Feature

The 2013 Nobel Prize in Chemistry

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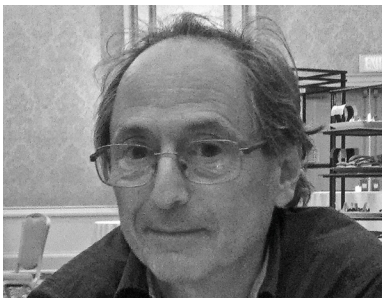
The Royal Swedish Academy of Sciences awarded the 2013 Nobel Prize in Chemistry to ***Martin Karplus*** of the Harvard and Strasbourg Universities, ***Michael Levitt*** of Stanford University School of Medicine, and ***Arieh Warshel*** of the University of Southern California, Los Angeles *for the development of multiscale models for complex chemical systems.*


Left: Martin Karplus (courtesy of Public Affairs, Harvard University); centre: Michael Levitt (from Wikimedia); right: Arieh Warshel (courtesy of Prof Warshel)

Summary

The developments in chemistry and biochemistry over the past 50 years have been rapid and significant. Older members of the Institute will recall with affection making models of molecules from plastic balls and sticks, tasks that are now routinely performed on the computer. The structure of a protein is obtained from X-ray crystallography or spin-spin couplings and nuclear Overhauser (nOe) measurements available from nuclear magnetic resonance spectroscopy. Programme development has been such that numerable protein structures have been solved and the results made available and accessible for download from a range of data bases. The viewer is now able to see the individual atoms of the substrate and rotate the 3D structure almost at will. Yet, computer programmes not only interpret experimental data, they can predict structures using models for the interactions between atoms that are based on the quantum mechanical electronic structure.

Emphasis today is not so much on structure as function. The: *What does it look like?* is now less important than *How does it happen?* Sophisticated experimental and spectroscopic methods can provide answers of function for some simple molecules but they are unable to solve the detailed questions pertinent to biochemical processes. Thus, the computer and its ability to model chemical processes is all-important to current day research. An experimental scientist requires input from specialist theoretical calculation – and the field of theoretical chemistry is itself growing rapidly, perhaps faster than any other sub-discipline of chemistry.

Chemical reactions are characterized by a transition state, the minimum (free) energy that a substrate must obtain for the given process to occur. It is that energy which links the product to the reactant. Experiment has yet to evolve adequately to gain transition state information for most reactions but the computational chemist can using theory. Theory is now an essential adjunct to experiment.

Classical theoretical methods gave us good information on groups of atoms by connecting them with springs, obeying Newton's laws of motion that allow the springs to stretch and compress. However, such simulations are unable to let the bonds actually break. In order to examine a reaction where bonds break and form the involvement of the electrons is vital - quantum mechanical equations that describe electron motion are needed. Even today's most powerful computers rapidly run out of storage space when these are used for molecules of even a few hundred atoms. The 2013 Nobel Prize in Chemistry awards three individuals who laid the foundations for detailed molecular modelling by combining classical and quantum mechanical theory.

The work for which the 2013 award was made focuses on the development of theoretical models that combine classical and quantum mechanical methods to allow modelling of large complex molecules and their reactions. The quantum mechanical approach concentrates on the atomic nuclei and the electrons of interest, while classical mechanics models atoms or groups of atoms. This latter procedure employs much simpler physics and far fewer degrees of freedom to describe the particles and this leads to a computational evaluation which is fast. To thoroughly assess aspects of reactivity in any complex molecule a combination of the two theoretical methods is needed. The laureates have provided the wherewithal now to do this so that the reactivity of a complex molecule can be better understood. Indeed, as a result of their studies, a computer may be able to simulate exactly how one complex biological molecule reacts with another in a cell at some point in the future.

The development of quantum mechanics stems from the early pioneering work of Planck, Bohr, de Broglie, Heisenberg, Schrödinger and Dirac who were awarded the Nobel Prize in Physics over the 1918-1933 period. It is from these studies that from about 1965 the construction of inter- and intramolecular potentials for complex systems was developed with Lifson and Warshel pioneering the Consistent Force Field (CFF) method in 1968.[1] Lifson, now with Levitt, used the method to give the first stable conformation of two macromolecules from experimental model co-ordinates, myoglobin and lysozyme. Here they found the deviations of peptide bonds from planar conformation, and the deviations in various bond angles from their respective average values, to contribute significantly to the refined protein conformation. A set of non-bonded potential functions, applicable to the equilibrium of a folded protein in an aqueous medium, were described and tested on myoglobin.[2] The advantage of such potential-based methods is that the calculations provide the energy easily and large molecules can be studied.

Given a complex molecule, the classical potential-based methods will provide the molecular energy of the complex molecule but not its conformation. Allinger was able to generate one characteristic conformation of a molecule with his molecular mechanics (MM) methods while statistical mechanics methods such as molecular dynamics (MD) or Monte Carlo (MC) generate many configurations, ideally with correct statistical weighting. The work of the laureates is independent of which method is chosen to obtain the conformation to be studied. What the 2013 Prize concentrates on are the ways changes in energy of the real system are accurately and efficiently assessed when there are relatively large changes in geometry (or electronic configuration) in a small part of the molecule that is coupled strongly with a surrounding that is only weakly perturbed. This can best be achieved using the Car-Parinello approach[3] but it is too demanding of computer time for large biomolecules. The solution is to combine classical modelling of the large surrounding with quantum mechanical (chemical) theory to model the core where the chemistry takes place.

