Faculty of Bio and chemical Engineering

Department of Biotechnology

Subject code: SBI1310

Subject Name: Molecular modelling and drug designing

UNIT 1

MOLECULAR MODELING

The term molecular modelling expanded over the last decade from the tools to visulalize three dimensional structures and to simulate, predict and analyse the properties and the behaviour of the molecules on an atomic level to data mining and platform to organize many compounds and their properties into database and to perform virtual drug screening via 3D database screening for novel drug compounds.

Molecular modelling allow the scients to use computers to visualize molecules means representing molecular structures numerically and simulating their behaviour with the equations of quantum and classical physics to discover new lead compounds for drugs or to refine existing drugs insilico.

Goal:

To develop a sufficient accurate model of the system so that physical experiment may not be necessary

The definition currently accepted of what molecular modeling is, can be stated as this:

"Molecular modeling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule" (Pensak, 1989). Methods used in the molecular modeling arena regard automatic structure generation, analysis of three-dimensional (3D) databases, construction of protein models by techniques based on sequence homology, diversity analysis, docking of ligands or continuum methods.

Thus, today molecular modelling is regarded as a field concerned with the use of all sort of different strategies to model and to deduce information of a system at the atomic level. On the other hand, this discipline includes all methodologies used in computational chemistry, like computation of the energy of a molecular system, energy minimization, Monte Carlo methods or molecular dynamics. In other words, it is possible to conclude that computational chemistry is the nucleus of molecular modeling.

Applications

Molecular modelling methods are now routinely used to investigate the structure, dynamics, surface properties and thermodynamics of inorganic, biological and polymeric systems.

The types of biological activity that have been investigated using molecular modelling include protein folding, enzyme catalysis, protein stability, conformational changes associated with biomolecular function, and molecular recognition of proteins, DNA, and membrane complexes.

Why models are used?

- a) to help with analysis and interpretation of experimental data
- b) to uncover new laws and formulate new theories
- c) to help solve problems and hint solutions before doing experiments
- d) to help design new experiments
- e) to predict properties and quantities that are difficult or even impossible to observe experimentally

Simulations and computer "experiments" can be designed to mimic reality, however, are always based on assumptions, approximations and simplifications (i.e. models).

Important characteristics of models are:

- a) Level of simplification: very simple to very complex
- b) Generality: general or specific, i.e. relate only to specific systems or problems
- c) Limitations: one must always be aware of the range of applicability and limits of accuracy of any model.
- d) Cost and efficiency: CPU time, memory, disk space

Computable quantities:

- a) molecular structures: closely tied to energy (best structure - one for which the energy is minimum)
- b) energy: potential energy surfaces (PES) - extremely important! PES dictate essentially everything about the molecule or system
- c) molecular properties that can be compared to/used to interpret experiments: thermodynamics, kinetics, spectra (IR, UV, NMR)
- d) properties that are not experimental observables: bond order, aromaticity, molecular orbitals

Three stages of Molecular Modeling

1. Model is selected to describe the intra and inter mol. Interactions in the system
    - Two common models
        - Quantum mechanics
        - Molecular mechanics

These models enable the energy of any arrangement if the atoms and mol to be calculated and allow the modeller to determine how the energy of the system varies as the positions of the atoms and molecular changes

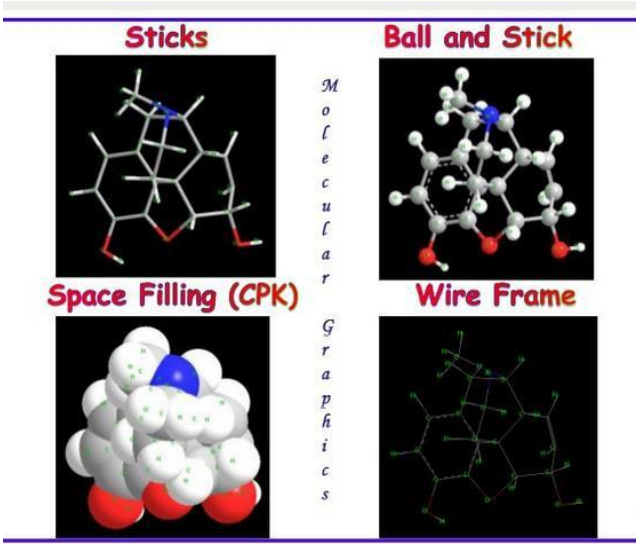
2. Calculation itself such as energy minimization, molecular dynamics or Monte carlo simulations or conformational search

