Biochemical Thermodynamics

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By

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Cambridge
Scholars
Publishing

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This book first published 2020

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-5359-0
ISBN (13): 978-1-5275-5359-0

To the memory of Brígida and Francisco Jiménez

CONTENTS

PREFACE

This book is dedicated to the study of the thermodynamics of biochemical processes, with a special emphasis on those in which proteins play an essential role. Instead of the conventional description, which begins with classical thermodynamics and ends with the statistical interpretation of thermodynamic properties, this book uses from the beginning, as far as possible, the macroscopic view of classical thermodynamics, together with the statistical point of view, as derived from quantum mechanics. The book tries to cover a range of issues from the elementary principles of physical chemistry, such as the essential quantum-mechanical description of the hydrogen atom or the particle-in-a-box quantum-mechanical model, to the most current topics of biochemistry, including those that may be the subject of some controversy, such as the enthalpy–entropy compensation or the basic models used at present to describe the folding process of proteins. The book's most original contribution lies in its interpretation of thermodynamic properties related to the stability and function of proteins from the microscopic point of view of statistical thermodynamics in a language that, without sacrificing conceptual rigor, is affordable and easy to read. It will be appropriate for students and, of course, teachers of chemistry, physics, biochemistry and biotechnology.

Chapter 1 is a basic introductory review of the main topics in general and physical chemistry which may be useful to undergraduate students of biochemistry or biotechnology. Chapters 2, 3 and 4 provide the reader with the basic principles of physical chemistry, mainly thermodynamics, trying to place the emphasis on those aspects more closely related to biochemical topics. The end of Chapter 3 includes an introduction to the statistical interpretation of entropy. Chapter 4 includes the influence of pH in the equilibrium constant of a chemical reaction, describing the convention used in biochemistry when working with species containing dissociable protons. Chapter 5 contains statistical thermodynamics, setting the boundaries between the application of statistical thermodynamics to ideal systems (as ideal gases) and to the much more complex biological systems in water solution. The rest of the book is dedicated to the thermodynamics of protein-ligand interactions (Chapter 6), protein structure transitions (Chapter 9), allostery (Chapter 8) and, finally, oxidative phosphorylation and protein phosphorylation (Chapter 10). The most relevant techniques for measuring thermodynamic properties, including isothermal titration calorimetry and surface plasmon resonance have been included in Chapter 7. Differential scanning calorimetry has been included in Chapter 9, because of its special relevance in studies concerning the thermal denaturation of proteins.

I want to express my gratitude and recognition to the groups supervised by Professors Manuel Cortijo and Pedro L. Mateo at Granada University, with whom I started my training in thermodynamics. I thank also friends and professors at our Universidad Autónoma de Madrid: María J. Benítez, Enrique Fatás, Pilar Ocón, Carlos Palacio, Jose M. López Poyatos, Pilar Herrasti and Jesús Ávila (from the Centro de Biología Molecular, Severo Ochoa) for their help, friendly discussions on biology and physics, and for their critical reading of the manuscript. I want to express my gratitude to the sabbatical year granted by my University, under whose course I was able to write the bulk of this book. I feel particularly grateful to those who were once my PhD students Antonio Parody, Carmen Barón, Alejandro Barrantes and Sergio Camero, and the hundreds of students who, for so many years, have helped me with their eagerness for learning and criticism. Finally, I thank my wife, Mar Company, for her patience and encouragement to write this book.

CHAPTER 1

INTRODUCTION

1.1 The Atomic Theory of John Dalton and the Hypothesis of Amedeo Avogadro

It could be accepted that modern chemistry was born with the atomic theory proposed by John Dalton, together with the hypothesis put forward by Amedeo Avogadro at the beginning of the 19th century, which both came to be generally accepted by the middle of that century. Initial atomic theories have been traditionally attributed to the thinking of classical Greeks, for example that of Democritus, five centuries BC. From a philosophical point of view, however, those initial theories from classical Greece have little relation with Dalton's atomic theory. The latter is a theory put forward to explain experimental observations. Moreover, the theory has evolved over the last two hundred years in the light of further experimental evidence. Greek philosophers, on the other hand, simply put forward proposals based on logical thinking. Not only did they not perform experiments, they felt no need to do so.

The set of experimental observations on the basis of which Dalton built his theory can be summarized as follows (Figure 1.1.1):

a) *The Lavoisier observations concerning mass conservation in chemical transformations*: the total mass of reactants and products remains constant in all chemical transformations. Mass does not disappear and cannot be created. Lavoisier established mass conservation as the most solid base of modern chemistry, using the balance with high precision.

b) *The proportions laws of Proust, Richter and Dalton*: the relative mass proportion of each one of the component elements remains constant in all compounds. Iron, for example, forms two main compounds with oxygen. In one of them (black) the mass percentage of iron is always 77.7%, independent of the full mass we consider. In the second compound (red-brown) the iron mass percentage is always 69.9%. Chemists of the 19th century went further. In the black compound they would observe that 3.48 grams of iron always bind 1 gram of oxygen (77.7/22.3 = 3.48), while in the red-brown, 1 gram of oxygen always binds 2.32 grams of iron (69.9/30.1 = 2.32). They then made the next simple calculation: 3.48/2.32 = 3/2. After working with different examples of this kind, the conclusion was that when an element forms two different compounds with a second one, the ratio between the masses that one of them (iron in our example) binds a fixed mass of the second one (1 gram of oxygen in our example) can always be expressed as the ratio between two small whole numbers.

