COMPUTATIONAL APPROACHES TO BIOCHEMICAL REACTIVITY (UNDERSTANDING CHEMICAL REACTIVITY) pdf

1: Computational chemistry - Wikipedia

COMPUTATIONAL APPROACHES TO BIOCHEMICAL REACTIVITY Understanding Chemical Reactivity Volume 19 Series Editor Paul G.

This page intentionally left blank PREFACE A quantitative description of the action of enzymes and other biological systems is both a challenge and a fundamental requirement for further progress in our understanding of biochemical processes. This can help in practical design of new drugs and in the development of artificial enzymes as well as in fundamental understanding of the factors that control the activity of biological systems. Structural and biochemical studies have yielded major insights about the action of biological molecules and the mechanism of enzymatic reactions. However it is not entirely clear how to use this important information in a consistent and quantitative analysis of the factors that are responsible for rate acceleration in enzyme active sites. The problem is associated with the fact that reaction rates are determined by energetics i. Even mutations of specific active site residues, which are extremely useful, cannot tell us about the totality of the interaction between the active site and the substrate. In fact, short of inventing experiments that allow one to measure the forces in enzyme active sites it is hard to see how can one use a direct experimental approach to unambiguously correlate the structure and function of enzymes. In fact, in view of the complexity of biological systems it seems that only computers can handle the task of providing a quantitative structure-function correlation. The use of computer modelling in examining the microscopic nature of enzymatic reactions is relatively young and this book provides a glimpse at the current state of this fast growing field. Moreover, it is clear that many studies are still missing crucial points in their attempt to model biological processes. Many of the problems are due to the complexity of enzyme-substrate systems and the fact that the strategies developed for QM calculations of isolated molecules in the gas phase are not adequate for studies of enzymatic reactions. The same is true for other chemical concepts that should be re-evaluated when applied to complex, non-homogeneous systems. This book presents different approaches that can be useful in theoretical treatments of biological activities. In doing so we try to bring together parts of the overall picture of what is needed in order to model and analyse the energetics and kinetics of enzymatic reactions. As editors, we do not necessarily fully agree with the philosophy of each chapter. However, we believe that presenting different approaches is an optimal way of exposing the reader to the current state of the field and for reaching scientific consensus. Chapter 1 considers the general issue of modelling of chemical vii viii processes in solution emphasising continuum approaches. Solvation energies provide the essential connection between gas phase QM studies and the energetics of processes in condensed phase. In fact, we chose this as the opening chapter since one of the main problems in elucidating the origin of enzyme catalysis has been associated with the difficulties of estimating solvation free energies. Chapter 2 presents attempts to advance the accuracy of the QM parts of reactivity studies by representing the solute using ab initio methods. Such methods will eventually become the methods of choice and early exploration of their performance is crucial for the development of the field. Here the emphasis is on the crucial aspect of combining the quantum mechanical and classical regions. Chapter 4 considers MM and molecular dynamic MD approaches. Such approaches are essential for representing the conformational energies of biological molecules and can be used for example in assessing the importance of strain effects or other ground-state properties. This chapter also presents attempts to use ground-state MD in studies of mechanistic issues. Here, it might be useful to caution that definitive information about different mechanisms can only be obtained by going beyond such approaches and considering the quantum mechanical changes that necessarily take place in chemical reactions. Chapter 5 considers calculations of electrostatic energies in proteins. This aspect is an essential part of analysing of the energetics of enzymatic processes because without reliable ways of estimating electrostatic energies it is impossible to ask any quantitative question about enzyme catalysis. The approaches considered in Chapter 1 are not always applicable to studies of electrostatic energies in proteins and one has to be familiar with