3. Calculation must be analyzed not only to calculate properties but also to check that it has been performed properly

Molecular Visualisation

Once 3D coordinates are available, they can be visualised, an important aid to interpretation of molecular modelling:

- **Wireframe**, **Ball and Stick** and **Spacefill** for small and medium sized molecules
- **Ribbon** for protein, nucleotide and carbohydrate structures to render the tertiary molecular structures, **Polyhedral modes** for eg ionic lattices.
- **Isosurfaces**, which are generated from the sizes of atoms, and onto which can be colour coded further properties such as MOs, charges etc.
- **Animation** to view molecular vibrations and the time dependent properties of molecules such as (intrinsic) reaction coordinates, protein folding dynamics, etc.
- **Integration and Scripting**. Programs such as Jmol or ChemDoodle allow seamless integration of models as part of lecture courses, electronic journals, podcasts, iPads, etc and increasingly elaborate scripting of the models to illustrate scientific points.



1.2 Coordinate Systems

It is obviously important to be able to specify the positions of the atoms and/or molecules in the system to a modelling program*. There are two common ways in which this can be done. The most straightforward approach is to specify the Cartesian (x, y, z) coordinates of all the atoms present. The alternative is to use *internal coordinates*, in which the position of each atom is described relative to other atoms in the system. Internal coordinates are usually written as a Z-matrix. The Z-matrix contains one line for each atom in the system. A sample Z-matrix for the staggered conformation of ethane (see Figure 1.1) is

*For a system containing a large number of independent molecules it is common to use the term 'configuration' to refer to each arrangement; this use of the word 'configuration' is not to be confused with its standard chemical meaning as a different bonding arrangement of the atoms in a molecule

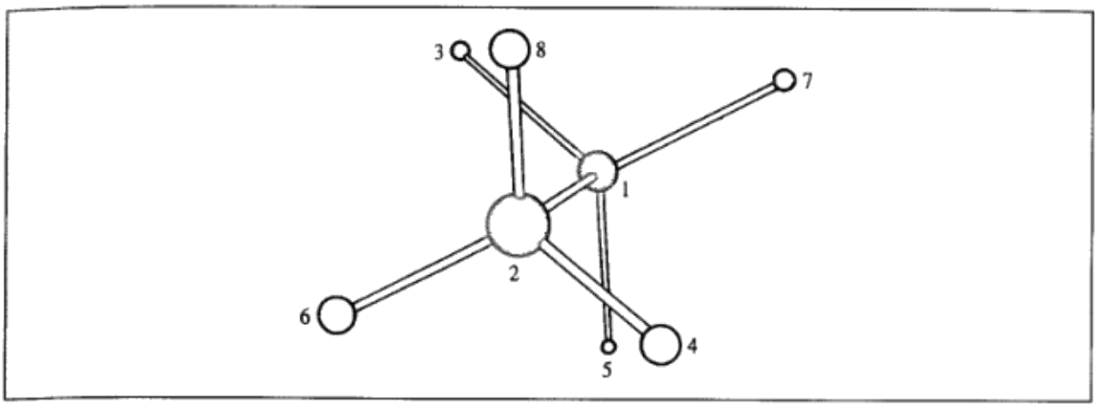


Fig. 1 1 The staggered conformation of ethane

as follows:

1	C						
2	C	1.54	1				
3	H	1.0	1	109.5	2		
4	H	1.0	2	109.5	1	180.0	3
5	H	1.0	1	109.5	2	60.0	4
6	H	1.0	2	109.5	1	−60.0	5
7	H	1.0	1	109.5	2	180.0	6
8	H	1.0	2	109.5	1	60.0	7

In the first line of the Z-matrix we define atom 1, which is a carbon atom. Atom number 2 is also a carbon atom that is a distance of 1.54 Å from atom 1 (columns 3 and 4). Atom 3 is a hydrogen atom that is bonded to atom 1 with a bond length of 1.0 Å. The angle formed by atoms 2–1–3 is 109.5°, information that is specified in columns 5 and 6. The fourth atom is a hydrogen, a distance of 1.0 Å from atom 2, the angle 4–2–1 is 109.5°, and the torsion angle (defined in Figure 1.2) for atoms 4–2–1–3 is 180°. Thus for all except the first three atoms, each atom has three internal coordinates: the distance of the atom from one of the atoms previously defined, the angle formed by the atom and two of the previous atoms, and the torsion angle defined by the atom and three of the previous atoms. Fewer internal coordinates are required for the first three atoms because the first atom can be placed anywhere in space (and so it has no internal coordinates); for the second atom it is only necessary to specify its distance from the first atom and then for the third atom only a distance and an angle are required.