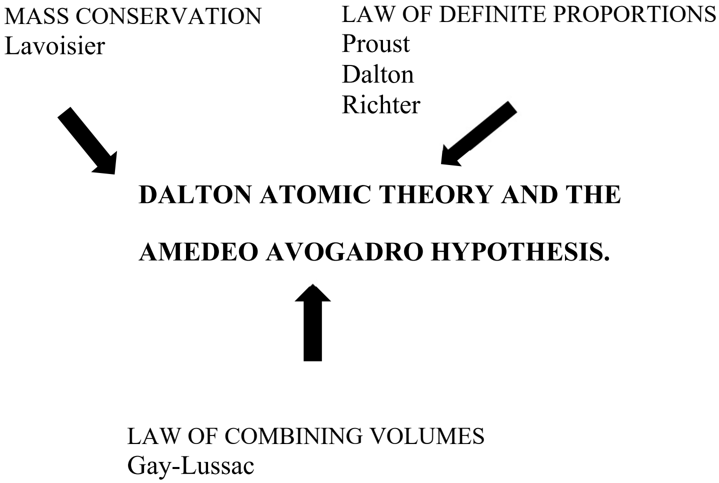


Figure 1.1.1.

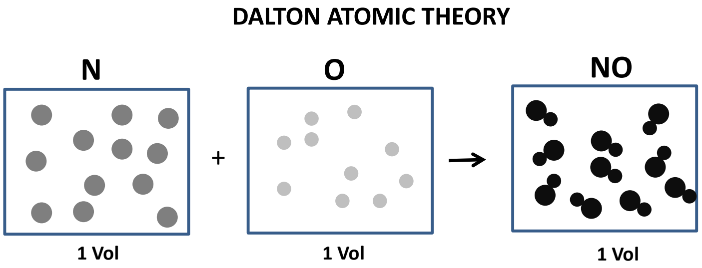
c) *The Law of combining volumes of Gay-Lussac*: In gaseous chemical transformations, the ratio between the volumes of the reactants and the products, as measured at constant values of pressure and temperature, can be expressed as the ratio between small whole numbers.

To summarize, the main points of the Dalton's atomic theory are as follows:

- Chemical elements are made of identical, indivisible particles, or atoms.

- Chemical compounds (or substances) are also made of identical atoms, which derive from the combination of atoms from the component elements.

- The chemical properties and masses of elements and compounds derive from the properties and masses of the constituent atoms.



-Elements and compounds are constituted by atoms, equal to each other and with the same mass.

-Compounds are constituted by atoms resulting from the binding of those atoms constituting the component elements.

-Atoms from different elements and compounds have different masses and properties.

Figure 1.1.2. Dalton concluded that, in equal volumes of two reacting gases, there is the same number of atoms. However, experiments conducted by Gay-Lussac showed that one volume of nitrogen reacted with one volume of oxygen to yield two volumes of NO!

Avogadro's hypothesis represented an essential contribution to Dalton's theory. It solved an apparent contradiction between Dalton's theory and some experimental observations of Gay-Lussac. It has been mentioned above that, according to the latter, the ratio between the volumes of the reactants and the products of gaseous chemical reactions, can be expressed as the ratio between small whole numbers. This type of observation led Dalton to assume that equal volumes of reactive gases must contain the same number of atoms. For example, nitric oxide can be formed from nitrogen and oxygen (Figure 1.1.2): N + O = NO.

Following Dalton's theory, one volume of nitrogen must react with a volume of oxygen to produce one volume of nitric oxide. The experiments of Gay-Lussac, however, showed that, at constant values of pressure and temperature, one volume of nitrogen reacted with one volume of oxygen to produce two volumes of nitric oxide! Avogadro solved the apparent discrepancy by proposing what we know today as the hypothesis that bears his name:

Elements may be made of molecules which result from the association of atoms of the same kind.

