measure distances in the interior of the model. Computer-graphic displays overcome all these disadvantages and can utilize the full range of display used in computer games. Colour, three-dimensional viewing, motion of atoms, the ability to rotate, cut away or highlight features. Even the techniques of virtual reality are already making an impact in molecular computer graphics. Beyond merely displaying models of molecules, graphics terminals and workstations can be used to reveal molecular properties such as electron densities or the energy of interaction of point charges with a molecule, to give some indication of reactivities or intermolecular binding preferences.

Neural networks

At its crudest level the human brain can be considered as a set of interconnecting cells or neurons with the process of learning being based on developing a range of connections of variable strength between these elements. This essential idea is the basis of the neural network. The network has a number of processing elements or nodes with connections between them. Each element takes in a signal from elements to which it is connected in the previous layer, and sends out a signal to the next layer. The strength of signal being passed depends on the 'weight' of each of the connections, and it is these weights which are varied. Once a set of input data is connected by the network to an output. When both input and output are known the weights are adjusted during `training' so that the output is appropriate to the input. For example, a set of molecular properties may be used as input so predict another property, perhaps an ionization potential. When the set is trained it gives the right answer for a training set of molecules it can then be tried on cases where the input properties are known but not the output. This technique is in many respects a form of pattern recognition and is becoming widespread as a way of predicting values of properties which are hard to measure accurately particularly in biochemical applications.

1.5 Summary

Computational chemistry is one of the fastest growing areas of chemistry. Although there are specialties in the field, increasingly the techniques are being applied by experimental chemists using the ever-growing power of ever-cheaper computers. A knowledge of the topic is important for anyone contemplating chemical research.

2 Quantum mechanics

2.1 Wave functions

The Schrödinger equation lies at the heart of much of modern science. In its basic form it states

$$\hbar \psi = E \psi$$

Here $\psi$ is the shorthand notation for an operator which operates on a mathematical function, the wave function $\psi$, and $E$ is the energy of the system. This notation disguises the fact that this equation is a differential equation, or rather a set of equations, with a function $\psi$ corresponding to each allowed energy $E$.

In the case of the simple hydrogen atom system with a single electron outside a positively charged nucleus, the equation may be solved exactly providing the wave function, $\psi$, obeys a set of reasonable restrictions on its behavior.

It must be emphasized that $\psi$ is just a mathematical function. It has no operational properties. Plotting a function $\psi$ against a coordinate $x$ is a familiar procedure (Fig. 2.1). In molecular quantum mechanics, since the problem concerns three-dimensional molecular systems, then the wave function also $\psi(x_1,x_2,x_3)$ in these coordinates. Because of the essentially spherical nature of atoms, polar coordinates ($r$ and $\theta$ and $\phi$) are generally preferred over Cartesian, $x$, $y$ and $z$ coordinates (Fig. 2.2).

For the hydrogen atoms the allowed wave functions or eigenfunctions are well known and an attempt to represent the three-dimensional functions in the two dimensions of the printed page is given in Fig. 2.3.

It can be seen in the figure that these resulting functions, one for each allowed energy or eigenvalue, do satisfy the postulates of quantum mechanics that they are `well-behaved' functions. They go to zero at infinity and change smoothly, never doubling back on themselves, having discontinuities or even violent changes in curvature.

Once the wave function is known for a particular state of a system then any physical observable may in principle be determined using the principle

$$\text{Observable} = \int \psi^* \Omega \psi \, dx$$

Integration over the element of space $dx$ means over all space and $\psi^* \Omega \psi$ is the complex conjugate of $\psi$ ($\psi^* \psi$) being the modulus of the square of the wave function. There is an appropriate operator for each different observable, be it...
2.2 Orbitals

The wave functions which satisfy the Schrödinger equation for the hydrogen atom are sometimes called orbitals. A hydrogenic atomic orbital is thus merely a three-dimensional mathematical function from which one can calculate the energy or other properties of the single electron system.

In polyatomic atoms we adopt the so-called orbital approximation. This involves treating each electron separately, each with its own one-electron wave function or orbital. This mathematical approximation is nothing more than the fundamental basis of the universal procedure of describing atoms by means of orbital configurations. Thus we write atomic electron configurations such as

\[ Ls^1 Ls^2 \]

or

\[ C: 1s^2 2p^3 \]

is actually a mathematical approximation which treats each electron separately. In lithium two electrons have functions associated with them which are of the 1s shape and one with 2s form.

An orbital is thus merely a synonym for a one-electron wave function. Each is a three-dimensional mathematical function which describes the behaviour of a single electron.

Generalizing this, with some formal notations, we may write for a polyatomic atomic system, the total wave function for an atom, \( \psi \), is a product of one-electron atomic wave functions \( \phi \), one for each electron, i.e.

\[ \psi = \phi_1 \phi_2 \phi_3 \cdots \phi_n \]

2.3 Spin-orbitals and antisymmetry

When we write the electronic structure of beryllium as \( 1s^2 2s^2 \) we understand this as being a shorted form of

\[ 1s^1 1s^1 1s^2 \]

where \( 1s \) and \( 1s \) represent the opposite directions of electron spin.

If we include the spin in our atomic orbitals writing either \( \psi \) or \( \phi \) as the equivalent shorthand, \( \frac{1}{2} \) for an orbital associated with \( \uparrow \) spin and \( \frac{1}{2} \) for one with \( \downarrow \) spin, then our wave function for the whole atom is a product of spin-orbitals, for example:

He: 1s(\( \uparrow \)) 1s(\( \downarrow \)),

and

Be: 1s(\( \uparrow \)) 1s(\( \downarrow \)) 2s(\( \uparrow \)) 2s(\( \downarrow \)).

In this expanded form of the common shorthand the numbers in parentheses indicate which electron is associated with each spin-orbital.

The expanded form of the notation enables us to see that we will need to make things a little more complicated before simplifying since more by means of a convenient notation.

Let us consider the case of the helium atom. If we write

\[ \psi_\sigma^\alpha = \frac{1}{\sqrt{2}}(\psi_\uparrow \uparrow + \psi_\downarrow \downarrow) \]

or alternatively and equivalently

\[ \psi_\sigma^\alpha = \psi_\uparrow(\uparrow \downarrow + \downarrow \uparrow) \]

we can see that we are not satisfying the Pauli principle. In its fundamental form this states that the wave functions for the system \( \psi \) must change sign if we interchange any pair of electrons, since electrons are identical fermion particles.

We have written our wave function as a simple product of orbitals when this is not sufficient, since

\[ \psi = \psi_\uparrow(\uparrow \downarrow + \downarrow \uparrow) \]

but on changing we get

\[ \psi = \psi_\uparrow(\uparrow \downarrow + \downarrow \uparrow) \]

and \( \psi \) is not the negative of \( \psi \).

To overcome this we can write the wave function for the atom in the orbital approximation as

\[ \psi = \frac{1}{\sqrt{2}}(\psi_\uparrow(\uparrow \downarrow - \downarrow \uparrow) - \psi_\downarrow(\downarrow \uparrow - \uparrow \downarrow)) \]

Now if we make the interchange, Pauli's principle will be satisfied and the \( \langle \psi | \psi \rangle \) remains the normalizing condition, \( \psi | \psi \rangle = 1 \). Conventionally we write a volume element in three dimensions as \( dV \), but if spins are also included the element is written as \( d\Omega \).