It is always possible to convert internal to Cartesian coordinates and vice versa. However, one coordinate system is usually preferred for a given application. Internal coordinates can usefully describe the relationship between the atoms in a single molecule, but Cartesian coordinates may be more appropriate when describing a collection of discrete molecules. Internal coordinates are commonly used as input to quantum mechanics programs, whereas calculations using molecular mechanics are usually done in Cartesian coordinates. The total number of coordinates that must be specified in the internal coordinate system is six fewer

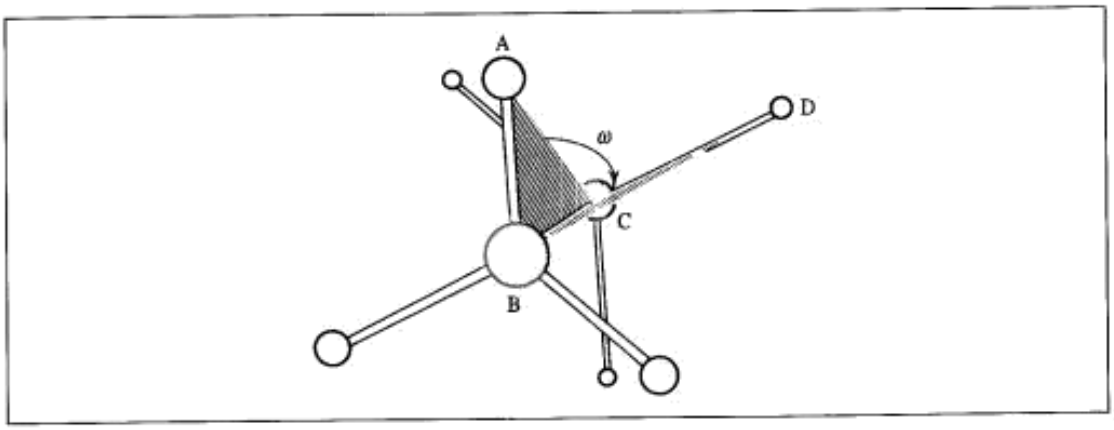


Fig. 1.2 A torsion angle A–B–C–D is defined as the angle between the planes A, B, C and B, C, D A torsion angle can vary through 360° although the range −180° to +180° is most commonly used We shall adopt the IUPAC definition of a torsion angle in which an eclipsed conformation corresponds to a torsion angle of 0° and a trans *or* anti *conformation to a torsion angle of 180°. The reader should note that this may not correspond to some of the definitions used in the literature, where the* trans *arrangement is defined as a torsion angle of 0° If one looks along the bond B–C, then the torsion angle is the angle through which it is necessary to rotate the bond AB in a clockwise sense in order to superimpose the two planes, as shown*

than the number of Cartesian coordinates for a non-linear molecule. This is because we are at liberty to arbitrarily translate and rotate the system within Cartesian space without changing the relative positions of the atoms

POTENTIAL ENERGY SURFACE

- A potential energy surface (PES) describes the energy of a system, especially a collection of atoms, in terms of certain parameters, normally the positions of the atoms. The surface might define the energy as a function of one or more coordinates; if there is only one coordinate, the surface is called a *potential energy curve*.

- The PES concept finds application in fields such as chemistry and physics, especially in the theoretical sub-branches of these subjects. It can be used to theoretically explore properties of structures composed of atoms, for example, finding the minimum energy shape of a molecule or computing the rates of a chemical reaction

