirical or ab initio MO methods, and enzymatic reactions are often very complex, with the need to include the active-site protein environment in the modeling. In the late 1980s, there were pioneering ab initio MO studies on the full catalytic cycle of olefin hydrogenation by the Wilkinson catalyst[37,38] and some other transition-metal-catalyzed reactions,[39] and examples of semiempirical MO studies included model calculations on the catalytic pathway of serine proteases.[40] However, it was only in the 1990s that the field of computational catalysis really got started, mainly because of the advent of improved methods (DFT, QM/MM) and more powerful hardware. The exponential growth in the number of such studies can be seen from a query on (*computation* and cataly**) in the Web of Science, which returns 6 papers in 1990, ca. 200 in 2000, ca. 800 in 2010, and ca. 1100 in 2013, with the corresponding number of citations increasing from close to zero in 1990 to almost 27 000 in 2013. The enhanced capabilities of computational work also became obvious when the new branch of organocatalysis became established around 2000, for example through the discovery of stereoselective proline-catalyzed aldol reactions;[41,42] soon thereafter, DFT calculations were used to reveal the detailed mechanism and the origin of enantioselectivity in such reactions[43] and in related asymmetric organocatalytic transformations.[44]

2.6. Olefin Polymerization as an Example

As noted above, computational studies on olefin polymerization were completely out of reach when the Ziegler catalysts were discovered at KOFO in the 1950s. With the advent of realistic and cost-effective DFT methods, it became possible to compute the detailed mechanism of such reactions, both for homogeneous metallocene-based catalysts and for heterogeneous catalysts. To quote just a few examples, starting in the 1990s, DFT studies on homogeneous olefin polymerization addressed the insertion and termination steps for specific metallocene and constrained-geometry catalysts[45,46] and for a systematic series of d^0 and d^0f^n transition-metal complexes,[47,48] the dynamics of ethylene insertion,[49,50] the mechanism, the role of bulky substituents, and the control of branching in nickel(II) diimine catalyzed olefin polymerization,[51–54] the design of living catalysts,[55] the role of ion-pair formation,[56] the structure and function of the methylaluminoxane cocatalyst,[57] the copolymerization of α-olefins with polar monomers,[58] the formation of stereoerrors and the role of site epimerization,[59,60] and the mechanistic relevance of two-state reactivity in the catalysis by Cr^{III} complexes.[61] Early computational studies on heterogeneous Ziegler–Natta olefin polymerization included first-principles MD simulations of the insertion and propagation steps for ethylene and propene[62,63] as well as DFT embedded-cluster studies of the proposed active sites in heterogeneous Ziegler–Natta catalysts.[64] Needless to say, there have been many more such computational studies (more than 1000 according to the Web of Science) that provide insight into virtually all mechanistic aspects of polymerization reactions.

2.7. Consequences

This boost in the capabilities of computational research on catalysis was of course recognized at KOFO. When the Institute was transformed in the 1990s by Manfred Reetz from a monolithic unit into five departments covering all branches of catalysis, it was decided to establish a Department of Theory along with four experimental departments. This reorganization was based on the concept of interdisciplinary fundamental research on catalysis, encompassing all major areas of catalysis to ensure the necessary diversity and to foster collaboration and scientific cross-fertilization. The Department of Theory was created in 1999, after 85 years of purely experimental work at KOFO.

3. Current Status

Giving the explosive growth of computational catalysis over the past two decades, and especially in recent years, it is clearly impossible in this Essay to provide a comprehensive up-to-date picture of the field. Instead of embarking on such a hopeless mission, this section provides a brief overview over computational research at KOFO during the past three years.[65] The intention is to provide snapshots of current application-oriented studies to convey an idea of the interplay between the present experimental and computational research at KOFO when it comes to solving real-world problems in catalysis.

3.1. Methods for Studying Homogeneous Catalysis and Organocatalysis

State-of-the-art DFT methods are employed at KOFO to explore ground-state potential energy surfaces and to characterize all relevant intermediates, transition states, and reaction pathways. Geometry optimizations are normally done with standard functionals (RI-BP86, B3LYP, B3LYP-D) and medium-sized basis sets, followed by higher-level single-point energy evaluations that utilize either correlated ab initio methods (e.g. local CCSD(T) treatments with large basis sets) or modern density functionals (e.g., from the M06 series) with large basis sets and dispersion corrections (if appropriate). Effective core potentials are normally used to represent the core electrons of heavy elements. Thermal and entropic corrections are computed at the level applied for geometry optimization.