For beryllium, however, we must allow for any possible interchanges between four electrons so then

\[ \psi = \psi_\uparrow(\uparrow \downarrow(2) (2) 2(4)) - \psi_\downarrow(\downarrow \uparrow(2) (2) 2(4)) + 2 \psi_\uparrow(\uparrow \downarrow(2) (2) 2(4)) - \psi_\downarrow(\downarrow \uparrow(2) (2) 2(4)) + \ldots \]

in all 24 such products.

Fortunately notation can help us. All these products are simply the expanded form of determinants. For He

\[ Ls(\uparrow \downarrow(2) - \downarrow \uparrow(2)) \]
is the expansion of
\[ \psi = c_1 \psi_1 + c_2 \psi_2 \]
which is certainly shorter. But for \(|\psi\rangle\) we now expand above can be summarized as
\[ \psi = \frac{1}{\sqrt{2}} (\psi_1 + \psi_2) \]
Since the diagonal of these determinants are sufficient to define them and because the value of the normalization constant is obvious (\(\pi^{-n/2}\) where \(n\) is the number of electrons), these expanded spin-orbital wave functions are usually written as simple products
\[ \psi_{2n} = 1/\sqrt{2} \text{ or even } \psi_{2n} = 1/2 \]
\[ \psi_{3n} = 1/\sqrt{2} \]
\[ \psi_{3n+1} = 1 \]

The fact that these expressions are shorthand notation for determinantal wave functions is hidden in this notation.

When we want the wave function of an atom, \(\psi\), we write it in the form
\[ \psi = \psi_1 \psi_2 \ldots \psi_n \]
remembering that this is not a simple product.

The problem then becomes one of finding \(\psi_i\) etc. Each of these is a one-electron function in coordinates \(r, \theta\) and \(\phi\) multiplied by a spin factor \(a\) or \(b\).

The individual \(\psi_i\) can be taken as being hydrogen-like analytical functions but with different exponents appropriate to the particular atom or alternatively expressed (in any function can be) as a numerical value for each point defined by the three coordinates. This latter type of atomic orbital is called a numerical function.

Hartree produced some extremely accurate atomic functions of this numerical type which were later fitted to analytic forms by Slater and are called Slater atomic wave functions. They have the form
\[ \psi_i = \text{Normalization constant} \times (\text{exponential function of } r) \times (\text{spherical harmonic in terms of } \theta \text{ and } \phi) \]

The spherical harmonic is identical to the angular variation found for hydrogen atom wave functions and the differences from atom to atom are found only in the \(r\)-dependent, or radial, part of the orbital. The quality of a wave function may be tested by using it to compute the energy of the system and using the well-known variation principle which states that the better the wave function the lower will be the resulting energy.

The atomic orbitals, \(\psi_i\), for all atoms encountered in chemical systems are well known and need only be taken from the literature.

A useful property of orbital functions of a given atom is that they may be made orthogonal. This means
\[ \int \psi_i \psi_j^* = \delta_{ij} \]

integrating over space and spin coordinates, but
\[ \int \psi_i \psi_j = 0 \text{ if } i \neq j \]

Generally we use wave functions which are normalized but not orthogonal, i.e.
\[ \int \psi_i \psi_j^* = \delta_{ij} \]
This is the definition of the overlap integral \(S_{ij}\).

2.4 Molecular orbitals

The wave function for a molecule is not in principle any different from that for an atom. We may use the symbol \(\Psi\) to represent the molecular wave functions and, as in the atomic case, we can make the orbital approximation,
\[ \Psi = \psi_1 \psi_2 \psi_3 \ldots \psi_n \]
where each function \(\psi_i\) will be a three-dimensional function which determines the properties of an individual electron in the molecule. We may include spin so that the wave function is a product of spin orbitals. We must also remember that the wave function has to be antisymmetric with respect to electron interchange, or reordering the electrons, with the result that the product as written represents the diagonal of a determinant.

The goal of most quantum molecular calculations is the production of a molecular wave function \(\Psi\). This will be achieved if we know all the constituent molecular orbitals \(\psi_i\). In most of the methods currently applied to molecular questions the problem is broken down one stage further: We expand each of the unknown molecular orbitals as a linear combination of the known atomic orbitals.

Thus
\[ \psi = \sum_i c_i \psi_i \]

Each of the \(c_i\) will be the function of the form
\[ c_i = \text{Constant} \times \text{(function of } r) \times (\text{spherical harmonic function in terms of } \theta \text{ and } \phi) \]
Here \( \mu \) is an index which labels the particular molecular orbital and \( k \) is a running index \( 1, 2, 3, \ldots \) whose range will depend on just how big an expansion is taken. Our problem in finding the wave function for the molecule, which means calculating the molecular orbitals \( \psi \), now reduces to finding the expansion coefficients \( c_k \).

For the simple case of a diatomic molecule like \( \text{Li}_2 \), this process can be illustrated pictorially by means of a molecular orbital diagram (Fig. 2.4), in which we represent each molecular orbital as a sum of two lithium atomic orbitals. The molecular orbitals are labelled \( \phi_1 \), \( \phi_2 \), and \( \phi_3 \) for reasons of symmetry.

The molecular wave function for the ground state of \( \text{Li}_2 \), where the lowest (most tightly bound) molecular orbitals are each doubly filled will thus be

\[
\Psi(\text{Li}_2, \text{ground state}) = c_1 \phi_1 \phi_2 + c_2 \phi_1 \phi_3 + c_3 \phi_2 \phi_3
\]

with

\[
\begin{align*}
\psi_{2g} &= c_1 \phi_1 \phi_2 + c_2 \phi_1 \phi_3 + c_3 \phi_2 \phi_3 \\
\psi_{1u} &= c_1 \phi_1 \phi_2 + c_2 \phi_1 \phi_3 + c_3 \phi_2 \phi_3 \\
\phi_1 &= \phi(2s) \\
\phi_2 &= \phi(1s) \text{ by symmetry} \\
\phi_3 &= \phi(2p_z) \\
c_1 &= c_2 \\
c_3 &= c_3
\end{align*}
\]

The use of symmetry is convenient in small symmetrical molecules but plays very little part in molecules of biological interest which only rarely have symmetry.

As an important principle in quantum mechanics, the variation principle, states that the more flexible the wave function the lower the energy and by implication the better the wave function. Zero on the energy scale has all particles separated at infinity. Calculated energies are thus negative numbers, the bigger the number the lower the energy.

In the \( \text{Li}_2 \) example we can get a 'better' or 'lower' energy by using a more flexible wave function, perhaps extending our molecular orbital expansion

\[
\Psi(\text{Li}_2, \text{expanded}) = \phi_{2g} + \phi_{1u} + \phi_{3u}
\]

However lengthy our expansion the problem will remain the same: to obtain the molecular wave function, \( \Psi \), we find the molecular orbital \( \phi \) in terms of known functions multiplied by coefficients which have to be determined. This is done by the solution of the secular equations.