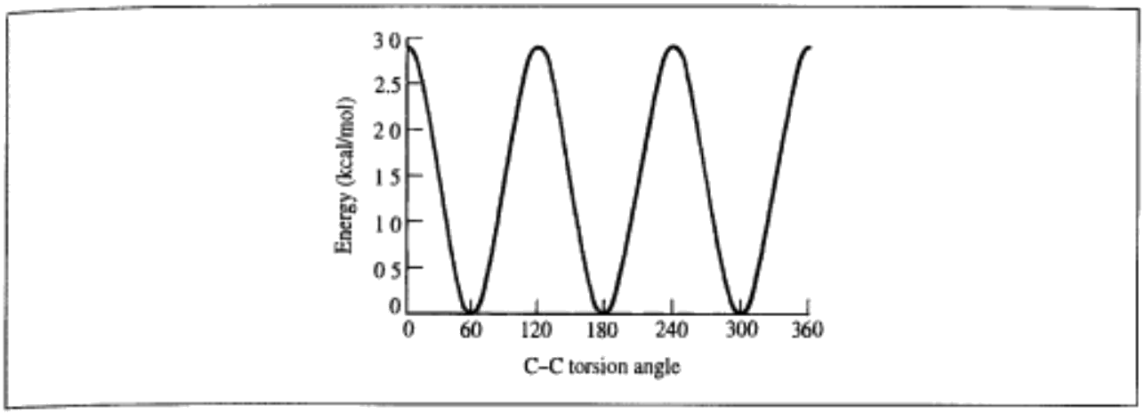


Fig. 1 3 Variation in energy with rotation of the carbon–carbon bond in ethane

Changes in the energy of a system can be considered as movements on a multidimensional 'surface' called the *energy surface*. We shall be particularly interested in stationary points on the energy surface, where the first derivative of the energy is zero with respect to the internal or Cartesian coordinates. At a stationary point the forces on all the atoms are zero. Minimum points are one type of stationary point; these correspond to stable structures. Methods for locating stationary points will be discussed in more detail in Chapter 5, together with a more detailed consideration of the concept of the energy surface.

1.4 Molecular Graphics

Computer graphics has had a dramatic impact upon molecular modelling. It should always be remembered, however, that there is much more to molecular modelling than computer graphics. It is the interaction between molecular graphics and the underlying theoretical methods that has enhanced the accessibility of molecular modelling methods and assisted the analysis and interpretation of such calculations.

Molecular graphics systems have evolved from delicate and temperamental pieces of equipment that cost hundreds of thousands of pounds and occupied entire rooms, to today's inexpensive workstations that fit on or under a desk and yet are hundreds of times more powerful Over the years, two different types of molecular graphics display have been used in molecular modelling. First to be developed were vector devices, which construct pictures using an electron gun to draw lines (or dots) on the screen, in a manner similar to an oscilloscope. Vector devices were the mainstay of molecular modelling for almost two decades but have now been largely superseded by raster devices. These divide the screen into a large number of small 'dots', called pixels. Each pixel can be set to any of a large number of colours, and so by setting each pixel to the appropriate colour it is possible to generate the desired image.

Molecules are most commonly represented on a computer graphics screen using 'stick' or 'space-filling' representations, which are analogous to the Dreiding and Corey–Pauling–Koltun (CPK) mechanical models. Sophisticated variations on these two basic types have

been developed, such as the ability to colour molecules by atomic number and the inclusion of shading and lighting effects, which give 'solid' models a more realistic appearance. Some of the commonly used molecular representations are shown in Figure 1.4 (colour plate section). Computer-generated models do have some advantages when compared with their mechanical counterparts. Of particular importance is the fact that a computer model can be very easily interrogated to provide quantitative information, from simple geometrical measures such as the distance between two atoms to more complex quantities such as the energy or surface area. Quantitative information such as this can be very difficult if not impossible to obtain from a mechanical model. Nevertheless, mechanical models may still be preferred in certain types of situation due to the ease with which they can be manipulated and viewed in three dimensions. A computer screen is inherently two-dimensional, whereas molecules are three-dimensional objects. Nevertheless, some impression of the three-dimensional nature of an object can be represented on a computer screen using techniques such as depth cueing (in which those parts of the object that are further away from the viewer are made less bright) and through the use of perspective. Specialised hardware enables more realistic three-dimensional stereo images to be viewed. In the future 'virtual reality' systems may enable a scientist to interact with a computer-generated molecular model in much the same way that a mechanical model can be manipulated.

Even the most basic computer graphics program provides some standard facilities for the manipulation of models, including the ability to translate, rotate and 'zoom' the model towards and away from the viewer. More sophisticated packages can provide the scientist with quantitative feedback on the effect of altering the structure. For example, as a bond is rotated then the energy of each structure could be calculated and displayed interactively.

For large molecular systems it may not always be desirable to include every single atom in the computer image; the sheer number of atoms can result in a very confusing and cluttered picture. A clearer picture may be achieved by omitting certain atoms (e.g. hydrogen atoms) or by representing groups of atoms as single 'pseudo-atoms' The techniques that have been developed for displaying protein structures nicely illustrate the range of computer graphics representation possible (the use of computational techniques to investigate the structures of proteins is considered in Chapter 10). Proteins are polymers constructed from amino acids, and even a small protein may contain several thousand atoms. One way to produce a clearer picture is to dispense with the explicit representation of any atoms and to represent the protein using a 'ribbon'. Proteins are also commonly represented using the cartoon drawings developed by J Richardson, an example of which is shown in Figure 1.5 (colour plate section). The cylinders in this figure represent an arrangement of amino acids called an α-helix, and the flat arrows an alternative type of regular structure called a β-strand. The regions between the cylinders and the strands have no such regular structure and are represented as 'tubes'.