3.2. Joint Projects with the Fürstner Group

Asymmetric gold catalysis with one-point binding ligands (phosphoramidites with TADDOL-related but acyclic structure) enables a number of difficult transformations with excellent enantioselectivity. DFT calculations on the cycloisomerization of enynes helped elucidate the origin of the enantioselectivity achieved with such gold catalysts.[66] Gold carbenoids are commonly considered as intermediates in many gold-catalyzed reactions. Attempts to prepare germane gold carbenoids devoid of stabilizing substituents through transmetalation led to remarkable hetero-bimetallic complexes (e.g., containing Au and Cr) that were characterized at the DFT level in terms of their electronic structure and chemical bonding.[67]

3.3. Joint Projects with the Alcarazo Group

The research in the Alcarazo group is directed towards the design and synthesis of unusual ligands and coordination compounds and their application in novel catalytic transformations. DFT calculations were performed to characterize the electronic structure of key species and to unravel the detailed mechanism of the catalytic reactions. Examples include the analysis of the electronic structure in the first observed dihydridoborenium cation,[68] in carbene-stabilized phosphorus(III)-centered trications,[69] in carbene-stabilized N-centered cations,[70] and in cationic germanium(II) complexes.[71] In the latter case, the stability of the complexes arises from the ability of the neutral monodentate hexaphenylcarbodiphosphorane ligand to donate two pairs of electrons and thus simultaneously form two dative σ and π bonds ($C \rightarrow Ge$).[71] The pronounced π-acceptor properties of phosphorus trications[69] can be exploited in platinum(II) catalysis[72] and in gold catalysis[73] to enable very demanding cyclization reactions. The underlying reaction mechanisms were elucidated by computing the free energy profiles for the cyclization of 2-ethynyl-1,1′-binaphthalene into pentahelicene[72] and of 2-ethynyl-2′,6-dimethylbiphenyl into 4,5-dimethylphenanthrene.[73]

3.4. Joint Projects with the List Group

Chiral phosphoric acids are able to catalyze asymmetric S_N2-type O-alkylations, which formally involve a nucleophilic attack at the σ* orbital of a carbon electrophile. DFT calculations on the mechanism of a representative intramolecular alkylation catalyzed by the phosphoric acid TRIP

(TRIP = 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate) showed that the Brønsted acid acts as a bifunctional activator bridging the pentacoordinate transition state.[74] High stereoselectivity can be achieved in the asymmetric epoxidation and hydroperoxidation of α,β-unsaturated carbonyl compounds using alkaloid-derived primary amines as catalysts and aqueous hydrogen peroxide as the oxidant. Here, the analysis of the computed pathways led to a qualitative model of enantioselectivity based on the structure of the crucial iminium intermediate.[75]

3.5. *Joint Projects with the Maulide Group*

Sulfur(IV)-mediated transformations can be used to achieve direct ylide transfer to and metal-free arylation of carbonyl compounds, depending on the reagent (Martin's sulfurane or activated sulfoxides). Mechanistic studies (using NMR spectroscopy and DFT calculations) support a common reaction pathway via very similar cationic S^{IV} species and showcase how subtle changes in reactant properties can lead to disparate and seemingly unrelated reaction outcomes.[76] On a different front, the Maulide group recently discovered the phenomenon of catalytic asymmetric diastereodivergent deracemization in palladium-catalyzed allylic alkylations. As part of a follow-up study, DFT calculations were performed that provide detailed insight into the palladium-catalyzed electrocyclic ring opening of cyclobutene units in large molecules, which proceeds as a conrotatory reaction in an intermediate palladium–cyclobutene complex, with competing isomer interconversion by η^1-η^3-η^1 allyl slippage.[77]