2.5 Secular equations

We have met the shorthand form of the Schrödinger equation

\[
\hbar \nabla \phi = \xi \phi
\]

A similar equation may be written for each of the molecular orbitals

\[
\hbar \nabla \phi_k = \xi_k \phi_k
\]

but now \( \hbar \) is a one-electron hamiltonian, whose specific nature we will discuss later, and \( \xi_k \) is the orbital energy or energy of one particular electron in orbital \( k \). However we have seen that \( \phi \) may be expanded as a linear combination of known atomic orbitals. Hence the one-electron equations may be rewritten as

\[
\hbar \sum_j \phi_j \nabla \phi_k = \xi_k \phi_k
\]

Now we may multiply each side of the equation by \( \phi^* \) (any one of the normalized set which includes \( \phi_k \) and integrate all over the electronic space coordinates \( \phi^* \), giving the secular equations

\[
\sum_k \left( \frac{\sum_j \phi_j \phi_j^* \partial}{\partial \phi_k^*} \right) = \xi_k \sum_k \left( \frac{\sum_j \phi_j \phi_j^* \partial}{\partial \phi_k^*} \right)
\]

Conventional notation writes

\[
H_k = \sum_j \phi_j \phi_j^* \partial
\]

and

\[
S_k = \sum_j \phi_j \phi_j^*
\]

By this means the equation may be tidied up into the form

\[
S_k (H_k - \xi_k S_k) = 0
\]

Such a set of equations will only have a non-trivial solution if the following conditions hold

\[
\det (H_k - \xi_k S_k) = 0
\]

This simple determinantal equation is the basis of all molecular orbital methods. In general the methods go directly to the secular determinants. All the terms (or matrix elements) \( H_k \) and \( S_k \) are computable. If the determinants were multiplied out this would yield a polynomial in \( \xi \), solutions of which would give the allowed molecular eigenenergies or orbital energies. Each \( \xi \) in turn is then put into the secular equations and hence the desired coefficients are found.
Example

Let us consider a rather formal example which will illustrate the principles involved in calculating molecular orbital coefficients and is closely related to some genuine applications.

Suppose we are expanding the molecular orbitals in terms of three atomic orbitals:

\[ \Phi_i = c_{i1} \phi_1 + c_{i2} \phi_2 + c_{i3} \phi_3 \]

The one-electron equation is

\[ H\Phi = \epsilon \Phi \]

so that we have three such equations and can determine three molecular orbitals. We now multiply both sides of the equation successively by \( \phi_1 \), \( \phi_2 \), and \( \phi_3 \) and integrat, giving three secular equations

\[
\begin{align*}
&c_{11} (\epsilon_1 - \epsilon_{12}) + c_{12} (\epsilon_1 - \epsilon_{13}) + c_{13} (\epsilon_1 - \epsilon_{13}) = 0 \\
&c_{21} (\epsilon_2 - \epsilon_{12}) + c_{22} (\epsilon_2 - \epsilon_{23}) + c_{23} (\epsilon_2 - \epsilon_{23}) = 0 \\
&c_{31} (\epsilon_3 - \epsilon_{13}) + c_{32} (\epsilon_3 - \epsilon_{23}) + c_{33} (\epsilon_3 - \epsilon_{23}) = 0
\end{align*}
\]

For solution we must solve the determinant equation

\[
\begin{vmatrix}
\epsilon_1 - \epsilon_{12} & c_{12} & c_{13} \\
\epsilon_2 - \epsilon_{12} & \epsilon_2 - \epsilon_{23} & c_{23} \\
\epsilon_3 - \epsilon_{13} & \epsilon_3 - \epsilon_{23} & \epsilon_3 - \epsilon_{23}
\end{vmatrix} = 0
\]

In this case we have a cubic equation in \( \epsilon_1 \) which has three roots.

Since most usually our expansions go well beyond three terms a more convenient method of solution of the determinant equation is employed which makes use of the strength of computers.

Rows and columns of determinants may be added and subtracted or factors divided out without altering the value of the determinant. If by such adjustments we could rearrange the determinant into the form

\[
\begin{vmatrix}
1 & x & y \\
0 & 1 & z \\
0 & 0 & 1
\end{vmatrix} = 0
\]

where \( x, y, \) and \( z \) are numbers and all the rest of the determinant is zero, on multiplying out we should have the simple equation

\[ (x - c_{12})(y - c_{13}) = 0 \]

Computational methods for doing this or easily equivalent simplifications are standard procedures. As a result there is no difficulty in solving the determinant equation and hence finding the molecular orbital coefficients, no matter how extensive the expansion. The actual computer programs are

naturally based on various diagonalization techniques which are equivalent to the above description, but particularly suitable for computers.

2.6 Matrix elements

Going directly to the secular determinant and hence to the secular equations to obtain molecular orbitals poses no serious problem providing all the matrix elements \( H_{ij} \) and \( S_{ij} \) are easily found.

The matrix elements \( S_{ij} \) are called overlap integrals as \( H_{ij} \) represent the overlap between the two three-dimensional functions \( \phi_i \) and \( \phi_j \)

\[
S_{ij} = \int \phi_i \phi_j \, d\tau
\]

These integrals are reasonably easy to evaluate and again standard computer programs are available.

The matrix elements \( H_{ij} \) or

\[
\int \phi_i \phi_j \, d\tau
\]

on the other hand include the one-electron operators. So far the precise nature of \( H \) has not been specified and it is in the definition, or lack of it, that most of the molecular orbital methods differ. In the more sophisticated methods \( H \) is precisely defined. In the less precise approximations it is never defined and all \( H_{ij} \) matrix elements are replaced by parameters.

2.7 Self-consistent molecular orbitals

The most clearly defined molecular orbital calculations are based on the Hartree-Fock method. A Hartree-Fock operator contains terms for the kinetic and potential energy of the system. A suitable choice of units makes the equations look rather simpler than standard units. If we choose to take the electronic charge, \( e \), and mass, \( m \), each as unity and the unit of length as the Bohr radius then the Schrödinger equation for the hydrogen atom becomes

\[
-\frac{1}{2} \frac{\partial^2 \Psi}{\partial r^2} - \frac{1}{r} \Psi = \epsilon \Psi
\]

where the kinetic energy is represented by the \(-1/2m \partial^2 / \partial r^2 \) term (\( \Psi \) is shorthand for \( d^2 \phi / d\rho^2 + d^2 \phi / dr\rho d\rho \)) and potential energy by the electron-nuclear attraction, \(-1/4\).