1.5 Surfaces

Many of the problems that are studied using molecular modelling involve the non-covalent interaction between two or more molecules. The study of such interactions is often facilitated

by examining the van der Waals, molecular or accessible surfaces of the molecule. The *van der Waals surface* is simply constructed from the overlapping van der Waals spheres of the atoms, Figure 1.6. It corresponds to a CPK or space-filling model. Let us now consider the approach of a small 'probe' molecule, represented as a single van der Waals sphere, up to the van der Waals surface of a larger molecule. The finite size of the probe sphere means that there will be regions of 'dead space', crevices that are not accessible to the probe as it rolls about on the larger molecule. This is illustrated in Figure 1.6. The amount of dead space increases with the size of the probe; conversely, a probe of zero size would be able to access all of the crevices. The *molecular surface* [Richards 1977] is traced out by the inward-facing part of the probe sphere as it rolls on the van der Waals surface of the molecule. The molecular surface contains two different types of surface element. The *contact surface* corresponds to those regions where the probe is actually in contact with the van der Waals surface of the 'target'. The *re-entrant* surface regions occur where there are crevices that are too narrow for the probe molecule to penetrate. The molecular surface is usually defined using a water molecule as the probe, represented as a sphere of radius 1.4 Å.

The *accessible surface* is also widely used. As originally defined by Lee and Richards [Lee and Richards 1971] this is the surface that is traced by the centre of the probe molecule as it rolls on the van der Waals surface of the molecule (Figure 1.6). The centre of the probe molecule can thus be placed at any point on the accessible surface and not penetrate the van der Waals spheres of any of the atoms in the molecule.

Widely used algorithms for calculating the molecular and accessible surfaces were developed by Connolly [Connolly 1983a, b], and others [e.g. Richmond 1984] have described formulae for the calculation of exact or approximate values of the surface area. There are many ways to represent surfaces, some of which are illustrated in Figure 1.7 (colour plate section). As shown, it may also be possible to endow a surface with a translucent quality, which enables the molecule inside the surface to be displayed. Clipping can also be used to cut through the surface to enable the 'inside' to be viewed. In addition, properties such as the electrostatic potential can be calculated on the surface and represented using an appropriate colour scheme. Useful though these representations are, it is important to remember that the electronic distribution in a molecule formally extends to infinity. The 'hard sphere' representation is often very convenient and has certainly proved very valuable, but it may not be appropriate in all cases [Rouvray 1997, 1999, 2000].

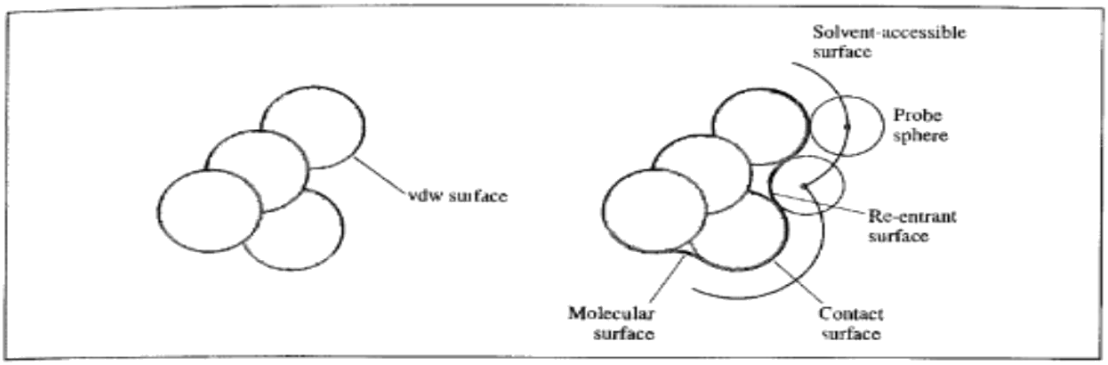


Fig 1.6· The van der Waals (vdw) surface of a molecule corresponds to the outward-facing surfaces of the van der Waals spheres of the atoms. The molecular surface is generated by rolling a spherical probe (usually of radius 1.4 Å to represent a water molecule) on the van der Waals surface. The molecular surface is constructed from contact and re-entrant surface elements. The centre of the probe traces out the accessible surface

The Molecular Modeling Toolbox

Molecular Mechanics Methods

Molecules modeled as spheres (atoms) connected by springs (bonds)

- Fast, $>10^6$ atoms
- Limited flexibility due to lack of electron

treatment Typical applications

- Simulating biomolecules in explicit solvent/membrane
- Geometry optimization
- Conformational search