3.6. *Joint Projects with the Rinaldi and Schüth Groups*

Cellulose consists of 1,4-β-linked glucose units, which can be converted to biofuel and industrial platform molecules. The depolymerization of cellulose to glucose is an important part of this conversion process. The first step in modeling this process addressed the electronic nature of the 1,4-β-glycosidic bond and of its chemical environment in cellobiose (glucose dimer) as well as its influence on the mechanism of the acid-catalyzed hydrolysis.[78] The DFT results imply that cellulose is protected against hydrolysis not only by its supramolecular structure (as commonly accepted), but also by its electronic structure, in which the anomeric effect plays a key role.[78] Ongoing follow-up work addresses the depolymerization of larger cellulose models in water and in ionic liquids using QM/MM calculations on the hydrolysis mechanism as well as classical metadynamics simulations on the influence of conformational changes.

3.7. *Methods for Studying Biocatalysis*

Enzymatic reactions are normally investigated using a combination of classical MD simulations and QM-only and QM/MM calculations. The emphasis at KOFO is on QM/MM studies that make use of geometry optimization techniques to identify and trace conceivable pathways on DFT/MM potential energy surfaces in order to determine the most favorable mechanism. Optimizations are normally done with efficient DFT approaches (e.g., RI-BP86 with moderate basis sets), while relative energies are determined using more refined functionals (e.g., B3LYP-D or M06 with larger basis sets) or even correlated ab initio methods (CCSD(T) or multireference treatments). If necessary, QM/MM free energy calculations are performed to capture entropic contributions. The corresponding QM/MM techniques and protocols were developed over the last decade[79,80] and were applied extensively at KOFO, for example in mechanistic studies on cytochrome P450 enzymes[81,82] and molybdenum-containing enzymes.[83] As an alternative or complement to the QM/MM approach, enzymatic reactions can also be studied through QM-only calculations of suitably chosen active-site model systems.[84]

3.8. *Joint Projects with the Reetz Group*

Motivated by experimental work on directed evolution in the Reetz group, the Baeyer–Villiger oxidation reaction in cyclohexanone monooxygenase (CHMO) was examined to elucidate its mechanism and the origin of its enantioselectivity. According to the QM/MM calculations on the wild-type enzyme,[85] the enzyme–reactant complex is quite rigid and contains an anionic deprotonated C4a-peroxyflavin that is stabilized by strong hydrogen bonds with the Arg329 residue and the $NADP^+$ cofactor. The CHMO-catalyzed reaction proceeds via a Criegee intermediate with pronounced anionic character. The fragmentation of this intermediate to the lactone product is the rate-limiting step. The QM/MM results for the parent cyclohexanone confirm the crucial role of the Arg329 residue and of the $NADP^+$ cofactor for the catalytic efficiency of CHMO. QM/MM calculations for the CHMO-catalyzed oxidation of 4-methylcyclohexanone reproduce and rationalize the experimentally observed *S* enantioselectivity for this substrate, which is governed by the conformational preferences of the corresponding Criegee intermediate and the subsequent transition state (TS2) for the migration step.[85] A subsequent QM/MM study addressed the effect of mutations of the Phe434 residue in the active site of CHMO on its enantioselectivity towards 4-hydroxycyclohexanone.[86] The enantiopreference was assessed by locating all relevant TS2 structures at the QM/MM level, for the wild-type enzyme and two mutants (Phe434Ser and Phe434Ile). The experimentally observed enantioselectivity was reproduced semiquantitatively in all three cases, including the pronounced reversal of enantioselectivity in the Phe434Ser mutant. The effect of point mutations could be explained at the molecular level, by an analysis of the specific interactions between the substrate and the active-site environment in the TS2 structures that satisfy the basic stereoelectronic requirement of anti-periplanarity for the migrating σ-bond.[86] Similar success had been achieved in previous joint work on lipases, which had offered an explanation of the highly improved enantioselectivity of a sixfold mutant created by directed evolution[87] and had predicted a similar performance for a particular double mutant that was later confirmed experimentally.[88]

3.9. Summary

The preceding examples from collaborative work at KOFO and many other studies in the literature show the benefits of a joint experimental and theoretical approach to problems in catalysis.[89,90] The synergistic advances in computational methods, software, and hardware over the past decades have now made it possible to model catalytic reactions in a realistic manner using the tools of computational chemistry. The calculations offer independent, reliable information that is often complementary to experimental data and that helps us to understand chemical phenomena. Particularly valuable are the characterization of the electronic structure of reactive species, intermediates, and transition states, the detailed analysis of all elementary steps in the catalytic cycle, the assessment of preferences between different conceivable pathways, and insights into the origins of stereoselectivity and in particular enantioselectity. Such theoretical information can be useful not only for rationalizing experimental observations, but also for guiding chemical thinking towards further experimental work.