calculations both in proteins and solutions if gaining a clear understanding of this challenging field is the objective. Chapter 6 considers the general issue of the catalytic power of enzymes and demonstrate that electrostatic energies are the most important factor in enzyme catalysis. This point is illustrated by both quantitative calculations and simple molecular electrostatic potential calculations where it is shown that enzymes provide a complementary environment to the charge distribution of their transition states. Chapter 7 considers in detail the important class of proteases and reviews the current theoretical effort in this specific case. Chapter 8 presents quantitative calculations of enzymatic reactions that and focuses on studies of proton transfer reactions using the empirical valence bond EVB method. This chapter illustrates and explains the catalytic role of the enzyme in providing electrostatic stabilisation to high energy intermediates and in reducing reaction reorganisation energies. At last, Chapter 9 deals with protein-ligand interactions that can be treated by using methods described in the previous chapters. Quantitative understanding of such interactions is of primary importance in rational drug design. While the chapters presented here reflect different aspects and opinions it is useful to emphasise some points that might not be obvious to the readers. These points are important since the current status of the field is somewhat confusing and some readers might be overwhelmed by the technological aspects rather than by logical considerations of the energetics. Thus we will outline below some of the main problems that should be considered in a critical examination whether a given approach ix for studies of enzymatic reactions is really useful. We start stating what should have been obvious by now, that calculations of enzymatic reactions must reflect the energetics of the complete enzyme-substrate-solvent system. Thus calculations of subsystems in the gas phase or even calculations that involve a few amino acids cannot be used to draw any quantitative conclusion about enzyme mechanism. That is, the gradual "build-up" process must involve an increasing sophistication of describing the complete system, rather than adding different physical parts to a rigorous but incomplete description. This might not be so clear to readers who are familiar with the use of accurate gas phase calculations and prefer rigorous treatments of isolated subsystems over an approximate but reasonable treatment of the whole system. However enzyme modelling does not lend itself to incremental studies where one can learn by considering parts of the system in a step by step process. The problem of incomplete description cannot be over-emphasised since it can lead to major conceptual problems, such as concluding that a helix macrodipole accounts for the catalytic effect of an enzyme while using unsolved protein as a model for the given enzyme. On the other hand, correct calculations might indicate that the solvent around the protein screens the helix effect and even leads to less stabilisation than that provided by the solvent for the reference reaction in water. Similarly, modelling an enzymatic reaction with an unscreened metal ion can lead one to believe that this ion alone provides enormous catalytic effect, but in reality the field of the ion might be largely screened. Another problem with regards to modelling of enzymatic reactions is the recent tendency to believe that ground state MD simulations can provide concrete information about enzyme mechanism and catalysis. This assumption is unjustified since ground state dynamics cannot tell us much about the probability of reaching the transition state in different feasible mechanisms. Thus, for example, finding a proton near a proton acceptor does not mean that the barrier for proton transfer is reduced by the given active site. Here one might assume that since the complete enzyme substrate system can be considered the results can be trusted blindly. This is unfortunately incorrect. First, many such studies do not consider the solvent molecules in and around the protein, and thus may lead to enormous errors. Secondly, even approaches that include the solvent molecules are likely to provide irrelevant results unless the free energy of the system is evaluated by reliable free energy perturbation FEP or related approach. Using energy minimisation in an enzyme active site might be quite ineffective. Even the use of convergent free energy calculations does not guarantee the accuracy of the calculated activation free energies since the given QM method might not be reliable enough. Thus, unless the method can reproduce the correct energetics in reference solution reactions it is unlikely to reproduce correctly the energetics of enzymatic reactions. Thus we believe that any approach that is used in studies of enzymatic reactions must be able to accurately reproduce electrostatic energies in enzymes e. The perspective given above might look somewhat critical and almost