Quantum Mechanical Methods

Molecules represented using electron structure (Schrödinger equation)

- Computationally expensive , <10-100 atoms, depending on method
- Highly flexible – any property can in principle be

calculated Typical applications

- Chemical reactions
- Spectra
- Accurate (gas phase) structures, energies

QUANTUM MECHANICS

Chapter 3 we then build upon this chapter and consider more advanced concepts. Quantum mechanics does, of course, predate the first computers by many years, and it is a tribute to the pioneers in the field that so many of the methods in common use today are based upon their efforts. The early applications were restricted to atomic, diatomic or highly symmetrical systems which could be solved by hand. The development of quantum mechanical techniques that are more generally applicable and that can be implemented on a computer (thereby eliminating the need for much laborious hand calculation) means that quantum mechanics can now be used to perform calculations on molecular systems of real, practical interest. Quantum mechanics explicitly represents the electrons in a calculation, and so it is possible to derive properties that depend upon the electronic distribution and, in particular, to investigate chemical reactions in which bonds are broken and formed. These qualities,

Fundamentals of Quantum mechanics

Light- energy- photons/quanta- wave –particle-duality

Schrodinger -Every quantum particle is characterized by wave function

Developed a differential equation which describes the evolution of ψ

Predicts analytically and precisely the probability of events/outcome (TIME)

- Represents electrons in a calculation
- Derive the properties that depend on electronic distribution – particularly the chemical reactions in which bonds are broken and formed

$$-\frac{\hbar^2}{2m}\frac{\partial^2\psi}{\partial x^2} + V(x)\psi = E\psi \qquad \text{or} \qquad \hat{H}\psi = E\psi$$

- H – Hamiltonian operator
- E – energy of the system
- ψ - wave function
- But SE can be used only for very small mol such as H and He
- So approximations must be used in order to extend the utility of the method to polyatomic systems

The starting point for any discussion of quantum mechanics is, of course, the Schrödinger equation. The full, time-dependent form of this equation is

$$\left\{-\frac{\hbar^2}{2m}\left(\frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2}\right)+\mathscr{V}\right\}\Psi(\mathbf{r},t) = i\hbar\frac{\partial\Psi(\mathbf{r},t)}{\partial t} \tag{2.1}$$

Equation (2.1) refers to a single particle (e.g. an electron) of mass m which is moving through space (given by a position vector $\mathbf{r} = x\mathbf{i} + y\mathbf{j} + z\mathbf{k}$) and time ($t$) under the influence of an external field $\mathscr{V}$ (which might be the electrostatic potential due to the nuclei of a molecule). $\hbar$ is Planck's constant divided by 2π and i is the square root of -1. Ψ is the *wavefunction* which characterises the particle's motion; it is from the wavefunction that we can derive various properties of the particle. When the external potential $\mathscr{V}$ is independent of time then the wavefunction can be written as the product of a spatial part and a time part: $\Psi(\mathbf{r},t) = \psi(\mathbf{r})T(t)$. We shall only consider situations where the potential is independent of time, which enables the time-dependent Schrödinger equation to be written in the more familiar, time-independent form:

$$\left\{-\frac{\hbar^2}{2m}\nabla^2+\mathscr{V}\right\}\Psi(\mathbf{r}) = E\Psi(\mathbf{r}) \tag{2.2}$$

Here, E is the energy of the particle and we have used the abbreviation ∇^2 (pronounced 'del-squared').

$$\nabla^2 = \frac{\partial^2}{\partial x^2}+\frac{\partial^2}{\partial y^2}+\frac{\partial^2}{\partial z^2} \tag{2.3}$$

It is usual to abbreviate the left-hand side of Equation (2.1) to $\mathscr{H}\Psi$, where $\mathscr{H}$ is the *Hamiltonian operator*:

$$\mathscr{H} = -\frac{\hbar^2}{2m}\nabla^2+\mathscr{V} \tag{2.4}$$

This reduces the Schrödinger equation to $\mathscr{H}\Psi = E\Psi$. To solve the Schrödinger equation it is necessary to find values of E and functions Ψ such that, when the wavefunction is operated upon by the Hamiltonian, it returns the wavefunction multiplied by the energy. The Schrödinger equation falls into the category of equations known as partial differential eigenvalue equations in which an operator acts on a function (the eigenfunction) and returns the

function multiplied by a scalar (the eigenvalue). A simple example of an eigenvalue equation is:

$$\frac{d}{dx}(y) = ry \tag{2.5}$$

The operator here is d/dx. One eigenfunction of this equation is $y = e^{ax}$ with the eigenvalue r being equal to a. Equation (2.5) is a first-order differential equation. The Schrödinger equation is a second-order differential equation as it involves the second derivative of Ψ. A simple example of an equation of this type is

$$\frac{d^2y}{dx^2} = ry \tag{2.6}$$

The solutions of Equation (2.6) have the form $y = A\cos kx + B\sin kx$, where A, B and k are constants. In the Schrödinger equation Ψ is the eigenfunction and E the eigenvalue.