For the hydrogen molecule there are two electrons and the Schrödinger equation for the molecular wave function \( \Psi \) is

\[
-\frac{1}{2} \left( \frac{\partial^2 \Psi}{\partial r^1} + \frac{\partial^2 \Psi}{\partial r^2} \right) - \frac{1}{2} \frac{1}{r_1} - \frac{1}{r_2} - \frac{1}{2} \frac{1}{r_1} \frac{1}{r_2} \Psi = \epsilon \Psi
\]

To this electronic energy \( E_e \) has to be added the nuclear-nuclear repulsion, \( E_{\text{nn}} = 1.6 \), where \( R \) is the separation of the nuclei A and B.
It may be seen that this equation is a sum of two separate hydrogen molecule ion wave functions with the additional term, $\lambda$, representing the repulsion between the two electrons. When we come to one-electron equations we want to include in the Hamiltonian terms for all the energy contributions of that one electron. These will be kinetic energy, nuclear attraction and electron-electron repulsion. The kinetic energy term in the operator is $-1/2 \nabla^2 \rho$ and the various nuclear attraction terms are:

$$\sum Z_i \frac{1}{r_i}$$

where the nuclei are labelled by $i$ and the particular electron we are considering is $\psi$. These two parts can be grouped together and designated as $H^N$. If there were no other electrons in the molecule this would be a sufficient Hamiltonian and the one-electron energy would be the full molecular electronic energy which we could call $\Phi$. When, as is usually the case, there are many electrons in the molecule a major part of the potential energy which must be represented in the Hamiltonian is electron-electron repulsion. Now if we have two electrons with orbitals $\Phi_1$ and $\Phi_2$ separated by a distance $r_{12}$, then the repulsion between them is given by

$$\int \Phi_1(1) \frac{1}{r_{12}} \Phi_2(2) \, dv_1 \, dv_2$$

since

$$\int \Phi(1) \, dv = 1$$

is the charge distribution of electron (1) (assuming $\Phi$ is real). If $\Phi$ is complex this should be replaced by

$$\int \Phi(1) \Phi^*(2) \, dv_1 \, dv_2$$

The expression

$$\int \Phi_2(2) \, dv_2$$

is the charge distribution for electron (2). Thus we must include terms of this type in the one-electron Hamiltonian, suggesting that an expanded form of

$$\hat{H} = \hat{H}^N + \hat{R}$$

might be

$$\hat{H} = \hat{H}^N + \hat{R} = -\frac{1}{2} \nabla^2 \rho + \sum Z_i \frac{1}{r_i} + \int \Phi(1) \frac{1}{r_{12}} \Phi(2) \, dv_1 \, dv_2$$

This equation due to Hartree would be correct if our orbital wave function were a simple product and not a determinant. To account for the dimensional form of $\Phi$ we use full self-consistent field equations or Hartree-Fock equations are

$$\hat{H}^N \Phi_i = \epsilon_i \Phi_i$$

when

$$\Phi^N = \left( \hat{H}^N + \sum Z_i \frac{1}{r_i} \right) \Phi_i$$

and the shorthand notation used is defined by

$$\int \Phi(1) \frac{1}{r_{12}} \Phi(2) \, dv_1 \, dv_2$$

with a prime on a summation indicating summing only over pairs of electrons of the same spin. The Hartree-Fock equations contain the $\epsilon_i$ as exchange terms in addition to the obvious Coulombic interactions interactions allowed for in the Hartree equations. These exchange terms arise as a result of the Pauli principle which leads to determinantal wave functions rather than products and exchange integrals between various cross-products of the expanded determinant. This specification of $H$ in the one-electron equation leads to a lot of terms, but that is not a particularly difficult problem if we are using a computer. More seriously the hamiltonian in $\hat{H} = \hat{H}^N + \hat{R}$ must contain the various $\Phi_i$ which we are trying to determine. That is to say the coefficients in

$$\Phi_i = \sum \frac{1}{\epsilon_i} \Phi_j$$

must be known before we start. This is the origin of the term 'self-consistent' field. Starting values of $\epsilon_i$ are given from educated guesses or from the results of simple calculations. The determinant equation

$$\det \left[ \Phi_i^N - \epsilon_i^N \Phi_i \right] = 0$$

is solved after calculating all the integrals involved in $\hat{H}_N$ and $\hat{S}_\Phi$. Solution yields values of $\epsilon$ which are substituted in the secular equations to give new values of the various $\epsilon_i$. The process may then be repeated until the $\epsilon_i$ resulting from one cycle are identical within prescribed limits with those used in the previous cycle. The results are then self-consistent. The various simplified methods of calculating molecular orbitals are essentially approximations of a greater or lesser degree which result in a reduction of the number of integrals necessary to build the matrix elements $\hat{H}_N$ and $\hat{S}_\Phi$ in the determinant equation.
2.8 Configuration interaction

We have already met the variation principle which tells us that the more flexible a wave function the better it will be in terms of the energy which results. One way of improving the wave functions which we have as a result of self-consistent field or approximate calculation is to allow the interaction of configurations.

Formally this means allowing a further linear mixing \( \Psi \) of given improved wave functions,

\[
\Psi_{\text{expanded}} = \Psi_1 + c_2 \Psi_2 + \ldots
\]

In this expression, \( \Psi \) is the wave function we first find and \( \Psi_1, \Psi_2, \ldots \) are wave functions which would be appropriate for excited configurations of the same symmetry. The coefficients \( c_2, \ldots \) are mixing coefficients whose values are chosen so that the energy improvement is maximized.

The problem with configuration interaction is knowing when to stop. Every extra configuration brings the energy a little. Although configurations closest in energy to the ground state may have an obvious influence, others which are highly excited may also be significant.

In many molecular orbital packages the effects of excited states are incorporated using perturbation theory as introduced by Muller and Plesset.

2.9 Ab initio methods

All molecular wave functions are approximate; some are just more approximate than others. We can solve the Schrödinger equation exactly for the hydrogen atom but not even, despite what many textbooks say, for the hydrogen molecule ion, H\(_2^+\). For H\(_2^+\) we raise the Born-Oppenheimer approximation which separates electronic and nuclear motion, and calculate the electronic energy of the ion with a given fixed internuclear distance and then obtain the total energy by adding the nuclear-nuclear repulsion term.

The term ab initio is perhaps unfortunate since it gives a spurious idea of quality, but it is universally used for calculations of orbital wave functions where the full Hartree-Fock self-consistent field operator is used in the form

\[
0 = \left( \hat{H} - \mathcal{E}_0 \right) \Psi = 0
\]

and all the integrals implied in \( \hat{H} \) and \( \mathcal{E}_0 \) are computed.

Each molecular orbital will be the form

\[
\psi_i = \sum \sqrt{\alpha} \phi_i
\]

If the expansion is infinite then we would achieve the most flexible wave function within the constraints of the self consistent field behaviour which we have defined. The resulting \( \mathcal{E}_0 \) would be the 'best' or biggest negative number we could obtain and is the Hartree-Fock limiting energy. In practice, if an expansion of thirty or forty terms is used for \( \mathcal{E}_0 \), then little improvement in \( \mathcal{E}_0 \) or energy results and we can safely assume that we are close to the limit.

The larger the expansion in terms of atomic orbitals, the more integrals have to be computed and the more expensive computer time required. Thus for large molecules rather short expansions are used so that the resulting energy may be far from the best possible limit, and the wave function even though of ab initio origin is approximate even within the constraints of the method.

