Towards predictive models in chemistry

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In 1828, A. Quetelet suggested that the degree of perfection to which a science has arrived may be judged by the facility with which it may be submitted to calculation. But not everyone seemed to agree. Around the same time, A. Compte wrote: 'Every attempt to employ mathematical methods in the study of chemical questions must be considered profoundly irrational and contrary to the spirit of chemistry. If mathematical analysis should ever hold a prominent place in chemistry—an aberration which is happily almost impossible—it would occasion a rapid and widespread degeneration of that science.' Much has happened since those early days of chemistry, even as the argument went on (or more correctly, goes on!). The progress made in enabling a significant number of chemical questions to be 'suggested to calculations' has culminated in the Nobel Prize for Chemistry in 1998 being awarded to two key players in the field, Walter Kohn and John A. Pople. Pople has been specifically recognized for his development of computational methods in quantum chemistry.

John Pople was born in 1925 in Burnham-on-Sea, Somerset, England. He studied mathematics at Cambridge and took a course in Quantum Mechanics offered by the great master, P. A. M. Dirac. Thus, Pople represents a direct link to one of the original developers of the mathematical framework needed to solve chemical problems. It is instructive to consider the status of quantum mechanical description of chemistry when Pople took up his graduate work under the guidance of John Lennard-Jones.

The situation was precisely summarized in the much (mis)quoted statement of Dirac: '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.' Exact quantum mechanical treatment was possible for the hydrogen atom and the hydrogen molecular ion, but for many-electron systems severe approximations were needed. Linus Pauling seized on a method developed by Heitler and London for the hydrogen molecule and worked out a general theory of structure and bonding in chemical systems. By combining qualitative and semi-quantitative concepts derived from quantum mechanics with empirical ideas derived from experimental data, Pauling could explain many facets of chemistry. In particular, valence bond theory in association with quantitative parameters like electronegativity, atomic radii, etc. provided a successful framework for interpreting experimental observations. But quantitative predictions were hard to come by.

Lennard-Jones worked out an alternative description of bonding in diatomic systems which turned out to be the forerunner of the Molecular Orbital method. Erich Hückel extended the idea to conjugated systems, while Robert Mulliken derived a generalized description for polyatomic molecules. Several useful insights and predictions about ground and excited states of molecules could be made using qualitative Molecular Orbital theory. But, again, quantitative formulations did not look promising. While the Hartree-Fock procedure offered a way, numerical solutions could be obtained only for atoms, too often after a good deal of labour. Polyatomic systems with their reduced symmetry remained intractable. Both Lennard-Jones and Mulliken were acutely aware of the need to find a way out of the impasse and were working out strategies.

There was also a rather unsavoury argument going on about the relative merits of VB and MO theory, even as a qualitative model. In organic systems, with well-defined two-centre two-electron bonds, Heitler-London product wave functions derived from pairs of hybrid orbitals seemed to be the simplest way of describing structure and bonding. The use of MOs distributed over an entire molecule appeared cumbersome. But these orbitals had the advantage of reflecting the symmetry properties of the molecule, a concept exploited by Mulliken for explaining spectroscopic features, and for predicting feasibility of chemical reactions, much later, by R. B. Woodward and R. Hoffmann.

For his doctoral work, Pople pointed out some common ground between the two theories. Lennard-Jones and Pople showed that any number of equivalent orbitals can be constructed by transformations of canonical MOs, leaving the total wave function unchanged. In particular, the directional character of bonds implicit in the VB model can be derived from suitable combinations of MOs. In a follow-up paper, Pople derived the rabbit-ear representation of lone pairs in the water molecule from the $\sigma$ and $\pi$-type lone pair MOs. Pople went on to convincingly demonstrate that the directionality of lone pairs had important implications. The displaced electron density was shown to be primarily responsible for the dipole moment of the molecule (and not just the polarized O–H bonds, as had been believed till then). The lone pairs were also the key to the formation of hydrogen bonds in liquid water and ice. Lennard-Jones and Pople worked out the basic rules governing molecular association in liquid water. Pople then showed that many of the anomalous properties of water can be accurately predicted using a statistical mechanical theory which invokes the presence of a distribution of hydrogen bonded structures, with varying angles. The 'best hydrogen bond model' has been vindicated by more elaborate numerical simulations which became possible decades later.

