

Computational Chemistry Column

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Computational Chemistry Events in Switzerland

In 1998 two major computational chemistry events took place in Switzerland: the 34. *Symposium für Theoretische Chemie* in Gwatt (BE), an event with great tradition hosted in alternation by Austria, Germany and Switzerland, and the *Summer School in Computational Quantum Chemistry (CQCS-98)*, an event with no tradition but with considerable potential for the future.

Whereas the 'Symposium' was a meeting of leading scientists in the area of large-problem computation, the focus of the 'Summer School' was to train students and researchers in the use of modern quantum-chemical methods. These two events with complementary missions are reviewed in this column.

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Theory Thinks Big

Michael Bühl*

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The image of theoretical chemists dealing mainly with the simplest and smallest molecules has changed long ago. Driven by continuing developments of theoretical methods, programs, and computer hardware, ever larger systems are becoming amenable to quantum-chemical studies with semiempirical, density-functional, and *ab initio* approaches. Today, extended systems, which used to be the unrivaled domain of classical force fields, can be explored quantum-chemically. Between September 20 and 24, 270 participants – more than ever – attended the annual Symposium for Theoretical Chemistry in Gwatt at Lake Thun, sharing new developments and applications in the field of large mol-

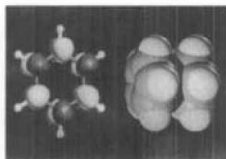
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Ab initio Methods

The development of methods for the efficient treatment of electron correlation was one of the main topics at the symposium. 'Linear scaling' continues to be a key issue, as applications to larger systems are only conceivable if the CPU time does not explode with growing molecular size. One way to achieve this goal is to

make use of local correlation methods, as outlined by *H. Werner* (Stuttgart). In these methods, electrons are correlated only within orbital domains defined by localized molecular orbitals. Long-range effects are approximated efficiently, rendering even highly accurate coupled-cluster

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methods linearly scalable. An interesting alternative to the 'Integrated MO-MO (IMOMO)' coupling schemes (see below) can be devised by 'switching on' electron correlation locally, for instance at the reactive center, and describing the rest of the system at *Hartree-Fock (HF)* level. *M. Schütz* (Stuttgart) pointed out another advantage of local correlation methods, namely the intrinsically small basis-set superposition error, which is very convenient for the global optimization of water clusters (*via* continuously MP2-adjusted model potentials). According to *G. Scuseria* (Houston), the 'Laplace-MP2' method can make use of generalized density matrices in order to avoid integral transformation, the usual bottleneck in conventional MP2 calculations. When the system can be divided into domains (as, for instance, in the case of molecular clusters), a formally linear scaling of the computation time with molecular size is possible, an approach that bears some resemblance to the local correlation methods described previously.

For highly delocalized systems such as metals, the conventional linear-scaling methods are not applicable. *M. Head-Gordon* (Berkeley) presented an alternative approach to overcome matrix diagonalization based on intermediate 'energy renormalizations', allowing, *e.g.*, tight-binding calculations of very large metal fragments (up to 16000 atoms). He also suggested to approximate complete-active-space-SCF wavefunctions using a coupled-cluster formalism rather than the usual truncated CI scheme. Significant savings in the computational expense and easier usage should make this new approach especially attractive for typical multiconfigurational cases, such as bond breaking, diradicals, *etc.*

C. Ochsenfeld (Mainz) presented density-matrix-based formalisms permitting the linear scaling of *HF* exchange and an enormous speedup in the computation of harmonic vibrational frequencies. According to *S. Kalvoda* (Dresden), the locality of electron correlation can be used to estimate energies of infinite, periodic systems *via* an increment scheme, by performing *HF* and correlated calculations for the whole crystal and smaller segments thereof, respectively.

S. Brode (BASF Ludwigshafen) gave a survey on quantum-chemical calculations in industrial research, with emphasis on homogeneous catalysis. He defined a 'large molecule' as one that is hard to calculate. In this spirit, *H. Müller* (Bochum) used highly correlated methods to approach spectroscopic accuracy for computed rotation-vibration spectra of the HF

molecule; explicitly correlated wavefunctions are especially effective for this purpose. With a similar motivation to overcome the cusp problem in electron correlation, *R. Polly* (San Diego) presented an approach for two-electron basis functions, termed geminals, which are expected to become useful in highly correlated calculations.