The most obvious set of atomic orbitals, \( \zeta_i \), to use in the expansion are Slater-type atomic orbitals which were found by fitting analytical exponential functions to numerical atomic wave functions. If we use one such function for each atomic orbital which is filled, e.g. for C employing 1s, 2s and 2p atomic orbitals, then the set of atomic functions or basis set is referred to as a minimal basis. If we use double that number, the basis set is of double-zeta quality. Each of the atomic orbitals is of the form

\[
\psi_i = C_i \zeta_i
\]

Here \( C \) is a normalizing constant; \( \zeta_i \) is the angular part of the function (a spherical harmonic) and \( \zeta_i \) is the orbital exponent, \( \zeta \). The \( C_i \) are well known for 1s, 2s, 2p etc., so that a basis set may be specified by listing the exponents for each type of orbital used. Suitable basis sets are available in the literature.

To overcome some of the problems in doing integrals with exponential or Slater-type wave functions, the more tractable gaussian form of basis set dependence is often employed. The gaussian radial dependence has the less appropriate exp(-r) form. To combine the suitability of exponential basis functions and the simplicity of calculating with gaussian, the obvious step of fitting gaussian shapes to an exponential has been taken. Thus one frequently sees in the literature expressions such as 'calculations performed with an STO-3G basis'. This indicates that a minimal basis set of Slater exponents has been used but for the integrals each exponential function was fitted by three gaussian functions. An STO-4G calculation is likely to be closer to a true minimal basis calculation but even that would be some way from the limit of the method in terms of energy.

When running an ab initio calculation the starting point is a particular molecular geometry, the names and coordinates of each atom being defined. Depending on which atoms are in the molecule a basis set of atomic orbitals is then decided upon. Although the choice may be built into the computer program, the program will then compute all the integrals required in building up \( \mathcal{H} \) and \( \mathcal{E}_0 \) using generic trial coefficients, build and diagonalize the determinant and produce a set of orbital energies and first-improved coefficients. As described earlier this process is repeated until self-consistency is achieved, when the program will print out a set of molecular orbitals \( \psi_i \) in the form of the coefficients, and associated with each an orbital energy \( \mathcal{E}_0 \).
It is important to realize that even if we can afford to have long expansions of molecular orbitals and even reach the Hartree-Fock limit, there are still defects in the wave functions which arise from approximations in the actual Hartree-Fock equations. There are two sources of error in the starting equations. The first comes about because the whole theory is based on the Schrödinger equation which is an inherently correct function. Fast-moving electron waves may move with speeds which are not negligibly by comparison with the velocity of light and relativistic effects thus contribute; mass is not constant. Since most chemical and biological transformations of molecules do not involve core electrons this error is normally a constant and causes no serious difficulty. The second error is more serious and is called the correlation energy error.

2.10 Correlation energy

Any defect in our wave functions will result in the calculated energy being less than the true energy. The correlation energy can be defined as:

\[ E_{corr} = E_{HF} - E_{exact} \]

and represents the remaining energy error between the limiting Hartree-Fock energy and true total energy taking into account the relativistic effect. Correlation energy errors arise because of an unquipped approximation in the self-consistent field Hamiltonian. We write as

\[ \mu = \left( \epsilon_0 + \sum_{i=1}^{n} \left( L_i - \sum_{j=1}^{n} K_{ij} \right) \right) \]

\[ \text{involved in } J \text{ and } K \text{ are terms of the type} \]

\[ \int |\phi|^2 \frac{\partial^2 |\phi|^2}{\partial \phi^2} \]

These are included to account for the interaction of one electron with another, the second electron being represented as a smeared-out averaged electron density. Thus if we are considering the helium atom, each of the 1s electrons, as far as the calculation is concerned, would interact with the other 1s electron as if the second electron was spherically distributed. In reality, of course, the two electrons will have their positions correlated, there being a higher probability of the two electrons being on opposite sides of the nucleus than there is of them being both on the same side, as self-consistent field theory allows.

The correlation energy error results from electron pair effects and is reasonably constant as molecular geometry changes provided the electron pairings in the molecule do not change. It is not a constant as bonds are stretched to the point of dissociation (Fig. 2.3). Corr are then quite active in calculations of dissociation energies, and also in the estimations of ionization potentials or even eV values. On the other hand, if we merely change configuration and leave the electron pairing essentially untouched, then the error may be constant (Fig. 2.4).

2.11 Semi-empirical calculations

All ab initio calculations are themselves not always perfectly successful in reproducing experimental observations. In addition the number of integrals required increases roughly as the fourth power of the number of basis functions in the molecule and for even quite small molecules many millions may be required. In consequence, a great deal of effort has been expended devising so-called semi-empirical molecular orbital methods. These are not governed by the deterministic equation but make a variety of approximations to reduce the amount of computer time required.

All the commonly used techniques are molecular electronic calculations, that is they predict the electrons since these play little part in chemical or molecular behaviour. The 1s electrons are defined as part of the "core" for first-row atoms and both K and L shell electrons for heavier atoms. The self-consistent field Hamiltonian thus becomes:

\[ H = E_0 + \sum_{i=1}^{n} L_i - \sum_{j=1}^{n} K_{ij} \]

and denominates incorporates kinetic energy and attraction to a core rather than to a bare nucleus. Integrals (or symmetry matrix elements) involving \( E_0 \) are usually replaced by empirical or calculated parameters. Particularly in instances where molecules of interest contain a heavy atom (such as a metal in an enzyme-binding site) an approximation at this level is introduced by incorporating a pseudopotential or effective potential into the Hamiltonian. The resulting computed properties are not significantly different from those of full ab initio calculations in the cases of electron density or orbital energies. Savings of computer time by 50% or more are however common.

There are two broad philosophies about the use of parameters in molecular orbital calculations. One school of thought takes the view that ab initio calculations themselves are far from perfect, empirical parameters should be introduced as an escape agreement with experience. In some ill-defined way this means that the parameterization includes correlation effects. Unfortunately correlation energy cannot be treated in this simple way as a universal function. Thus in so far as the parameterization is related to experimental data which are closely related to those which one is trying to calculate, then this approach works perfectly. In the latter, of course, if you put some experimental data into the calculation you should get very little at all able to get them out again. Generally semi-empirical methods using this philosophy give good agreement with experiment providing the experiment and the nature of parameterization are related.

Alternatively there are methods which use parameters based on ab initio calculations and attempt to reproduce what a more costly rigorous calculation would have produced. This approach has the advantage of being easily defined and is not essentially based on its parameterization towards any type of experiment or another. On the other hand the results can never be better than ab initio calculations.

The actual choice of method to be used in any research project will depend on the computer time available, the number of calculations required.
and above all on the agreement of test calculations of properties which are related to the problem with physical measurements.

2.12 Neglect of differential overlap

The matrix elements $R_{ij}$ in the secular determinant involve a large number of integrals over atomic orbital functions $\chi$ of the type

$$\int \chi_{i}(\mathbf{r}) \chi_{j}(\mathbf{r}) \chi_{i}(\mathbf{r}) \chi_{j}(\mathbf{r}) \, d\mathbf{r}$$

which are often written in the shorthand form (mibj). These integrals are particularly difficult to evaluate if the atomic functions, $\chi_{i}$, etc., are centered on different atoms. In particular these integrals involving three or four centres are time consuming, perhaps prohibitively so, even using a computer. An approximation which will surmount this problem as a strike is to assume

$$\langle mibj \rangle = R_{ij} \delta_{mibj}$$

with $R_{ij}$ and $\delta_{mibj}$ being Kramersdenes which are equal to zero unless the subscripts are equal. In this way, neglecting differential overlap of functions based on different centers, we eliminate not only all three-center and four-center integrals but most two-center integrals where different atomic orbitals are involved in either of the two electrons.