4. Perspectives

In the field of computational catalysis, some future trends can be anticipated rather confidently by extrapolating from recent advances whereas others can only be guessed at in a more subjective manner. In the following, we comment on some selected issues from a quantum-chemical viewpoint.

4.1. Higher Accuracy

Theoretical chemistry thrives on progress in methodology and programming, which fuels novel applications. In recent years, new algorithms have been developed to extend the applicability of first-principles methods to much larger molecules, for example by implementing linear scaling techniques at the Hartree–Fock and DFT levels[91] and through local correlation approaches at the coupled cluster level.[92–98] The latter have already been demonstrated to yield accurate energies in real-world case studies on homogeneous catalysis[99] and biocatalysis,[100] and it would thus seem safe to assume that in the future such local coupled cluster approaches will be employed regularly in single-point calculations at DFT-optimized geometries to derive accurate energy profiles for catalytic transformations. In the realm of heterogeneous catalysis, hybrid schemes that combine periodic DFT calculations with correlated ab initio calculations on cluster models have been shown to yield nearly chemical accuracy for barriers in zeolite-catalyzed reactions.[101] Applying dispersion corrections[102,103] to lower-level QM energies has obvious merits in general and will thus become standard (even more so than already now). Undoubtedly, there will also be further efforts to develop more accurate density functionals,[104,105] improved semiempirical methods with integrated orthogonalization and dispersion corrections,[106] and more robust and reliable polarizable force fields.[107,108] In the long run, it would seem likely, however, that the most significant progress towards higher accuracy will come from wavefunction-based ab initio methods. Particularly desirable is the development of accurate, efficient, and robust multireference coupled cluster methods and of other high-level correlated ab initio methods, in order to enable an improved treatment of the electronically challenging open-shell species that are often encountered in catalytic reactions.

4.2. High-Performance Computing

The doubling of computer power approximately every 18 months (Moore's law) has facilitated ever more demanding computational studies in catalysis over the past decades. Breakthroughs in higher hardware performance normally arise from new technology and novel computer architectures, which can often only be exploited after a corresponding adaptation of the computer programs and the underlying algorithms. For example, current efforts target the development of codes that run efficiently on massively parallel systems with hundreds of thousands of processors and on hybrid systems with fast graphics processors, in order to increase the available processing power by orders of magnitude. While not always successful because of inherent algorithmic limitations, computational chemists have in the past generally managed to cope with such tasks, and one may thus realistically assume that this will also be the case in the future—allowing for more extensive exploration of catalytic processes through enhanced hardware and software performance.

4.3. Multiscale Modeling

Computational studies of catalysis require the choice of a model system. Simplification of the real system is unavoidable, but all chemically important components should of course be retained in the model. While strongly simplified model systems may yield valuable insight, it is clearly preferable to use systems that are as complete and realistic as possible. This calls for an adequate consideration of the environment around the catalytically active site, be it the solvent in homogeneous catalysis (possibly with counterions and additives), the extended surface and the solid support in heterogeneous catalysis, or the surrounding protein in biocatalysis. Multiscale modeling appears to be the method of choice for handling such complex systems, with the level of the theoretical treatment adapted to the relevance of a given region to the problem being studied. Multiscale approaches are already widely used in computational biology,[109,110] the simplest variant being two-layer QM/MM treatments.[35,79,80] Multiscale models are inherently flexible; for example, they can go beyond atomistic QM and MM approaches by incorporating coarse-grained force fields[111,112] and continuum solvation models.[113,114] Three-layer treatments are already available, for example QM/MM/continuum models that employ boundary potentials[115,116] for use in biocatalysis studies.[117] The general impact of multiscale approaches is evident from the fact that the Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt, and Arieh Warshel "*for the development of multiscale models for complex chemical systems*". While the research of the three laureates was mostly focused on biomolecular systems, multiscale techniques can obviously be applied to any complex chemical system. Therefore, with the move towards ever more realistic models of catalytic processes, one may safely expect multiscale modeling to become more important in this field.