pessimistic. However, most of the warnings given here are related only to the current and short term status of the field. There is no doubt that once grown out of its infancy, computer modelling will provide the most powerful way of using structural and biochemical information in quantitative description of biological reactions. We believe that this maturation will occur in the next several years and will involve a major progress in the use of theoretical methods in studies of enzymatic reactions and related processes. We hope that this book will contribute to this progress. Naive picture of liquids and chemical reactions in liquids. Models in theoretical chemistry are often quite complex, but at the same time they are always based on simple and naive pictures of the real systems and the processes which are the object of modelling. To gain a better understanding of a given model, with its subtleties and characterizing features, it is often convenient to go back to basic naive pictures. Also the opposite way, i. Simple pictures emphasize different aspects of the problem, and their comparison is of great help in grasping both merits and limits of the theoretical and computational methods proposed in scientific literature. We shall start with a couple of such naive models for the liquid state, and for reactions occurring in solution. A molecular liquid in macroscopic equilibrium may be viewed as a large assembly of molecules incessantly colliding, and exchanging energy among collision partners and among in1 G. Printed in the Netherlands. A limited number of collisions leads to more drastic effects, perturbing the internal electronic distribution of collision partners, and causing the formation of molecules with a different chemical composition. This model of the liquid will be characterized by some macroscopic quantities, to be selected among those considered by classical equilibrium thermodynamics to define a system, such as the temperature T and the density This macroscopic characterization should be accompanied by a microscopic description of the collisions. As we are interested in chemical reactions, one is sorely tempted to discard the enormous number of nonâ€” reactive collisions. This temptation is strenghtened by the fact that reactive collisions often regard molecules constituting a minor component of the solution, at low-molar ratio, i. The perspective of such a drastic reduction of the complexity of the model is tempered by another naive consideration, namely that reactive collisions may interest several molecular partners, so that for a nominal two body reaction: This is the naive picture on which many tentative models of chemical reactions used in the past were based. Such material model may be studied in detail with quantum mechanical methods if A and B are of modest size, and the number of S molecules is kept within narrow limits. Some computational problems arise when the size of reactants increases, and these problems have been, and still are, the object of active research. This model is clearly unsatisfactory. It may be supplemented by a thermal bath which enables the description of energy fluxes from the microscopic to the outer medium, and vice versa, but this coupling is not sufficient to bring the model in line with chemical intuition and experimental evidence. Now we proceed to consider another naive picture of liquid systems. A liquid system is disordered on a large scale, but more ordered locally. The properties of the liquid may be understood by looking at this local order, and examining how it fades away at larger distances. The local order is due to the microscopic characteristics of the intermolecular interaction potential. By introducing interaction potentials of different type in the computational machinery of the corresponding theoretical model, and starting, for example, from shortâ€”range repulsive potentials and then adding appropriate medium and longâ€”range terms, one may learn a lot about the properties of the liquid. Using more and more realistic interaction potentials, one has the perspective of gaining a sufficiently accurate description of the liquid. However, it is hard to introduce chemical reactions in this naive picture. To study them one has to force the model, bringing into contact two local structures based on molecules A and B, in our example, and then studying the evolution of such local structures in the whole liquid. We are so led once again to consider a microscopic event, i. The main theoretical approach to describe the reactive event is still quantum mechanics QM. Alternative semiclassical models can be used only after an accurate calibration on very similar processes studied at the appropriate QM level. However, in this case, things are more complex than in the previous model. The description of local liquid structures, and their decay at long distances, cannot be made at the QM level. Severe limitations are necessary: There is now experience and availability of computational resource which are sufficient to make

the derivation of a two body potential a feasible task if the two partners are at a fixed geometry. In chemical reactions the change of internal geometry, and of electronic structure, is a basic aspect that cannot be grossly approximated. Therefore the soluteâ€”solvent interaction potential must be re-evaluated for a sufficient number of nuclear conformations of the reactive subsystem Aâ€”B, with the additional problem, hard to be solved, that the charge distribution of Aâ€”B, and then its interaction potential with a solvent molecule S, critically depends on the interactions with the other S molecules nearby. In addition the introduction of explicit solvent molecules in the reactive system say an subsystem is not easy.

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2: Computational Approaches to Biochemical Reactivity : Arieh Warshel :

