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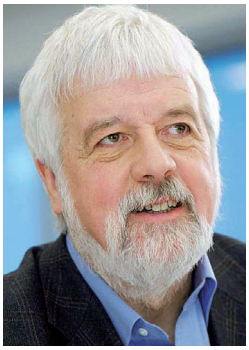
Theoretical Chemistry—Quo Vadis?

*Walter Thiel**



Walter Thiel, Direktor, Max-Planck-Institut für Kohlenforschung, Department of Theory

Give us insight, not numbers.
Charles Coulson, theoretical chemist, 1960

Theoretical concepts permeate chemistry more thoroughly than we often think. Chemists are intuitively familiar with different types of chemical bonding; with the structure, spectroscopy, and dynamics of molecules; and with the variety of different possible chemical reactions. They use theory-based concepts, for example from quantum mechanics or statistical mechanics, to describe and analyze chemical phenomena. The primary task of theoretical chemistry has always been to provide the conceptual and terminological framework that is necessary to understand chemistry.

The dynamic boom that theoretical chemistry has experienced in recent decades, however, arises mostly from the increased accuracy and efficiency of numerical calculations and simulations, due to synergistic advances in computational methods, software, and hardware. These developments have made it possible to model broad areas of chemistry using the tools of computational chemistry. Typical examples of such applications include highly accurate ab initio calculations of the spectroscopy and dynamics of small molecules, density functional calculations of reaction mechanisms and transition-metal catalysis, quantum mechanical/molecular mechanical calculations of enzymatic reactions, and molecular dynamics simulations of biomolecules. These examples are quite varied, but in each case the calculations offer independent, reliable information that is often complementary to experimental data and that helps us to understand chemical phenomena. For this reason, the computational sciences view simulations, along with theory and experiment, as the third pillar of science.

Method Development

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed.
Paul Dirac, physicist, 1929

What is left to do in methodology? It would, of course, be the wrong approach to be satisfied with the status quo. Theoretical chemistry thrives on advances in methodology and programming. One obvious challenge is the accuracy of theoretical predictions, which can be improved if the underlying approximations are improved. This is being attempted across the board (e.g., explicitly correlated ab initio methods, multireference methods, refined theory-based density functionals, polarizable force fields, ab initio quantum dynamics). A second challenge concerns the complexity of chemical processes. Strongly simplified model systems may yield valuable insight, but it is preferable to use systems that are as complete and realistic as possible. This will require consideration of the environment, either explicitly or through coarser methods all the way to continuum models (e.g., multiscale methods, mesoscopic simulations), as well as an adequate treatment of the enormous number of degrees of freedom in such systems (e.g., sampling of the configurational space, entropy). Generality and robustness are further goals in all method development. Computational methods should ideally be applicable to any type of system (i.e., all elements of the periodic table and any type of compound) and should guarantee a uniform precision (i.e., no unreasonable outliers). Another important ongoing task in program development is the technological adaptation to new, more powerful computer types and architectures. Currently, this means writing 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. Taken together, these trends ensure that the capabilities of computational chemistry will continue to grow rapidly—as long as method and program development keeps pace.

Practical Applications

There is nothing more practical than a good theory.
Kurt Lewin, psychologist, 1951

What about applications, the solution of specific chemical problems on the computer? At the risk of oversimplifying, we can differentiate between three groups of users (even if the boundaries are a bit blurry and a given person might

[*] Prof. Dr. W. Thiel
Max-Planck-Institut für Kohlenforschung
Mülheim (Germany)

belong to more than one group): Theoreticians are primarily interested in testing the performance and limitations of newly developed computational methods, for example by systematic validation on established benchmarks or through proof-of-principle calculations. Computational chemists are generally motivated by chemical questions and apply appropriate (state-of-the-art) methods to gain qualitative chemical insight through broad theoretical investigation of a given field. Experimentalists are interested in solving specific problems, and they use standard computations as an additional tool for the characterization and elucidation of experimental results. These different uses are all legitimate—the variety of possible applications is clearly a strength of theoretical chemistry.

But where are the pitfalls in applications, especially for experimentalists? In theoretical chemistry, the technology transfer to experimental groups is fairly easy. In the conceptual framework of a "model chemistry" (John Pople) there are well-defined computational methods that are accessible in program packages (some of which are commercially available) and can be easily implemented and used in a black-box fashion. In an experimental lab group, there are usually a few computer-savvy students or postdocs who will enjoy performing such applications. What should they keep in mind? First, they need to ask themselves if theoretical calculations make sense at all for a given problem in light of the expected results. The next step is to decide which model system should be used for calculations. Simplification of the real system is unavoidable, but all important components must be retained in the model; errors in this essential step are virtually impossible to correct later on. The choice of model system is closely linked to the choice of computational method and the specific procedures to be followed. A certain degree of expertise is necessary here, as theoretical chemistry offers a hierarchy of methods that differ in their application range, computational cost, and accuracy. Even if a standard method such as density functional theory is chosen, other decisions must be made (e.g., regarding functional, basis set, and computer program), and methodological advances may well make standard approaches such as B3LYP/6-31G* obsolete. The execution of the calculations themselves is generally less of a problem, although technical problems may arise (e.g., lack of convergence, failed optimizations, etc.). These, however, can generally be handled by sufficiently experienced co-workers. The interpretation of results is potentially more difficult. Faith in the infallibility of the computer is as unjustified as a fundamental mistrust of the numbers in the output. Instead, users must be able to assess the error bars associated with theoretical results, and the best approach is to consider all computationally available information and to combine it with the experimental results to arrive at an overall picture of the system in question. "Give us insight, not numbers" (Charles Coulson)—this is the attitude we should have when analyzing results.

Collaborations

You cannot believe in astronomical observations before they are confirmed by theory.

Sir Arthur Eddington, astronomer, quoted by S. Chandrasekhar, *Nature* **1974**, *252*, 15

The considerations described above apply to all sorts of application-oriented computations, regardless of who is performing them. Professional theoreticians and computational chemists can be expected to be aware of all of these aspects, and they should be able to support local experimental groups that run into problems. It is certainly a good idea for standard computations to be performed directly in the experimental lab groups, because they have the direct connection to the chemical problem to be solved. In any event, help from local theoreticians, if needed, should come naturally, along with a general openness to discussion, which can lead to exciting new collaborations. This sort of cooperation might initially seem like a chore for theoreticians, but it has the potential to enrich their own research.

Perspectives

We may even judge the degree of perfection to which a science has arrived by the facility with which it may be submitted to calculation.

Adolphe Quetelet, mathematician, 1828

Which long-term developments will lead us forward? There are two obvious answers for universities. First, chemistry students must receive a modern education in theoretical chemistry, encompassing not only the fundamentals of the subject but also the practical application of the tools of computational chemistry. Second, the field should be supported by a suitable mix of faculty members. Both theoreticians and computational chemists will be needed as professors to represent the breadth of the field and to enter into fruitful collaborations with experimentalist colleagues.

Quo vadis? Theoretical chemistry has developed over the past decades from rather esoteric beginnings into an important and independent part of chemistry and a valuable companion of experiment. The rapid advance of the field becomes clear when we consider how realistic computations and simulations are today in comparison to 10, 20, or 30 years ago. This dynamic progress is still at work and promises to continue in the future. Experiments will always remain central to chemistry, but theory will play an increasingly important role in the design of experiments (by making predictions) and the interpretation of experimental results (by providing independent information from accompanying calculations). Finally, theory will be challenged to test and expand qualitative chemical concepts on the basis of increasingly accurate computations—in the end, the primary aim is not number crunching but understanding chemistry.