Time-Dependent Schrodinger Wave Equation

$$i\hbar\frac{\partial}{\partial t}\Psi(x,t) = -\frac{\hbar^2}{2m}\frac{\partial^2}{\partial x^2}\Psi(x,t) + V(x)\Psi(x,t)$$

Total E term

K.E. term

P.E. term

PHYSICS NOTATION

$$\Psi(x,t) = e^{-iEt/\hbar}\psi(x)$$

Time-Independent Schrodinger Wave Equation

$$E\psi(x) = -\frac{\hbar^2}{2m}\frac{\partial^2}{\partial x^2}\psi(x) + V(x)\psi(x)$$

- Eigen value equation
- Operator (H) acts on function (eigen function) (ψ)
- Returns the function (ψ) multiplied by a scalar value (eigen value) (E)
- Hamiltonian operator

2.1.1 Operators

The concept of an operator is an important one in quantum mechanics. The *expectation value* (which we can consider to be the average value) of a quantity such as the energy, position or linear momentum can be determined using an appropriate operator. The most commonly used operator is that for the energy, which is the Hamiltonian operator itself, $\mathscr{H}$. The energy can be determined by calculating the following integral:

$$E = \frac{\int \Psi^* \mathscr{H} \Psi \, d\tau}{\int \Psi^* \Psi \, d\tau} \tag{2.7}$$

The two integrals in Equation (2.7) are performed over all space (i.e. from $-\infty$ to $+\infty$ in the x, y and z directions). Note the use of the complex conjugate notation (Ψ^*), which reminds us that the wavefunction may be a complex number. This equation can be derived by pre-multiplying both sides of the Schrödinger equation, $\mathscr{H}\Psi = E\Psi$, by the complex conjugate of the wavefunction, Ψ^*, and integrating both sides over all space. Thus:

$$\int \Psi^* \mathscr{H} \Psi \, d\tau = \int \Psi^* E \Psi \, d\tau \tag{2.8}$$

E is a scalar and so can be taken outside the integral, thus leading to Equation (2.7). If the wavefunction is normalised then the denominator in Equation (2.7) will equal 1.

The Hamiltonian operator is composed of two parts that reflect the contributions of kinetic and potential energies to the total energy. The kinetic energy operator is

$$-\frac{\hbar^2}{2m}\nabla^2 \tag{2.9}$$

and the operator for the potential energy simply involves multiplication by the appropriate expression for the potential energy. For an electron in an isolated atom or molecule the potential energy operator comprises the electrostatic interactions between the electron and the nucleus and the interactions between the electron and the other electrons For a

single electron and a single nucleus with Z protons the potential energy operator is thus:

$$\mathcal{V} = -\frac{Ze^2}{4\pi\varepsilon_0 r} \tag{2.10}$$

Another operator is that for linear momentum along the x direction, which is

$$\frac{\hbar}{i}\frac{\partial}{\partial x} \tag{2.11}$$

The expectation value of this quantity can thus be obtained by evaluating the following integral:

$$p_x = \frac{\int \Psi^* \frac{\hbar}{i}\frac{\partial}{\partial x}\Psi \, d\tau}{\int \Psi^* \Psi \, d\tau} \tag{2.12}$$

2.2 One-electron Atoms

In an atom that contains a single electron, the potential energy depends upon the distance between the electron and the nucleus as given by the Coulomb equation. The Hamiltonian thus takes the following form:

$$\mathcal{H} = -\frac{\hbar^2}{2m}\nabla^2 - \frac{Ze^2}{4\pi\varepsilon_0 r} \tag{2.16}$$

In atomic units the Hamiltonian is:

$$\mathcal{H} = -\frac{1}{2}\nabla^2 - \frac{Z}{r} \tag{2.17}$$

For the hydrogen atom, the nuclear charge, Z, equals +1. r is the distance of the electron from the nucleus. The helium cation, He^+, is also a one-electron atom but has a nuclear charge of +2. As atoms have spherical symmetry it is more convenient to transform the Schrödinger equation to polar coordinates r, θ and ϕ, where r is the distance from the nucleus (located at the origin), θ is the angle to the z axis and ϕ is the angle from the x axis in the xy plane (Figure 2.1). The solutions can be written as the product of a radial function $R(r)$, which depends only on r, and an angular function $Y(\theta, \phi)$ called a *spherical harmonic*, which