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From Computational Chemistry to Process Systems Engineering 1 Some Challenges for Chemists and Chemical Engineers Develop computer methods that will accurately predict the properties of unknown compounds. Develop reliable computer methods to calculate the detailed pathways by which reactions occur in both ground states and excited states, taking full account of molecular dynamics as well as quantum and statistical mechanics. Develop reliable force fields for molecular mechanics calculations on complex systems, including those with metallic elements. Invent computer methods to predict the three-dimensional folded structure of a proteinâ€”and the pathway by which folding occursâ€”from its amino acid sequence, so information from the human genome can be translated into the encoded protein structures. Devise experimental tests to establish the reliability of new theoretical treatments. Invent new computer tools and logistics methods to reduce significantly the time needed for commercializing new drugs. Invent new algorithms to globally optimize at the worldwide level the use of raw materials, energy, and environmental impact of chemical processes. Develop new and powerful computational methods, applicable from the atomic and molecular level to the chemical process and enterprise level, that will enable multiscale optimization. The phenomenal increase in speed and computational power of computersâ€” as well as their dramatic reduction in costâ€”has continued at an astonishing pace over the last decade. At the same time, key advances in areas such as ultraviolet lithography techniques, nonleaking complementary metal oxide semiconductor CMOS transistors, and multiple instruction, multiple data MIMD computer architecture are already in place to support clock-speeds at the GHz plateau with power requirements at 1 V or lower. Finally, 10 years ago, few could envision how the dimension of communicationsâ€”via the Internetâ€”would enhance computing in what may have been the most revolutionary development in the late 20th century. Chemistry and chemical engineering, like many other disciplines, are being profoundly influenced by increased computing power. This has happened in part by enhancing many existing computational procedures, providing a new impetus to quantum mechanical and molecular simulations at the atomic level, and optimizing processes and supply chain management at the macrosystem level. Furthermore, these computational tools have helped test new conceptual approaches to understanding matter and molecules. While we expect all these developments to continue, the important challenge is likely to arise in dramatic growth of new computing needs. These needs are driven by the increasing shift in the chemical industry toward biotechnology products and pharmaceuticals, the emergence of industrially relevant nanotechnologies, the requirement to optimize existing large-scale commodity chemicals plants, and the increased size and complexity of many new problems and systems. Instruments used by chemists and chemical engineers are already substantially controlled by on-board computer systems, the complexity of which will increase with that of the purpose and use of the instruments. Computational chemistry and process systems engineering play a major role in providing new understanding and development of computational procedures for the simulation, design, and operation of systems ranging from atoms and molecules to industrial-scale processes. The supply chain starts with the set of chemicals that industry must synthesize and characterize at the molecular level. Subsequent steps aggregate these molecules into clusters, particles, and filmsâ€”as single and multiphase systems that finally take the form of macroscopic mixtures. At the process engineering scale, the figure illustrates the design and analysis of production units that are integrated into a chemical process, which in turn is part of a site with multiple processes. Finally, this site is part of the commercial enterprise that is driven by business considerations. The multiple scales of this chain are a fact of life in chemical sciences and technology. To date, the field has neither sufficient tools nor enough trained people to pursue computational chemistry and chemical engineering across all these scales. The field will qualitatively changeâ€”in new insights, in what experiments are done and how chemical