An important breakthrough occurred around the same time Pople completed his doctoral work. Mulliken's student C. C. J. Roothaan converted the integro-differential Hartree-Fock equations into a more manageable set of algebraic equations, by representing each MO as a linear combination of basis functions, such as atomic orbitals. Simultaneously and independently, G. G. Hall, working in the group of Lennard-Jones, derived the same set of equations. The Roothaan–Hall equations essentially require setting up of an energy matrix and subsequent diagonalization. The second step is ideally solved using digital computers, provided the matrix elements can be computed. But again there was a bottleneck. If atomic orbitals are chosen as the basis functions, a logical choice for chemists, the matrix...
elements involve computation of multi-
centre integrals, involving products of
atomic orbitals (termed differential over-
lap). Analytic expressions for computing
close and four-centred integrals involving
Slater-type orbitals (commonly used to
represent atomic orbitals) were just not
available.

Several approximation were being tried
out for getting around the problem of
computing the more difficult integrals by
Geppert-Mayer, Sklar, Mulliken and
others. One such was the zero differential
overlap (ZDO) approximation in which
the product of two different atomic
orbitals is set to zero. R. Pariser and
R. G. Parr worked out such a scheme,
which was the first generally successful
quantitative attempt to solve the
Roothaan-Hall equations, although limi-
ted only to \( \pi \) systems\(^6\). The integrals
which survived the ZDO approximation
were partly computed using the uniformly
charged sphere approximation and the
rest parameterized. The resultant pro-
cedure was a quantitative theory, which
went well beyond Hückel theory, by
explicitly taking into account electron
repulsions. Pariser and Parr used the pro-
cedure for predicting spectral properties
of conjugated systems. Independently, on
the other side of the Atlantic, Pople used
the ZDO approximation to work out
exactly the same computational strategy.\(^9\)

Pople used the method to understand and
predict variations in bond lengths in aro-
matic systems. The procedure is now
generally referred to as the PPP method,
after Pariser, Parr and Pople. It is still
widely used, especially for predicting
excited state properties, with inclusion of
configuration interaction.

Perhaps to avoid even a trace of con-
troversy, Pople moved on to a distinctly
different area, viz. magnetic properties
of molecules, although he did make one
important contribution to quantum
chemistry in 1954. He suggested an ex-
tension to the Hartree–Fock method for
handling open shell systems like radicals
and triplet states.\(^10\) In systems having
different number of \( \alpha \) and \( \beta \) spin electrons,
the exchange correlation will be different
for the two spins. Hence, the spatial
description for \( \alpha \) and \( \beta \) spin orbitals
should be different. This generalized pro-
cedure is known as the Unrestricted Har-
tree–Fock (UHF) method. While the
resultant wavefunction has a few flaws
(such as not being an eigenfunction of
the \( \langle S^2 \rangle \) operator and being contami-
nated with functions with higher spin), the
method also is characterized by several
pleasing features. Many important and
useful theorems applicable to the
Hartree–Fock method hold good for open
shell systems only within the UHF model.

Further, a key electronic interaction
known as spin polarization, which deter-
mines many spin and magnetic properties,
is effectively captured by the UHF wave
function. Naturally, Pople was quite fond
of the method and his school rarely used
the Restricted Hartree–Fock or other vari-
ants for open shell systems.

Pople spent several years in the fifties
working on theoretical problems associ-
ated with the newly developed spectral
tool, Nuclear Magnetic Resonance. He
was fascinated as much by the relation
between spectral characteristics and model
spin hamiltonians as by the chemical
information contained in the spectral
parameters, such as chemical shifts and
nuclear spin coupling constants. He
derived atomic and multi-centre contrib-
utions to magnetic properties using per-
turbation theory in conjunction with
semi-quantitative MO calculations invok-
ing the ZDO approximation. Pople’s
intense association with magnetic reso-
nance culminated in a classic book,
co-authored with Schneider and
Bernstein.\(^11\)

Pople moved to Carnegie-Mellon
University, Pittsburgh and became a
professor in 1964. A decade had gone
by since his first attempt at developing a
quantitative MO procedure for \( \pi \) sys-
tems. He had assumed that the theory
would have been generalized to include
the \( \sigma \) framework as well, enabling the
study of any polyatomic system. To his
surprise, not enough progress had been
made in the intervening period. Of course,
many groups had tried to generalize the
ZDO approximation to all-valence calcula-
tions. But the results were far from
satisfactory. Pople took a fresh look
himself and came up with remarkable
insights. He showed that the magnitude
of errors resulting from the ZDO
approximation depends, among other
things, on the coordinate system chosen.
Thus, the results do not have some
essential and some desirable invariances.