The study of ab initio results where these neglected integrals are computed confirms that they are significantly smaller than the integrals which remain but they may be by no means negligible. Consequently further approximations and parameterizations are normally added to counteract the omission.

In the CNOO, or complete neglect of differential overlap method, this approximation is fully applied for the valence electrons with 1s electron being treated as part of a nuclear "core". Integrals which remain are further approximated. The electron repulsion integral (mibj) is supposed to depend only on the atoms A and B on which $\chi_{i}$ and $\chi_{j}$, are centered and are equal to the parameter $R_{ij}$ which may be found from an actual calculation for a simple example such as (2s2p2s2p2s2p) or by the use of empirical data. Matrix elements of $R_{ij}$ are also parameterized and in particular, atomic ionization potentials are frequently used to replace integrals which approximately represent the energy with which an electron is held by an atom. There are a number of alternative parameterizations, details of which can be found in the references.

Slightly less dramatic in the application of the neglect of differential overlap are intermediate neglect of differential overlap (INDO) schemes. These contain a defect in CNOO which results in there being no distinction between single and triplet electronic states. There are respectively two electrons paired in one case and of parallel spins in the other. Their energy difference is related to an exchange integral, $K$. Integrals of the form (mnib) are not now neglected if $\delta_{mibj}$ and $R_{ij}$ are centered on the same atom.

In the form of INDO used by Pople and co-workers the philosophy of keeping close to ab initio calculations is favoured. The more empirical line is followed by Dewar whose variant is given the acronym MNDO. The most important parameterizations of the latter, AMI and PM3, do give very satisfactory results when compared with a range of experimental observables.

2.13 Calculated energy properties

Every physical observable associated with it a quantum mechanical operator, $\hat{O}$. The value of an observable or eigen-value, $\hat{a}$, can in principle be found by using the eigenvalue equation in which the operator operates on the wave function appropriate to the state and condition of the molecule in which we are interested,

$$\hat{O}\psi = E\psi$$

Mean values of $a$ may be extracted from such equations using the formula

$$\langle a \rangle = \frac{\langle \hat{a} \psi \rangle}{\langle \psi \psi \rangle}$$

In the natural and powerful formulation of Dirac this equation is written in the form

$$\langle a \rangle = \frac{\langle \psi \hat{a} \psi \rangle}{\langle \psi \psi \rangle}$$

In fact, apart from the case of energy, $\hat{O}$ is the Hamiltonian operator, $H$, this pure approach is rarely used and calculated properties are generally based on the orbital energies $\varepsilon_{i}$ and the expansion coefficients of the molecular orbitals in terms of atomic orbitals, $c_{i}$. Molecular energies are particularly important as so many other properties may be inferred from a study of the variation of energy with some molecular parameter such as bond length or angle.

A calculation is run for a particular defined geometrical arrangement of the constituent atoms yielding molecular orbitals and their orbital energies. From these we calculate the electronic energy, $E_{e}$. To this must be added the nuclear-nuclear repulsion terms

$$\sum_{i} Z_{i}^{2} \alpha_{i}/R_{ij}$$

where $Z_{i}$ and $Z_{j}$ are the charges on the nuclei $\mu$ and $\nu$, and $R_{ij}$ their separation. The total energy $E_{total}$ is thus a smaller negative number than $E_{e}$.

The electronic energy, $E_{e}$, can be expressed in terms of integrals involving the molecular orbitals, $\psi_{i}$

$$E_{e} = \sum_{i} \varepsilon_{i} c_{i}^{2} - \sum_{i} \sum_{j} K_{ij} c_{i} c_{j}$$
Molecular geometries are more often used to confirm the validity of calculations than calculations are used to determine geometries, since there is as abundance of experimental techniques available for investigating molecular geometry. The principles may, however, be carried over to determine other molecular energy variations which are less amenable to experiment.

One such example is the case of vibration frequencies. The energy of a molecule may be calculated as a function of stretching a bond or bending as angle. If the resulting potential curve is then fitted to a suitable expression (even a simple quadratic expansion will do in many cases) then rough estimates of vibration frequencies may be obtained. Such quantities are on the other hand more of interest to spectroscopists than to medicinal chemists.

An important aspect of the calculation of accurate geometries for small molecules is the current interest in optimising programs. Such programs calculate an ab initio molecular wave function and then optimize the geometry using the gradient of the energy with respect to the 3N nuclear coordinates (N being the number of atoms).

**Conformation**

The molecular energy property which is of most interest to researchers interested in small biologically active molecules is conformation. Quantum mechanical calculations may be answered with the aid of molecular models, but these leave open a whole range of conformations because of free rotation about single bonds.

Experimental techniques such as crystallography and nuclear magnetic resonance spectroscopy cannot give more than a small portion of the whole conformational picture.

Quantum mechanical calculations may reveal conformation exactly like geometry. A calculation is performed for a series of positions of one part of a molecule with respect to another and the energies for each position compared. If there is only one bond about which rotation can occur then the results may be presented in the form of a curve of energy against angle (Fig. 2.7). For biological species it is frequently the case (e.g. norepinephrine, histamine, epinephrine) that two rotational angles are required to specify conformations. In this case it is sensible to present the required three-dimensional diagram (energy, torsion angles t1 and t2) as contour diagrams as in Fig. 2.8. On these maps, minima indicate stable conformational structures with the relative depths being indicative of relative stability or enthalpy. The maps also give the heights and shapes of barriers between conformational isomers from which it is possible to calculate rates of interchange.

As with geometries, the normal computational practice is to start with the bond lengths and angles fixed from the molecule in the crystal structure and then in this fashion to do calculations, optimising both the bond set and the geometry for each point on the potential surface. Thus, in a calculation on the conformation
of either one would allow for the fact that in eclipsed conformations the H-C-H angles would differ from those in a staggered conformation.

Conformational free energies:

The advent of conformational energy maps, largely owing to increasingly rapid molecular orbital calculations, underlines an obvious point of them—quantum chemistry is often ignored. If there are several minima on a surface then the relative populations depend upon free energy differences and not just the calculated energy differences which are internal energies. Energy effects will frequently be two orders of magnitude. The relative populations of two dihedral angles in a potential surface will depend heavily on how difficult it is to get out of a valley and the ease with which molecules can enter the bowl unless you vary widths.

In Fig. 2.8 the case of a wide shallow depression and a narrow deep one are contrasted for both the one-dimensional and two-dimensional conformational diagrams. In both cases the populations of molecules with the conformation labeled A with a broad shallow depression of the surface might be more abundant than the internal energy favored B with a deep narrow hole in the potential surface but with a low probability.