products and processes are designedâ€”when this is achievable. Courtesy of Professor Wolfgang Marquardt. Advances in computing have facilitated major progress in computational chemistry and biochemistry, computational materials design, computational fluid dynamics, process synthesis, planning and scheduling, model-based process control, fault diagnosis, and real-time process optimization. This progress has been enabled by parallel advances in fundamental chemical physics theory, mathematics, operations research, and computer scienceâ€”including computational techniques for simulation and optimization of chemical systems. This chapter shows how areas that span computational chemistry, from the atomic level to process systems engineering at the macrosystem level, are full of exciting computational challenges that await solutions from bright minds. Simple experimental facts without a theory to interpret them do not satisfy our need for understanding. Indeed, many experimental measurements cannot be interpreted without theory, and as experiments probe phenomena and structures at ever smaller spatial and temporal scales, the role of theory in interpreting experiment increases. However, theory without experiment can lead to unrealistic dreams. The birth of modern science came when it was realized that truth is obtained from facts, not just from speculation. Theory validated by experiment runs through all of chemistry, and almost all its branches now use computers. Structures are determined by computer treatments of x-ray data, potential new drugs are analyzed by computer modeling, and even synthetic strategies to make a desired target molecule are developed using computer programs created for the purpose. Quantum Mechanics The chemical sciences are built on a set of fundamental mathematical theories that have increasing utility as computational hardware and software become more powerful. As the basis for calculating the electronic structure of molecules, quantum mechanics permits calculations, often based on rational approximations, of structure and properties of molecules, and of reactivity and reaction mechanisms. A continuing, important goal is to devise better and more accurate ways to obtain predictions of molecular structures, bond energies, molecular properties, transition state structures, and energies for systems of increasing size. Good approximate quantum calculations usually can be done reliably only for isolated molecules. Another important objective in this field is to develop methodologies for solvated molecules and molecules that are parts of membranes or other organized biological systems. Engineers are attempting to use quantum mechanical calculations to predict practical phenomenaâ€”for example, making and breaking of bonds in adhesion and fractureâ€”that are based on electronic interactions. Additional goals are to learn how to accurately include heavier elements and to calculate the properties of molecules as a function of time, when they are interacting with other species. Quantum calculations are the starting point for another objective of theoretical and computational chemical science, multiscale calculations. The overall objective is to understand and predict large-scale phenomena, such as deformation in solids or transport in porous media, beginning with fundamental calculation of electronic structure and interactions, then using the results of that calculation as input to the next level of a more coarse-grained approximation. An important goal is to improve or supplement quantum mechanical methods in order to calculate reliably the energy and geometry of a transition state. This is one piece of information that can lead to the larger objective of predicting the rates of unmeasured reactions, but a second goal must also be met to achieve this. The accurate prediction of reaction rates also depends on our knowledge of dynamical properties of molecules and the dynamics of their sampling of accessible electronic, rotational, and vibrational states. Another goal is to predict the course of excited-state reactions, often initiated by adsorption of light. Such molecules do not traverse the lowest energy paths, and they usually form products that are different from those produced in ground-state reactions. Molecules that absorb light are transformed into various different excited states, depending on the energy of the light that is absorbed. Each excited state can in principle undergo a unique photochemical transformation. The development of successful theoretical treatments for such complex phenomena presents a substantial challenge. This goal also extends to the calculation of magnetic, optical, electrical, and mechanical properties of molecular and extended solids in both the ground and excited states. Yet another related goal is to be able to predict the catalytic activity of a given surface for a particular reaction. Using computational quantum chemistry, it is becoming possible to predict with reasonable accuracy the

energy barriers and transition states of molecules reacting on catalytic surfaces, thus leading to insights into reaction rates. This is enabling a new field of rational catalyst design, which offers the promise of designing and optimizing new catalysts computationally so that synthetic efforts can be focused on high-priority candidates. Molecular Mechanics One tool for working toward this objective is molecular mechanics. In this approach, the bonds in a molecule are treated as classical objects, with continuous interaction potentials sometimes called force fields that can be developed empirically or calculated by quantum theory. This is a powerful method that allows the application of predictive theory to much larger systems if sufficiently accurate and robust force fields can be developed. Predicting the structures of proteins and polymers is an important objective, but at present this often requires prohibitively large calculations. Molecular mechanics with classical interaction potentials has been the principal tool in the development of molecular models of polymer dynamics. The ability to model isolated polymer molecules in dilute solution is well developed, but fundamental molecular mechanics models of dense systems of entangled polymers remains an important goal. A particular goal of chemical theory is to predict protein structure from the amino acid sequenceâ€”to calculate how polypeptides fold into the compact geometries of proteins. One strategy is to develop methods often based on bioinformatics for predicting structures approximately and then refining the structures using atomic-level molecular modeling methods. Molecular mechanics is also the theoretical approach employed in calculating how a proposed drug might bind into a protein. Modeling and Simulation Modeling and simulation are extremely important tools in the chemical sciences. The understanding and engineering of complex chemical processes, such as combustion or atmospheric chemistry and transport, generally rely heavily and increasingly on modeling and computation. Recent advances in computing not only have enabled more accurate and reliable calculations, but they have also provided new tools for interpreting the output of the calculations. Modern computer graphicsâ€”including molecular graphics, simulations, and animationsâ€” have greatly enhanced the ability of scientists and engineers to understand and utilize the results of their computations. Yet modeling can be no better than its assumptions. It often suffers from the problem that we cannot follow any computed process for a long duration many time steps â€”primarily because the computer time needed per time step is significant, but also because of the cumulative propagation of round-off errors. The typical time step is on the order of 1 femtosecond i. Consequently, modeling phenomena on the femtosecond time scale would require about time steps, which is not difficult, and modeling on the picosecond time scale time steps is fairly routine. However, many phenomena of interest e. Another goal is to learn how to improve the calculations by overcoming these problems. One approach is to use stochastic approaches based on cleverly chosen Monte Carlo methods; another is to reduce the level of detail in the models for the molecules so-called coarse grained models. Statistical Mechanics and Fluid Mechanics Sometimes the theoretical or computational approach to description of molecular structure, properties, and reactivity cannot be based on deterministic equations that can be solved by analytical or computational methods. The properties of a molecule or assembly of molecules may be known or describable only in a statistical sense. Molecules and assemblies of molecules exist in distributions of configuration, composition, momentum, and energy. Sometimes, this statistical character is best captured and studied by computer experiments: Interaction potentials based on quantum mechanics, classical particle mechanics, continuum mechanics, or empiricism are specified and the evolution of the system is then followed in time by simulation of motions resulting from these direct interparticle, stochastic, or fluid mechanical forces. The larger the size of the computation, the better the statistical representation of the system. Statistical mechanics is the science that deals with average properties of the molecules, atoms, or elementary particles in random motion in a system of many such particles and relates these properties to the thermodynamic and other macroscopic properties of the system. One advantage of statistical mechanics is that a good model often reveals some underlying generality governing the system, thereby permitting analogies to be made between properties or behaviors that superficially are quite different. Simulations and statistical mechanics are key tools for physical chemists and engineers working on understanding rheological behavior, mass transport, modeling of microfluidic devices,