Rearrangements of C_8H_8 radical cations can be surprisingly complex; *T. Bally* (Fribourg) could identify interesting intermediates by comparison of experimental and theoretical (CASPT2) photoelectron spectra. *T. Klüner* (Berlin) nicely visualized complicated dynamic processes involved in the laser-induced NO desorption from Ni surfaces. The detailed motion of the wavepacket on the excited-state potential energy surface determines the observed velocity distributions.

Density Functional Methods

Further development of existing density functionals is a key research area. *A. D. Becke* (Kingston) demonstrated that thermochemical data can be better reproduced when both first and second derivatives of the electron density are included in the functional. However, this requires the fitting of nine parameters (ten with inclusion of *HF* exchange, affording hybrid functionals) to experimental data. Rationalizations were given why the delocalization of the exchange-correlation hole can be described without explicit *HF* exchange, which can be achieved by using additional parameters (a total of 15). A fitting of parameters to experimental data was also advocated by *D. J. Tozer* (Cambridge), who introduced additional corrections for the asymptotic behavior of the functionals in order to improve the description of excited states (including *Rydberg* states).

C. v. Wüllen (Bochum) suggested to modify the original formulation of the 'Regular Approximation' for relativistic effects in density-functional theory so that certain unphysical properties of the underlying operators are corrected, which makes the approach attractive for calculations of compounds of the heavier transition metals. *T. A. Wesolowski* (Geneva) presented a method for approximating the *Kohn-Sham* energy of a system from the densities of two subsystems. This method can be advantageous for the description of electrostatic interactions, such as physisorption of CO on metal-oxide surfaces.

Chemisorption of benzene on Si-surfaces is a complicated process. Based on the calculated vibrational frequencies,

U. Birkenheuer (München) could identify one of the species involved as the 1,4-adduct. *A. M. Köster* (Hannover) used local density-functional theory to study nonlinear optical properties of substituted stilbenes; at that level, the first hyperpolarizabilities can be well reproduced and rationalized.

Molecular dynamics on density-functional potential-energy surfaces can furnish valuable insights into the course of chemical reactions. This was shown by *T. Ziegler* (Calgary) for elementary reactions involved in homogeneous alkene polymerization. Certain reactions, for example monomer capture by the active catalyst, can have no barrier on the ΔH surface, but can be activated on the ΔG surface due to entropy. 'Static' QM/MM methods can be used to model substituent effects on the relevant activation barriers; it was, thus, possible to suggest specific modifications in the ligand sphere of a poorly active Zr-based catalyst, which in fact resulted in a significant increase of its activity.

When hydrogen atoms are involved in the dynamic process, their motion may need to be described quantum-mechanically. As shown by *D. Marx* (Stuttgart) for the proton in aqueous solution, this can result in broad distribution functions; consequently, the classical textbook examples $H_9O_4^+$ and $H_5O_2^+$ should be regarded as limiting structures rather than as realistic representations.

Semiempirical and Force-Field Methods

K. M. Merz (Penn State) uses linear-scaling methods based on the 'Divide-and-Conquer' technique for semiempirical calculations of proteins with thousands of atoms. He presented computational evidence that electronic charge on the level of one or two electrons can be transferred from the protein to the surrounding medium, which could contribute significantly to the interaction of both systems.

K. Jug (Hannover) showed conventional SINDO1 applications to the adsorption of small molecules on crystal surfaces. The computation of successively larger cluster fragments permits extrapolation of the properties to those of the periodic crystal with infinite surface. *M. Elstner* (Paderborn) closed the bridge between density-functional and semiempirical methods by implementing the tight-binding formalism in an approximate *Kohn-Sham* framework. In terms of accuracy and speed, this method can compete with

the usual semiempirical programs and it seems promising for the treatment of large biological systems, despite some problems with the description of hydrogen bonds.

To a large extent, molecular modeling of proteins is still dominated by classical force-field methods. Industry-relevant modeling of protein-substrate interactions was illustrated by *K. Müller* (*F. Hoffmann-La Roche AG*, Basel) for the design of thrombin inhibitors. He concluded that better force fields and larger structural databases are necessary to make the existing 'high-throughput' technologies more efficient. *A. Caflisch* (Zürich) used the same example, thrombin, to demonstrate the possibility of near-automatic search of suitable 'keys', *i.e.*, potential inhibitors, for a given 'lock', *i.e.*, the protein pocket. The estimation of solvent effects turns out to be an important step towards more accurate theoretical data.