2.3 Polyelectronic Atoms and Molecules

Solving the Schrödinger equation for atoms with more than one electron is complicated by a number of factors. The first complication is that the Schrödinger equation for such systems cannot be solved exactly, even for the helium atom. The helium atom has three particles (two electrons and one nucleus) and is an example of a *three-body problem*. No exact solutions can be found for systems that involve three (or more) interacting particles. Thus, any solutions we might find for polyelectronic atoms or molecules can only be approximations to the real, true solutions of the Schrödinger equation. One consequence of there being no exact solution is that the wavefunction may adopt more than one functional form; no form is necessarily more 'correct' than another. In fact, the most general form of the wavefunction will be an infinite series of functions.

A second complication with multi-electron species is that we must account for electron spin. Spin is characterised by the quantum number s, which for an electron can only take the value $\frac{1}{2}$. The spin angular momentum is quantised such that its projection on the z axis is either $+\hbar$ or $-\hbar$. These two states are characterised by the quantum number m_s, which can have values of $+\frac{1}{2}$ or $-\frac{1}{2}$, and are often referred to as 'up spin' and 'down spin' respectively. Electron spin is incorporated into the solutions to the Schrödinger equation by writing each one-electron wavefunction as the product of a spatial function that depends on the coordinates of the electron and a spin function that depends on its spin. Such solutions are called *spin orbitals*, which we will represent using the symbol χ. The spatial part (which will be referred to as an orbital and represented using ϕ for atomic orbitals

2.3.1 The Born–Oppenheimer Approximation

It was stated above that the Schrödinger equation cannot be solved exactly for any molecular systems However, it is possible to solve the equation exactly for the simplest molecular species, H_2^+ (and isotopically equivalent species such as HD^+), when the motion of the electrons is decoupled from the motion of the nuclei in accordance with the Born–Oppenheimer approximation. The masses of the nuclei are much greater than the masses of the electrons (the resting mass of the lightest nucleus, the proton, is 1836 times heavier than the resting mass of the electron). This means that the electrons can adjust almost instantaneously to any changes in the positions of the nuclei. The electronic wavefunction thus depends only on the positions of the nuclei and not on their momenta. Under the Born–Oppenheimer approximation the total wavefunction for the molecule can be written in the following form:

$$\Psi_{\text{tot}}(\text{nuclei, electrons}) = \Psi(\text{electrons})\Psi(\text{nuclei}) \tag{2.31}$$

The total energy equals the sum of the nuclear energy (the electrostatic repulsion between the positively charged nuclei) and the electronic energy. The electronic energy comprises

the kinetic and potential energy of the electrons moving in the electrostatic field of the nuclei, together with electron–electron repulsion: $E_{tot} = E(\text{electrons}) + E(\text{nuclei})$.

When the Born–Oppenheimer approximation is used we concentrate on the electronic motions; the nuclei are considered to be fixed. For each arrangement of the nuclei the Schrödinger equation is solved for the electrons alone in the field of the nuclei. If it is desired to change the nuclear positions then it is necessary to add the nuclear repulsion to the electronic energy in order to calculate the total energy of the configuration.

Helium atom

$$\left\{-\frac{\hbar^2}{2m}\nabla_1^2 - \frac{Ze^2}{4\pi\varepsilon_0 r_1} - \frac{\hbar^2}{2m}\nabla_2^2 - \frac{Ze^2}{4\pi\varepsilon_0 r_2}\right\}\Psi(\mathbf{r}_1,\mathbf{r}_2) = E\Psi(\mathbf{r}_1,\mathbf{r}_2) \tag{2.32}$$

Or, in atomic units,

$$\left\{-\frac{1}{2}\nabla_1^2 - \frac{Z}{r_1} - \frac{1}{2}\nabla_2^2 - \frac{Z}{r_2}\right\}\Psi(\mathbf{r}_1,\mathbf{r}_2) = E\Psi(\mathbf{r}_1,\mathbf{r}_2) \tag{2.33}$$

We can abbreviate this equation to

$$\{\mathscr{H}_1 + \mathscr{H}_2\}\Psi(\mathbf{r}_1,\mathbf{r}_2) = E\Psi(\mathbf{r}_1,\mathbf{r}_2) \tag{2.34}$$

$\mathscr{H}_1$ and $\mathscr{H}_2$ are the individual Hamiltonians for electrons 1 and 2. Let us assume that the