flow of granular media, and behavior of dense particle suspensions. At the next higher level of coarse-graining, fluid mechanics and other continuum mechanics methods are active arenas of theory and computation. For example, electrorheology and magnetorheology have provided tremendous impetus in the last decade. Efforts to determine the dependence of basic scaling on field strength and particle volume fraction quickly require answers to questions about material properties. The links between the thinking of chemical engineers studying transport and chemists designing and producing materials are crucial for progress. Granular media is another area where the clear interplay between science and technology is facilitating progress in solving sophisticated scientific questions that have immediate impact on technology and practice. From the viewpoint of computation and simulation, engineers working in granular media are addressing problems of flow and mixing such as those arising in the processing of powdered pharmaceuticals ; discrete computational approaches encompass particle dynamics, Monte Carlo, and cellular automata calculations. Spanning Length and Time Scales Many of the problems cited above highlight the need for being able to bridge calculations across several length and time scales. It is thus worthwhile to consider this in some additional detail. For example, reactions involve changes in the molecules, and hence are inherently quantum mechanical in nature. But a reaction taking place in a solution at finite temperature implies that the reaction is influenced by a dynamic environment more pragmatically described by classical molecular simulation methods. Hence, a scale-bridging method is needed to allow the dynamics of the solvent around the reactants to influence the electronic structure of the reactants in various conformations, as well as the reactants influencing the motion of the solvent molecules around them. Other hybrid methods, which treat just the environment around reactants quantum mechanically, are less accurate in principle but allow much longer time scales and much larger spatial scales to be accessed, since the vast majority of the molecules are treated by classical molecular simulation. Chemical processes at the commercial scale ultimately involve spatial scales on the order of meters, and time scales corresponding to processing times in reactors and separations equipment ranging from seconds to hours and, in the case of many bioengineering processes involving fermentations, days or weeks. How do we connect phenomena at the electronic and molecular scale to the commercial chemical process scale?

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3: Computational Approaches to Biochemical Reactivity - PDF Free Download

Understanding Chemical Reactivity Computational Approaches to Biochemical Reactivity reactions. Thus we believe that any approach that is used in studies of.