4.4. Complexity

Computational reactivity studies on small gas-phase model systems are simple in the sense that there are generally only a few relevant stationary points and pathways, and it is thus feasible to explore the underlying potential energy surface in a systematic manner. By contrast, complex model systems for condensed-phase catalytic processes will involve many degrees of freedom, there will normally be many low-energy conformations, and hence there can be many relevant stationary points and pathways. This makes it challenging to search and to sample conformational space. This problem has long been addressed in the biomolecular force field community, and many techniques are available to cope with it.[118] Search- and sampling-enhancement methods include local elevation,[119] conformational flooding,[120] and metadynamics,[121,122] which all allow moving towards and finding new local minima by removing previously found minima through a suitable local deformation of the potential energy surface. There are also techniques for automatically finding pathways between two given minima, for example transition path sampling[123,124] and the nudged elastic band method.[125,126] A related but more difficult problem is the automatic prediction of reaction mechanisms in a complex catalytic system, starting only from given reactants and catalysts. The artificial force-induced reaction (AFIR) method[127] has been introduced for this purpose; it identifies reactive sites and provides approximate transition states and product structures that can serve as starting points for subsequent optimizations. The AFIR approach has been shown to enable the semiautomatic determination of the full catalytic cycle of the $[HCo(CO)_3]$-catalyzed hydroformylation, in a fully systematic search without any initial mechanistic input.[128] Even though automated explorations of complex potential energy surfaces[119–128] will generally be computationally very costly when accurate QM methods are used (more so than the targeted search for a plausible reaction pathway), they have the advantage of being unbiased and systematic. It will thus be most desirable to further improve such approaches, especially for handling complex model systems such as those encountered in computational catalysis.

4.5. Free Energy Calculations

Chemical reactivity is governed by free energy changes along reaction pathways. In computational reactivity studies on small gas-phase molecules, the thermal and entropic corrections to the computed energies are usually evaluated from statistical thermodynamics in the rigid-rotor/harmonic-oscillator approximation. With increasing complexity of the model systems for condensed-phase catalytic processes, this approach quickly becomes unfeasible because of the multitude of accessible low-energy conformations and pathways. Proper ensembles of configurations must then be used to compute free energy differences using statistical mechanics.[129] For each elementary step in a catalytic cycle, one needs to compute the free energy profile (also called the potential of mean force) along the reaction pathway, which involves extensive sampling around this path using MD simulations with restraints (umbrella sampling) or with constraints (thermodynamic integration). Much experience on these issues and on approximate free energy treatments is available in the classical force field community.[129] It will clearly be helpful for the computational catalysis community to benefit from this expertise—of course taking into account that energy and gradient computations can be computationally very expensive in catalysis research because of the need to use reliable QM methods for describing bond-forming and bond-breaking processes.

4.6. Kinetic Analysis

Assuming that computed free energy profiles are available for all relevant catalytic cycles and their interconnections in a complex model system, the next task is to convert this data into mechanistic insight and kinetic information. In simple cases, it is possible by inspection to identify the rate-determining and selectivity-determining steps in the catalytic cycle using traditional kinetic rate equations or their translation into the energy domain by means of the energy-span model.[130] In more complicated cases, it may become necessary to move towards a more quantitative evaluation, by solving the coupled differential rate equations for the investigated catalytic reaction network or—equivalently—by performing corresponding kinetic Monte Carlo simulations.[131–135] For given free energy profiles and starting conditions (e.g., concentrations and temperature), such kinetic analysis will yield relative rates for the various competing reaction channels, and the kinetic bottlenecks and the selectivity-determining steps can be identified by sensitivity analysis (e.g., by variation of the input data for specific barriers).[132,133] As computational catalysis moves towards higher accuracy in the computed free energies and towards more complex models, one may expect that there will be an increasing need for quantitative kinetic analysis in this field—of course keeping in mind the inherent limitations in the accuracy of the underlying quantum chemical results.