Pople went on to suggest a simple solu-
tion.\(^12\) To obtain results which are
invariant, additional approximations had
to be made. This, in effect, led to further
simplification of the computational
problem. Pople and his group came up with
a semi-empirical MO procedure called
the Complete Neglect of Differential
Overlap (CND0) method, which incor-
porated all these features. With a minor
modification to the parameterization
scheme, the first semi-quantitative all-
valence computational procedure, CNO0/2,
was released. Soon afterwards, one-centre
integrals were included without ZDO
approximation. The resulting Intermediate
Neglect of Differential Overlap (INDO)
theory was as easy to use as the CND0
method, but included contributions which
are essential for predicting nuclear spin
coupling and electron-nuclear hyperfine
coupling constants accurately.

Although semi-empirical methods
seemed the most promising approach to
examine chemical problems quantita-
tively, especially for large molecules of
interest to experimentalists, a large group
of influential theoretical chemists were
not fully convinced. In a perceptive anal-
ysis, C. A. Coulson spoke about the
polarization of theoretical chemists into
two groups.\(^13\) Group I was concerned
with accurate calculations involving ex-
tensive computations on small molecules.
Group II preferred using highly approxi-
mate and partly empirical calculations
on large molecules. Since the two groups
were pursuing different agendas, the
divergence of views between them kept
increasing. With a wider vision, Pople
pointed out how the two groups could
cooperate for the general advancement of
computational chemistry. At a symposium
in honour of Mulliken in 1965, Pople
proposed a concrete strategy: 'Group I
should be encouraged to extend some
of their simple calculations (such as
minimal-basis set LCAO-SCF) to larger
molecules, even though we all recognize
the limitations. It would at least be
valuable to get more experience of these
limitations, particularly for series of
homologous or related molecules, so that
the nature of semiempirical corrections
introduced by Group II can be better
understood. At the same time, Group II
should keep their methods continuously
under review, always looking for ways
in which they can be tested against
more precise calculations on smaller
systems'.\(^14\)

Pople practised what he preached. He
tried to systematically review and improve
the performance of semi-empirical
methods. He allowed a large group of theoretical chemists the world over to join the efforts through another best-seller, co-authored with D. L. Beveridge. The book had a listing of the Fortran code for performing CNDO and INDO calculations. The methods became big hits. A variety of problems, ranging from structure and energetics of molecules and reactive intermediates, like ions and free radicals, to conformational effects and intermolecular interactions, including hydrogen bonding, were studied. Of course, not all predictions were correct. But the models spurred theoreticians to consider improvements and generated interest amongst experimentalists to pose new questions. M. J. S. Dewar, in particular, modified the parameterization schemes drastically and derived a number of procedures which are popular with chemists even now, especially for studying reactivity in complex substrates.

Pople then moved on to join Group I who preferred to do more rigorous calculations and went about it in a systematic manner. He began to go for full-fledged solutions to the Roothaan–Hll equations, using a set of gaussian functions for describing each atomic orbital. Such calculations, which do not use any experimental information other than the fundamental constants, like the charge and mass of the electron, Planck's constant, etc. are referred to as \textit{ab initio} procedures. There were indeed many groups which had developed \textit{ab initio} code, but the general impression was that it required enormous amount of memory, disk space and time to do the calculations. Pople and his group wrote more efficient codes. A key simplification made by Pople was to use the shell concept. The s and p orbitals on an atom were forced to share the same orbital exponents. While the purists felt that it was an unnecessary restriction, Pople showed that the effort needed to compute integrals was drastically reduced. Attention to details, such as reducing DO LOOPS and writing out the expressions explicitly, made all the difference. The program called Gaussian 70 program was fast and user-friendly.

In addition to developing the program, Pople also focused on the nature of the basis functions used in \textit{ab initio} calculations. The results depend critically on the choice of these functions. There were different prescriptions. It was common to find different groups, sometimes even the same groups, using different basis functions. While qualitatively the trends were similar, the absolute values of energies changed a lot. As a result, calculations carried out on different chemical systems could not be compared on a uniform basis. For example, high level calculations to determine the equilibrium geometries may have been reported on propane and its isomer cyclopropane. But because the basis sets used were not identical, it was not possible to answer other questions concerning the same two molecules, such as their relative energies. Pople preferred to create models which offer many internal comparisons. Therefore, he systematically developed several basis sets, varying in sophistication and flexibility. In particular, he worked out minimal, split-valence and polarized basis sets and tested them out on a number of standard chemical problems. Pople's basis sets did not always give the lowest total energies (within each class), but the use of 'molecular scale factors' generally resulted in useful predictions of energy differences of importance in chemistry. The extensive calibration and the ease with which they could be used within the Gaussian series of programs made STO-3G, 4-31G, 6-31G* and 6-31G** basis sets the preferred choice for many computational chemists. Later, he added a smaller split-valence basis set, 3-21G, which now represents the starting point for most \textit{ab initio} calculations on large chemical systems. To those who wanted more complete basis sets, triple zeta plus diffuse and polarization functions were made available.