History[edit] Building on the founding discoveries and theories in the history of quantum mechanics , the first theoretical calculations in chemistry were those of Walter Heitler and Fritz London in The books that were influential in the early development of computational quantum chemistry include Linus Pauling and E. With the development of efficient computer technology in the s, the solutions of elaborate wave equations for complex atomic systems began to be a realizable objective. In the early s, the first semi-empirical atomic orbital calculations were performed. Theoretical chemists became extensive users of the early digital computers. A very detailed account of such use in the United Kingdom is given by Smith and Sutcliffe. For diatomic molecules, a systematic study using a minimum basis set and the first calculation with a larger basis set were published by Ransil and Nesbet respectively in The first configuration interaction calculations were performed in Cambridge on the EDSAC computer in the s using Gaussian orbitals by Boys and coworkers. Of these four programs, only Gaussian, now vastly expanded, is still in use, but many other programs are now in use. At the same time, the methods of molecular mechanics , such as MM2 force field , were developed, primarily by Norman Allinger. Computational chemistry has featured in several Nobel Prize awards, most notably in and Walter Kohn , "for his development of the density-functional theory", and John Pople , "for his development of computational methods in quantum chemistry", received the Nobel Prize in Chemistry. In theoretical chemistry, chemists, physicists, and mathematicians develop algorithms and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions. Computational chemistry has two different aspects: Computational studies, used to find a starting point for a laboratory synthesis, or to assist in understanding experimental data, such as the position and source of spectroscopic peaks. Computational studies, used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms not readily studied via experiments. Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects. Several major areas may be distinguished within computational chemistry: The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied. Storing and searching for data on chemical entities see chemical databases. Identifying correlations between chemical structures and properties see quantitative structureâ€”property relationship QSPR and quantitative structureâ€”activity relationship QSAR. Computational approaches to help in the efficient synthesis of compounds. Computational approaches to design molecules that interact in specific ways with other molecules e. Accuracy[edit] The words exact and perfect do not apply here, as very few aspects of chemistry can be computed exactly. However, almost every aspect of chemistry can be described in a qualitative or approximate quantitative computational scheme. Molecules consist of nuclei and electrons, so the methods of quantum mechanics apply. Therefore, a great number of approximate methods strive to achieve the best trade-off between accuracy and computational cost. Accuracy can always be improved with greater computational cost. Significant errors can present themselves in ab initio models comprising many electrons, due to the computational cost of full relativistic-inclusive methods. This complicates the study of molecules interacting with high atomic mass unit atoms, such as transitional metals and their catalytic properties. For geometries, bond lengths can be predicted within a few picometres and bond angles within 0. The treatment of larger molecules that contain a few dozen atoms is computationally tractable by more approximate methods such as density functional theory DFT. There is some dispute within the field whether or not the latter methods are sufficient to describe complex chemical reactions, such as those in biochemistry. Large molecules can be