Protein dynamics is another important area of research. *M. Karplus* (Harvard) emphasized that the native form of a protein is not resting in a deep featureless well in the potential energy surface. Rather, there are many neighboring shallow minima between which the system jumps on a timescale of tenths of picoseconds. Model studies of the protein-folding problem showed that the enormous number of possible denatured configurations could be substantially reduced by intramolecular forces which would drive the system rapidly toward 'semicompact' structures; a much smaller number of the latter would have to be 'screened' in order to find the correctly folded form.

W. van Gunsteren (ETH-Zürich) presented the first realistic molecular-dynamics simulations of the folding of model β -peptides. The relevant thermodynamic data can be evaluated from many reversible folding and unfolding events. Interestingly, even at larger simulation temperatures, the denatured state consists of only few so-called clusters of structures, rather than of a stochastic mixture of all possible conformers (for a heptamer as many as 10^{10} !).

Coupling Schemes

Coupling or hybrid schemes (QM/MM or IMOMO) are specifically designed for large systems with a smaller active site. *J. Sauer* (Berlin) surveyed QM/MM methods where the electronically interesting part of the system is described by quantum mechanics, and the remainder by classical mechanics. He illustrated some metho-

dological problems of current interest, for instance in locating transition states, and outlined possible solutions for these. Selected examples in the area of zeolite chemistry demonstrated the applicability of the methods for geometries, as well as for proton affinities and mobilities. According to *S. Dapprich* (Karlsruhe), the otherwise quite robust IMOMO scheme can fail when long-range effects are important, for instance in case of bond energies at the perimeter of extended graphite-like sheets.

QM/MM methods have also been applied in two lectures mentioned already. *T. Ziegler* (Calgary) demonstrated that density-functional results for model organometallic compounds and reactions are significantly improved by accounting classically for the steric influence of the 'real' ligands. *M. Karplus* (Harvard) showed that the catalytic action of the enzyme triosephosphate isomerase can be elucidated through semiempirical calculations combined with a force-field description of the protein environment.

Other Topics

In his experimental guest-lecture, *F. Diederich* (ETH-Zürich) described the properties of large organic molecules such as oligo-triacetylenes or methanofullerenes. The former have to be composed of a large number of monomers in order to converge the properties to those of the ideal polymer. Thus, one can arrive at estimates for an 'effective conjugation' extending over no more than 30 multiple bonds. Reversible cyclopropanation of fullerenes was presented as a versatile method for the separation of isomeric mixtures and for selective functionalization of fullerenes. Details of the reactions involved are yet unknown, for instance the proposed 'walk on the sphere' of methano bridges, calling for theoretical studies of the underlying mechanisms.

B. Paizs (Heidelberg) showed a way to more efficient optimization algorithms, indispensable for large systems, making use of 'natural internal coordinates' which are similar to those used in vibrational spectroscopy.

Efforts of the European Union to widen international contacts in scientific research were outlined by *J. Weber* (Geneva). Thousands of laboratories all over Europe are currently involved in collaborations supported by the COST programs. Sponsorship of the 34th Symposium for Theoretical Chemistry by COST was possible because of the international charac-

ter of the conference, emphasized by the fact that English was chosen as the official language for the first time.

Finally, two poster sessions comprising a total of 170 posters offered a multifaceted survey of current research activities. The scientific program was augmented by a boat tour on Lake Thun and a ride to the top of the Niederhorn with a splendid view of the alpine panorama.

Perspectives

The conference clearly showed that the tools for quantum-mechanical treatment of truly large molecules are already at hand. Numerous examples ranging from catalysis and material sciences to biomolecules provided ample evidence for the usefulness of the techniques currently available. Additional applications in practice, *i.e.*, accompanying or leading experiments, will follow in due course as 'more realistic' systems can be treated with more accurate theoretical methods. Many challenges remain, of course, including the continuing quest for higher accuracy and the explicit treatment of dynamics in large molecules with many degrees of freedom.

It also became obvious during the symposium that the different theoretical approaches available are often complementary to each other, in the sense that their combined use may solve a given chemical problem best. Theoretical methods will continue to be developed and diversified, but when it comes to large molecules, they are going to join forces.