The diagrams also highlight a semantic difficulty in deciding just what area of the map can be referred to as ‘conformation’ A or B. The boundaries are essentially arbitrary. This point is of relevance to experimental work as well as theoretical calculations since it would remain true even with perfect, real potential surfaces. For this reason many published solution conformation population ratios derived from NMR coupling constant measurements are not very accurate numbers.

If we use some statistical ideas it is possible to compute conformational free energies from the energy maps and hence partition equilibrium constants. It is reasonable to assume that altering conformation has only a minimal effect on volume so that the maps may be considered as entropic, sd, surfaces, Md being equal to Md a PAS for each region which we define as a conformation, a Boltzmann partition function may be calculated. The partition function F is a number which indicates how the molecules are spread amongst available energy levels. For the single angle case this would be defined as

\[ Z_{\text{conformation}} = \sum \exp[-E_l(T)/kT] \]

and in the two variable angle instance

\[ Z_{\text{conformation}} = \sum \exp[-E_l(T, \tau)/kT] \]

where \( E_l \) or \( E_l(T, \tau) \) is the calculated energy for a conformation defined by \( \tau \) or \( \tau, \tau \), \( k \) is the Boltzmann constant, and \( T \) is the temperature (normal 37°C). The summations have to be taken over a regular grid of points, four enough to reflect the shape of the surface appropriate for a given conformation. Effectively we are using a numerical form of integration, assuming that the statistical energy levels are very close together. The appropriate portion of the surface can be defined by taking a local minimum point and defining as a conformer all space within a contour set at \( 2kT \) above the minimum.

\[ Z_{\text{conformation}} = \exp(-E_l(T)/kT) \]

There is a further important application of the use of conformational partition functions which is of particular value when we wish to compare the conformational flexibility of a series of similar molecules. We may be interested in knowing for a series of similar, conformationally flexible, compounds, just how flexible they are and what range of conformations is likely at body temperature for each molecule.

This information is contained in the potential energy map but there is too much detail that comparisons are far from obvious. As in computing free energies we can associate with each point on the energy surface a probability

\[ Z = \exp[-E_l(T, \tau)/kT] \]

The probability function can then be integrated numerically over the total surface using Savage’s rule to yield \( Z \) and normalizing by comparing the points using

\[ \sum E_l(T, \tau)/kT = \int \sum E_l(T, \tau)/kT \]

so that the function integrates to unity.

We can now generate probability maps, single-component diagrams with the same axes, \( T \) and \( \tau \), where the contour will contain within it an indication of a given percentage of molecules for a chosen temperature. If we consider the two-rotation angle case which is appropriate for all the transmembrane alpha helices, clearly the square defined by the axes contains 100 per cent of molecules but, as we become more restrictive, we can emphasize just how flexible a molecule is, as in Fig. 2.10.

With these ‘population maps’ it is possible to see at a glance just how flexible a molecule may be and which regions of conformational space are favored. Even more usefully we can compare many members of a series by taking, for example, the 99 per cent contour line for each compound and ask the question whether, if biological data are available, there is any indication of conformational requirements for activity.

Isolating potential and electron affinities:

The intrinsic potential and electron affinity of a molecule should, in principle, be simple to calculate. All that seems necessary is to do a calculation for the neutral molecule in its ground-state geometry and conformation and similar calculations for the positive and negative ions, thus by difference we will obtain the desired energies. In practice this obvious plan is not usually followed.

One reason why it is not popular is that such a procedure would only be expected to yield values in accord with expectation if the correlation energy error, the relativistic error and the discrepancy from the Hartree-Fock binding energy were accounted for in the calculations on the molecule and on the
Unfortunately, the correlation energy error, being dependent on a fine approximation of the number of electron pairs in the molecule or ion will certainly differ in the two situations even though the other two errors may cancel.

A further problem when considering electronic affinities but not ionization potentials is that self-consistent field calculations frequently do not converge for negative ions.

In consequence a much more drastic but simply applied approximation is often employed. This equates the ionization potential of an electron with the orbital energy $E$ associated with that electron. This is known as Koopmans' theorem. It implies that not only are the absolute and correlation energies the same in the molecule and in the ion but also that there is no reorganization of electronic structure or distribution on ionization. Clearly such approximations are not valid. Once again, however, when considering differences between ionization potentials for a series of similar molecules many of the errors are constant and an acceptable indication of trends is obtained as chemical modifications can be obtained. The energy of the highest occupied molecular orbital which approximates to the ionization potential is often given the acronym $HOMO$ and used as a parameter in correlations with reactivities.

For electronic affinities the energy of the lowest unoccupied molecular orbital $E_{u}$, for the free virtual orbitals, may give an indication of the $E_{u}$ which the molecule may accept an electron. In addition to the assumptions involved in Koopmans' theorem this approximation is made even less acceptable since there is no definite physical meaning for the virtual orbitals.

If an ab initio computation is run, the virtual orbitals are very variable as a function of the size of the basis set, the only mathematical constraint upon them being one of orthogonality between themselves and with occupied orbitals. The energy of the lowest unoccupied molecular orbital is frequently referred to as the LUMO and again is used in statistical correlations.

Electronic affinities are not well calculated although the sample equation of ionization potential with orbital energy is satisfactory for comparative purposes. Abundance calculations require a lot of work.

### 2.14 Charge distribution calculations

Possibly more important than nuclear configuration are the details of electronic charge distribution or potential revealed by calculations. Even since the earliest days of quantum mechanics the square of a wave function at a point in space has been interpreted as a probability. If we have an electronic wave function $\psi$, and integrate this function squared over a volume $dV = dx \times dy \times dz$ then the result will be a sum of the probabilities of finding the electron at this volume element or an electron density $\rho$, with

$$\rho = \int |\psi|^2 \, dV$$

The direct break-on calculation of the charge within a defined volume in a molecule has been used to produce charge distribution data. The problem which hindered the use of the direct approach was the difficulty of doing the integrals for volumes of space which bear an awkward relationship to the coordinate system being used for the molecular calculation.

An attractive way of using the direct integration approach to charge distribution is to plot contours of charge density. This is full of information but has the disadvantage of difficulty of presentation when a molecule has little symmetry.

### Mulliken population analysis

A commonly programmed way of gaining an idea of charge distribution in molecules comes from the so-called Mulliken population analysis. In one line of a computer program we can produce values associated with each atom in a molecule, these being the number of electrons "associated" with the particular atom. In this way all the electrons in the molecule are assigned to nuclei, even though they may not spend much time very close to the particular nucleus. Thus the meaning in physical terms is imperfect although mathematically Mulliken population analysis are clearly defined.