Pople substantially enhanced the capabilities of the Gaussian program in successive revisions. Electron correlation could be included through \textit{Møller-Plesset} perturbation theory to second, third and fourth orders. Configuration interaction and alternative post-Hartree–Fock schemes were added. While the methodologies were often known for a long time, Pople's group worked out additional strategies whenever needed. Perhaps the most important feature of the Gaussian program was the inclusion of efficient code using analytic gradients for locating minima and, later, transition states on complex potential energy surfaces. This was crucial for the study of chemical reactivity problems. In recent versions, many new capabilities have been added, such as magnetic properties. In the nineties, the Gaussian program was extended to use density functional theory. The availability of new computational procedures, like the B3LYP method, which is a hybrid Hartree–Fock and DFT procedure, as yet another option within the Gaussian program enabled many computational chemists to check out their usefulness for numerous chemical applications. The methods are now very popular, especially for studying complex reactions involving organic and organometallic systems. In a significant way, Pople contributed to the general awareness among chemists of the power of DFT methods, which used to be confined to the domain of physicists and theoretical chemists for a long time.

Pople did not just develop programs, but applied them to a number of important chemical problems, such as the anomeric effect. Many chemists were attracted to the power of theory through his contributions. He had a highly successful collaboration with P. v. R. Schleyer, with whom he published a series of important papers on the structure and energetics of organic molecules, carbocations, and organonitrogens, especially organolithium compounds. As before, he authored a popular book summarizing the methodologies and applications of \textit{ab initio} theory.

After his formal retirement at Carnegie-Mellon, Pople was offered a position at Northwestern University where he continues to work. He has received many honours and awards, including the highest recognition from the American Chemical Society and the prestigious Wolf Prize in Chemistry. He became a Fellow of the Royal Society as early as in 196! The Nobel Prize is clear recognition of a lifetime of achievements and leadership in the area of computational chemistry. All along, he has shown great vision and never wavered from his goals. He has uncompromisingly insisted on certain minimum characteristics which theoretical models in chemistry ought to possess. His views have been influential in shaping the development of the field. He has been remarkably objective while assessing the reliability of his own models and has gently frowned on extravagant claims made by some overenthusiastic computational chemists. His sense of balance and the emphasis he placed on standardization and repeated calibration have been crucial in convincing many experimentalists.
Ammonia synthesized at atmospheric pressure

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Ammonia plays an important role in all economies, especially in agricultural economies, as it forms the basis for the manufacture of nitrogenous fertilizers. Surprisingly, despite its importance, it is still made by Haber’s process developed in the early twentieth century. In this process, N₂ and H₂ are reacted at high pressures (50 to 300 atm) and temperatures (500°C). The severity of the reaction conditions contributes both to the cost and complexity of the process. Marescellos and Stoukides from the Chemical Engineering department of the Aristotle University, Greece, have recently announced (Science, 1998, 282, 98) an electrochemical synthesis of NH₃ from N₂ and H₂ at atmospheric pressure, which has the potential of being an alternative to Haber’s process.

Chemical conversion of N₂ and H₂ into NH₃ is limited by thermodynamic equilibrium. As there is a decrease in the number of moles in the course of the reactions, Le Chatelier’s principle would indicate that increased pressure favours the formation of NH₃. Reciprocating compressors were used in the early versions of the process to generate high pressures, but due to noise and wear and tear produced by the reciprocating movements, these made way in favour of turbo.compressors. Turbo.compressors are, however, uneconomical beyond 300 atm, which sets the upper limit on operating pressure.

The formation of NH₃ is exothermic, and it can be inferred, once again from Le Chatelier’s principle, that lower temperatures would enhance the conversion to NH₃. However, even with the iron-based catalyst, the rates of formation of NH₃ fall to inacceptable levels at temperatures below about 400°C.

At 450°C and 300 atm, about 53% of N₂ in a stoichiometric mixture with H₂ can be converted to NH₃, provided chemical equilibrium can be achieved. If the pressure is lowered to 100 atm, the conversion falls to a low value of 25%. The performance in practice is much lower. The iron-based catalyst has to be made strong enough to withstand the high pressures as well as sudden changes in pressure, and this makes the catalyst less permeable to reactants. As a result, only about 10% to 15% yields of NH₃ are achieved in industrial practice.

In contrast to this, the electrochemical synthesis developed by Marescellos and Stoukides achieves conversions of 78% of electrochemically supplied hydrogen (in the form of H⁺) at atmospheric pressure itself and at a temperature of 570°C. Despite the caveat of limitations of electrochemical supply of H⁺, the