4.7. Catalyst Design

Most of the current research on computational catalysis (see the examples in Section 2) focuses on the mechanistic understanding of catalytic processes, often in the context of a close collaboration with experimental partners, which may then guide further experimental work. A more ambitious goal is to actually design improved or novel catalysts on the basis of computations. Corresponding strategies have been proposed both in homogeneous catalysis[136] and heterogeneous catalysis.[137] In biocatalysis, there are two computation-based strategies for producing new enzymes, namely redesign of active sites and de novo design.[138] Examples for the latter approach are the development of new enzymes for Kemp elimination[139] and Diels–Alder cycloaddition.[140] Currently, such computational de novo design seems capable of producing novel protein scaffolds with limited activity, which can then be optimized to acceptable performance using the techniques of directed evolution.[141] The partial success of these ambitious de novo efforts indicates that computation can indeed contribute to catalyst design. In view of the expected advances on the theoretical side (see above), it seems safe to expect that computations will play a more important role in future catalyst design.

4.8. Concepts

One important task of computational catalysis is to propose, test, and extend qualitative concepts on the basis of increasingly accurate calculations. One example is the notion of two-state or multistate reactivity[142] involving different spin states (and hence intersystem crossing between potential energy surfaces of different multiplicity). Intersystem crossing had of course long been known in spectroscopy and photochemistry, but had not been fully appreciated in transition-metal chemistry. Its mechanistic importance in this area was recognized by joint experimental and theoretical work[142] and has since been firmly established both for homogeneous transition-metal catalysis[61,142–144] and for biocatalysis by metalloproteins.[80–82] A second example is the long-standing debate about the importance of dynamic effects in enzymatic reactions and about the idea that enzymes may have evolved to optimize a particular nuclear motion that facilitates reaching the catalytically relevant transition state.[145–149] There are many facets to this issue, which can be addressed through simulations once the "dynamic effects" have been properly defined.[149] In the framework of transition state theory (TST), dynamic nonequilibrium effects due to protein motion will cause the transmission coefficient to be smaller than unity; however, computational studies of various enzymes have revealed only slight deviations from unity, by factors of 3 or less.[138,149] Tunneling is a nuclear quantum effect not covered by standard transition state theory; it is clearly important in some enzymatic reactions (e.g., those involving proton, hydrogen, or hydride transfer), but not significantly more so than in the corresponding reference reaction in aqueous solution.[148,149] The evidence from simulations thus suggests that the dynamic effects of non-TST behavior and tunneling make only a very minor contribution to the catalytic power of enzymes. To summarize, two-state reactivity and dynamic effects in enzymes are examples of qualitative concepts that have been successfully explored and clarified in the past decade through contributions from experimental and computational work. One obvious general challenge for future studies in computational catalysis is to find, scrutinize, and refine such qualitative concepts that guide chemical thinking.

5. Conclusions

Since the inauguration of KOFO in 1914, it has taken theoretical chemistry decades to develop from rather esoteric beginnings into an important branch of chemistry. Computational research in catalysis started its exponential growth around 1990 and has now become a valuable companion of experimental research. With the continuing advances in computational methodology, software, and hardware performance, theory is expected to play an increasingly important role in the field of catalysis. Currently, quantum-based computations mostly aid in the interpretation and understanding of experimental results by providing independent reliable information from simulations. In the future, they are expected to become more predictive and to contribute to the design of new catalysts and catalytic processes.

One final note: This Essay has addressed computational catalysis in a bottom-up manner from a quantum-chemical perspective, with emphasis on the microscopic understanding of catalytic reactions and the electronic structure of the reactive species involved. It has not covered the top-down branch of computational catalysis that is concerned with engineering issues such as the optimum reactor design, the modeling of macroscopic heat and mass transfer, mesoscopic fluid dynamics simulations, and the analysis of complex catalytic networks. True multiscale modeling of catalytic processes will need to bring together all these aspects and integrate the bottom-up and top-down approaches. This is clearly a challenge for the future.

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