If we are dealing with molecular orbital wave functions, then the net atomic population of a given atomic orbital, $z_{k}$, is defined as

$$\rho_{k} = \sum \rho_{k}$$

Here the subscript $k$ labels the molecular orbital and $\rho$ refers to the atomic basin function $\chi_{k}$. In this we use the concept of the square of a wave function representing a charge density and the atomic basin functions are assumed to be normalized.

$$\int |\chi_{k}|^{2} \, dx = 1$$

The overlap population -- the population shared by atomic orbitals $\chi_{k}$ and $\chi_{l}$ -- is further defined as

$$\rho_{kl} = \sum \rho_{kl}$$

with

$$\rho_{kl} = \int \chi_{k} \chi_{l} \, dx$$

Since $\rho_{k} = \sum \rho_{k}$ we can write the gross population of atomic orbital $z_{k}$ as

$$\rho_{k} = \sum \rho_{k}$$
The total population at any nucleus can be found by adding all the values of $P_r$ for orbitals $\psi_r$ which are centered on atom $a$.

Most molecular orbital programs incorporate the facility of computing multiple population analyses. The numbers so generated are often frequently used in applications to biological problems. It is therefore necessary to add a few cautionary words.

To state the obvious, the only charge on an atomic nucleus is its nuclear charge. This will not change with the environment of the nucleus in a molecule. We are more interested in the charge state to a molecule but 'net' has to be defined. In population analyses all the charge is associated with nuclei. The charge between two nuclei is divided equally between the two, even if the nuclei have very different electronegativities. A more worthy feature of population analyses emerged if all intra-molecular orbital functions are used. The resulting populations are not invariant to the basis set. In particular, if the basis set is gradually increased in size the results may become inaccurate. It is even possible to produce negative populations since $\int r$ integrals can be both positive and negative. Experience has shown that the picture of charge distributions derived from minimal basis set computations is frequently more realistic in terms of accord with experiments than when an extended basis set is employed.

These observations are included in more caution when using population analyses. They are not unknown by many means, but their intrusion is often as clear-cut as it is often inferred from the presentation of a diagram: a molecule together with a number (the net charge) associated with each atom. The weakness of the rough pattern of charge distribution is alleviated by the population analysis. Plots of population analyses against (approximate) computed charge densities are linear. Above all, when comparing charge distributions of similar molecules the analysis is valuable in elucidating trends. Differences are more meaningful than the absolute values.

### Molecular potential fields

In some ways more revealing than even an accurate picture of the charge distribution is a molecular orbital would be an indication of the molecular potential field. The molecular electronic potential is taken as the interaction energy between a unit positive charge and the unpermeated molecular charge distribution. The latter is due to negative electrons and positive nuclei so that the electronic potential energy $V$ at a point in space is

$$V(x) = -\mu(\psi) \cdot \mathbf{r}$$

where $\mathbf{r}$ is the nuclear charge of each nucleus.

The first-order density $\rho(x)$ may be derived from an ab initio calculation by taking the occupied molecular orbitals and squaring them, i.e.

$$\rho(x) = \sum \zeta^2 |\psi| \phi$$

A full calculation of this nature can provide what is sometimes referred to as an 'exact' potential. However, more frequently, further approximations are introduced. Often semi-empirical wave functions are used and the electronic distribution replaced by a set of point charges computed from the wave function, perhaps by the use of population analyses.

Because of the speed with which potential field computations may be carried out using primitive basis functions it becomes possible to treat large molecules of pharmaceutical interest and present the results in the form of isopotential maps. The potential maps represent contours connecting points at which the energy of interaction of the unpermeated molecule with a probe is identical or 'isopotential'.

Semi-empirical charges may be obtained by the fitting of the molecular electronic potential to that obtained from effective charges on individual atoms.

### Frontier electron density

The frontier electron theory was originally developed to explain the difference in reactivity at each position in an aromatic hydrocarbon. It is based on the intuitive idea that the reaction should occur at the position of the largest density of the electrons in the frontier orbitals, which are defined according to the type of reaction:

- In an electrophilic reaction, the highest occupied molecular orbital (HOMO).
- In a nucleophilic reaction, the lowest unoccupied molecular orbital (LUMO).
- In a radical reaction, both of these.

This theory was later given a sound theoretical basis by Fukui, who then introduced the concept of superlocalizability. Denoting the occupied molecular orbital by $1, 2, \ldots, n$, and the unoccupied levels by $n+1, n+2, \ldots N$, the superlocalizability $S$ is given for the three types of reaction by:

- For an electrophilic reaction:
  $$S_{el} = \sum_{i=1}^{2n} \frac{S_i}{\mu_i^2}$$

- For a nucleophilic reaction:
  $$S_{nu} = \sum_{i=1}^{N-n} \frac{\rho_i}{\rho_{i-2}}$$

- For a radical reaction:
  $$S_{rad} = \sum_{i=1}^{N-n} \frac{S_i}{\rho_i^2}$$

where $\rho_i$ is the coefficient of the $i^{th}$ molecular orbital in the $n$th molecular orbital, and $\beta_i$ is the coefficient in the orbital energy, which is given in the form $\alpha + \beta \mathbf{r}$ (in an anionization potential and $\beta$ is the empirical energy parameter used in the simple n-electron Hartree theory).

The orbital which mainly determines the value of $S$ in each type of reaction is the same as the frontier orbital previously considered.
There are problems in the use of both frontier electron density and superdelocalization methods. The latter concept was originally put forward considering the former of the molecule only, with the energetics of the orbitals being given in terms of the resonance integral of a C-C bond is helpful. 1. This means that in a series of molecules there would be a common zero of energy using all-electron molecular methods, the energies obtained are absolute terms, so that the zero of energy is in the unoccupied orbitals. This is obviously not consistent in a series of molecules.

The frontier electron density strictly permits only a comparison of reactivities at different positions within the same molecule. In order to extend this concept for use over a series of molecules, a further quantity, \( F \), may be considered:

\[
F = \frac{f}{N}
\]

where \( f \) is the frontier electron density, \( N \) is the energy of the appropriate frontier orbital.

\( F \) may be thought of as a weighted frontier electron density, in the sense that one of removal of the particular electron is also considered.

Frontier orbital theory may be made more rigorous if both initial sphere charges which have been described above are used to provide the charge is specified region of particular orbitals. Particularly for comparative purposes it is simple using freely available programs to calculate the charge is a sphere of defined radius on an atom, in a bond or indeed at any suitable point in space. This charge may be broken down into orbital contributions by giving an occupation number (the number of electrons in the orbital) equal to zero for all molecular orbitals other than the one of interest. The orbital of interest is likely to be the HOMO if the molecule is thought to be donating charge but LUMO if it is positioned to be acting as an electron acceptor.

2.15 Static Indices

The use of charges, frontier electron densities and other static indices derived from calculations on an unperturbed molecule as a guide to its reactivity is very dangerous. Reactivity is dependent on transition states and not on the unreacted starting materials as illustrated in Fig. 2.11. All that the calculations on an isolated species may indicate which is of any relevance to the reactivity is the initial slope of the curve.

2.16 Summary

Quantum mechanics provides molecular wave functions in the form of coefficients which multiply known basis functions. Most applications involve computing the energy of a molecule for a given arrangement of atomic nuclei. The calculations of energy properties are now of comparable accuracy to experimental determinations. This is currently true for geometries and static properties, but reactivity is more of a problem.

The methods have developed to the point where virtually any question about an isolated molecule can be answered by quantum mechanical calculation be it ab initio or semi-empirical. In molecules in solution however the techniques of statistical mechanics become essential.