It was Martin Karplus with Arieh Warshel who made the first breakthrough in 1972.Warshel had a background in inter- and intramolecular potential modelling and Karplus had the quantum chemical experience. Between them a computer programme was constructed that provided the ground and excited state potential surfaces of conjugated molecules by formally separating the σ- and π-electrons.[4] The σ-electron framework was computed using a (classical) empirical potential function and the π-framework by a semi-empirical (quantum chemical) model of the Parriser-Parr-Pople (PPP) type. Initially this was applied to 1,3-butadiene, 1,3,5-hexatriene, 1,3-cyclohexadiene and 1,8-diphenyloctatetraene with excellent results. This early procedure was limited to planar molecules whose symmetry provided a natural separation of the σ- and π-electrons. However, in 1976 Warshel and Levitt constructed a general scheme that partitioned the electrons included in the classical model from those of the quantum chemical method and they applied it to an enzyme reaction by studying the stability of the carbonium ion intermediate formed in the cleavage of a glycosidic bond by lysozyme.[5] They had, in particular, to evolve coupling terms for the interaction between the classical and quantum chemical system and each of these with the surrounding dielectric. Their procedure considered the whole enzyme-substrate together with the surrounding solvent system and it included all the energetic factors[6] that might contribute to the reaction. This allowed them to evaluate all the different quantum mechanical and classical energy factors that could affect the reaction pathway. Incorporation of the polarizability of the atoms of the protein into the calculation allowed them to reproduce, for the first time, the energetic balance found in hydrogen transfer reactions and deal properly with electrostatic interactions.

The electrostatic polarization of the enzyme atoms and the orientation of the dipoles of the surrounding water molecules were simulated by a microscopic dielectric model. Warshel and Levitt found that the solvation energy resulting from this polarization was considerable and, therefore, that it had to be included in any realistic calculation of every chemical reaction involving more than an isolated molecule *in vacuo*. Without it, acidic groups never became ionized and the charge distribution on the substrate was never reasonable. They found that this same dielectric model could follow the reaction of the substrate in solution that then allowed appropriate comparison with the enzymic reaction. In this early study the electrostatic stabilization was important in increasing the rate of the step that led to the carbonium ion formation while steric factors, such as the strain of the substrate on binding to lysozyme, did not contribute significantly.

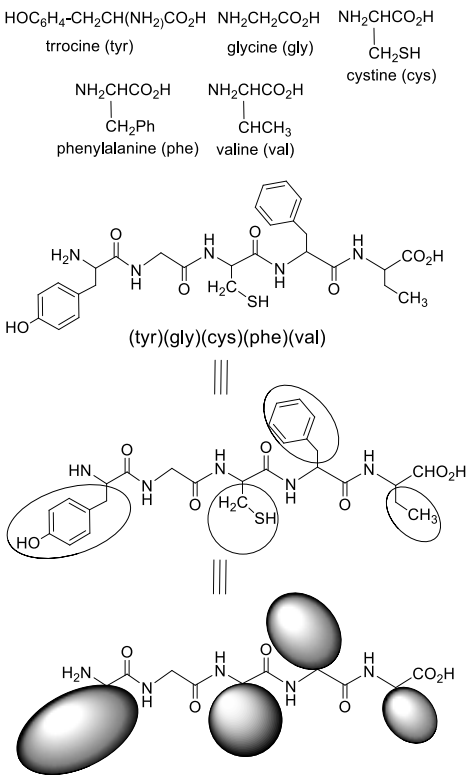


Fig. 1. The amino acids (upper) can give the polypeptide chain (tyr)(gly)(phe)(val) that is simplified by assigning each residue acid an interaction volume that results in the string of pearls structure (lower).

A further step by Levitt and Warshel in 1975 made possible the study of larger systems.[7] Here the pair examined the folding of the protein Bovine Pancreas Trypsin Inhibitor (BPTI), one of the smallest and simplest globular proteins comprised of a single-chain polypeptide with 58 amino acid residues and a molecular mass of 6512. It contains both α helical and β-sheet regions, as well as three disulfide bonds, which help to stabilise the tertiary structure of the molecule. Levitt and Warshel simplified the wrapping of the protein from an open to a folded conformation by assigning each amino acid residue in the chain an interaction volume. This led to a string of pearls-like structure that treated the atoms as rigid units for use as pseudo atoms in the classical simulation (see Fig.1). As will be appreciated, the approach sped up the computation even more.

With the larger part of the biomolecule now able to be treated appropriately and with the classical and quantum chemical procedures coupled, the pathway was opened for advances in big molecule computation by other chemists. Many have advanced the field not simply for organic and biochemical study but also to deal with heterogeneous catalysis and a number of molecules together in a liquid. It is due to the early observations and advances made by Karplus, Levitt and Warshel that computational chemistry is now better able to deal with the complexity of modern chemistry.

References and Notes

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