studied by semi-empirical approximate methods. Even larger molecules are treated by classical mechanics methods that use what are called molecular mechanics MM. Methods[edit] One molecular formula can represent more than one molecular isomer: Each isomer is a local minimum on the energy surface called the potential energy surface created from the total energy i. A stationary point is a geometry such that the derivative of the energy with respect to all displacements of the nuclei is zero. A local energy minimum is a stationary point where all such displacements lead to an increase in energy. The local minimum that is lowest is called the global minimum and corresponds to the most stable isomer. If there is one particular coordinate change that leads to a decrease in the total energy in both directions, the stationary point is a transition structure and the coordinate is the reaction coordinate. This process of determining stationary points is called geometry optimization. The determination of molecular structure by geometry optimization became routine only after efficient methods for calculating the first derivatives of the energy with respect to all atomic coordinates became available. Evaluation of the related second derivatives allows the prediction of vibrational frequencies if harmonic motion is estimated. More importantly, it allows for the characterization of stationary points. The frequencies are related to the eigenvalues of the Hessian matrix , which contains second derivatives. If the eigenvalues are all positive, then the frequencies are all real and the stationary point is a local minimum. If one eigenvalue is negative i. If more than one eigenvalue is negative, then the stationary point is a more complex one, and is usually of little interest. When one of these is found, it is necessary to move the search away from it if the experimenter is looking solely for local minima and transition structures. This leads to the evaluation of the total energy as a sum of the electronic energy at fixed nuclei positions and the repulsion energy of the nuclei. A notable exception are certain approaches called direct quantum chemistry , which treat electrons and nuclei on a common footing. Density functional methods and semi-empirical methods are variants on the major theme. For very large systems, the relative total energies can be compared using molecular mechanics. The ways of determining the total energy to predict molecular structures are: Ab initio methods[edit] Main article: This does not imply that the solution is an exact one; they are all approximate quantum mechanical calculations. It means that a particular approximation is rigorously defined on first principles quantum theory and then solved within an error margin that is qualitatively known beforehand. Diagram illustrating various ab initio electronic structure methods in terms of energy. Spacings are not to scale. The simplest type of ab initio electronic structure calculation is the Hartreeâ€"Fock method HF , an extension of molecular orbital theory , in which the correlated electron-electron repulsion is not specifically taken into account; only its average effect is included in the calculation. As the basis set size is increased, the energy and wave function tend towards a limit called the Hartreeâ€"Fock limit. Many types of calculations termed post-Hartreeâ€"Fock methods begin with a Hartreeâ€"Fock calculation and subsequently correct for electron-electron repulsion, referred to also as electronic correlation. To obtain exact agreement with experiment, it is necessary to include relativistic and spin orbit terms, both of which are far more important for heavy atoms. In all of these approaches, along with choice of method, it is necessary to choose a basis set. This is a set of functions, usually centered on the different atoms in the molecule, which are used to expand the molecular orbitals with the linear combination of atomic orbitals LCAO molecular orbital method ansatz. Ab initio methods need to define a level of theory the method and a basis set. The Hartreeâ€"Fock wave function is a single configuration or determinant. In some cases, particularly for bond breaking processes, this is inadequate, and several configurations must be used. Here, the coefficients of the configurations, and of the basis functions, are optimized together. The total molecular energy can be evaluated as a function of the molecular geometry ; in other words, the potential energy surface. Such a surface can be used for reaction dynamics. The stationary points of the surface lead to predictions of different isomers and the transition structures for conversion between isomers, but these can be determined without a full knowledge of the complete surface. A particularly important objective, called computational thermochemistry , is to calculate thermochemical quantities such as the enthalpy of formation to chemical accuracy. To reach that accuracy in an economic way it is necessary to use a series of post-Hartreeâ€"Fock methods and combine the

results. These methods are called quantum chemistry composite methods. Density functional methods[edit] Main article: Density functional theory Density functional theory DFT methods are often considered to be ab initio methods for determining the molecular electronic structure, even though many of the most common functionals use parameters derived from empirical data, or from more complex calculations. In DFT, the total energy is expressed in terms of the total one- electron density rather than the wave function. In this type of calculation, there is an approximate Hamiltonian and an approximate expression for the total electron density. DFT methods can be very accurate for little computational cost. Some methods combine the density functional exchange functional with the Hartreeâ€"Fock exchange term and are termed hybrid functional methods. Semi-empirical quantum chemistry methods Semi-empirical quantum chemistry methods are based on the Hartreeâ€"Fock method formalism, but make many approximations and obtain some parameters from empirical data. They were very important in computational chemistry from the 60s to the 90s, especially for treating large molecules where the full Hartreeâ€"Fock method without the approximations were too costly. The use of empirical parameters appears to allow some inclusion of correlation effects into the methods. Primitive semi-empirical methods were designed even before, where the two-electron part of the Hamiltonian is not explicitly included. Molecular mechanics In many cases, large molecular systems can be modeled successfully while avoiding quantum mechanical calculations entirely. Molecular mechanics simulations, for example, use one classical expression for the energy of a compound, for instance the harmonic oscillator. All constants appearing in the equations must be obtained beforehand from experimental data or ab initio calculations. The database of compounds used for parameterization, i. A force field parameterized against a specific class of molecules, for instance proteins, would be expected to only have any relevance when describing other molecules of the same class. These methods can be applied to proteins and other large biological molecules, and allow studies of the approach and interaction docking of potential drug molecules. Computational chemical methods in solid state physics Computational chemical methods can be applied to solid state physics problems. The electronic structure of a crystal is in general described by a band structure , which defines the energies of electron orbitals for each point in the Brillouin zone. Ab initio and semi-empirical calculations yield orbital energies; therefore, they can be applied to band structure calculations. Since it is time-consuming to calculate the energy for a molecule, it is even more time-consuming to calculate them for the entire list of points in the Brillouin zone. The potential representing the interatomic interaction is given by the potential energy surfaces. In general, the potential energy surfaces are coupled via the vibronic coupling terms.

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