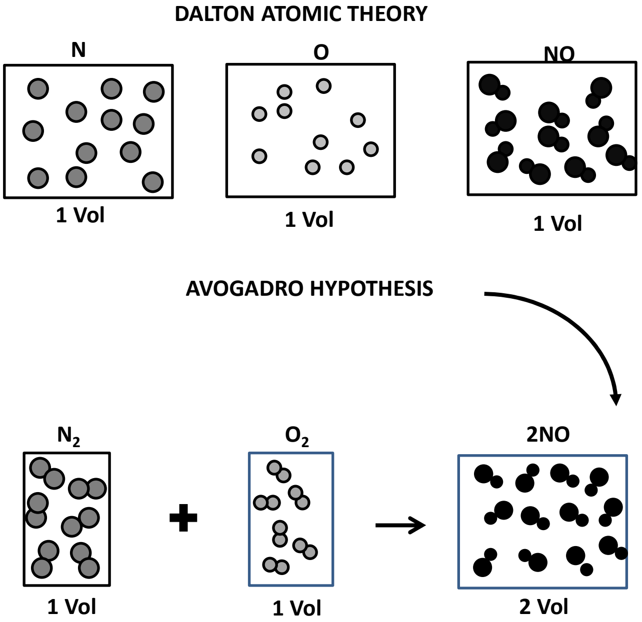


Figure 1.1.3. Gaseous elements are constituted by aggregates of atoms called MOLECULES. Equal volumes of all gases, at the same p and T, have the same number of MOLECULES.

The constituent molecules of compounds derive from the combination of atoms from the component elements, while molecules of elements are made up of atoms of the same kind. Therefore, nitrogen and oxygen would be made of diatomic molecules and the chemical transformation in nitric oxide would be represented by

$$N_2 + O_2 = 2NO.$$

According to the last scheme, one volume of nitrogen would react with one volume of oxygen to yield two volumes of nitric oxide, in accordance with the experimental observations of Gay-Lussac (Figure 1.1.3).

1.2 The Mole and Avogadro's Number

In accordance with Dalton's theory (and obviously the experiments of Gay-Lussac), equal volumes of two gaseous substances (elements or compounds) contain the same number of molecules when pressure and temperature are kept constant. Consequently, the mass ratio between both volumes will be equal to the mass ratio of the constituent molecules of each one of the substances. Therefore, we can obtain the dimensionless **molecular mass** of every gaseous substance, Mm, with respect to a particular one, selected as a reference. Since hydrogen was the lightest gas known, this gas was selected as a reference:

$$Mm_{,A} = m_A / m_R \qquad [1.1]$$

where m_A and m_R represent the molecular masses of substance A and reference, respectively.

One **mole** (or molar mass) of any compound, A, is defined as the number of grams of that compound, which is numerically equal to its molecular mass, $Mm_{,A}$.

Avogadro's number, N_A, is the number of molecules contained in one mole of any substance, A. Therefore:

the mole of A (g/mol) = N_A (molecules/mol) x m_A (g/molecule)
and using [1.1]:

the mole of A (g/mol) = N_A (molecules/mol) x $Mm_{,A}$ x m_R (g/ molecule)

Solving for N_A:

$$N_A = \frac{\text{mol of A (g/mol)}}{Mm_{,A} \times m_R \text{ (g/molecule)}} = \frac{1}{m_R} \quad \text{(molecules/mol)}$$

Both concepts, the mole and Avogadro's number derive directly from John Dalton's atomic theory and the Amedeo Avogadro hypothesis. Obviously, N_A is a universal constant, the numerical value of which is equal to the inverse of the mass of the molecules constituting the reference species. The species selected as a reference is hydrogen (atomic). The mass of a hydrogen atom (or 1 / 12 that of a carbon atom) is $1.66056\ 10^{-24}$ g, from which we can calculate the value of Avogadro's Number:

$$\mathbf{N_A} = 1/1.66056\ 10^{-24} = 6.022\ 10^{23} \text{ molecules / mol.}$$

1.3 The Ideal Gas Model

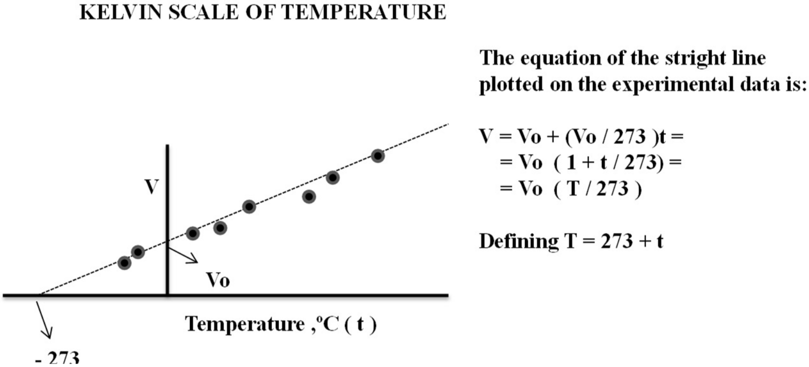
The second relevant model in chemistry may be the ideal gas model. It was developed together with Dalton's theory during the 19th century. The most important experiment was probably that which lead in the middle of the 17th century to the Boyle–Mariotte Law, which was one of the initial quantitative expressions of physical chemistry. It states that the product of the pressure of a mass of gas by its volume, at constant temperature, is a constant number, dependent on the type of gas and its mass:

$$pV = \text{cte.} \qquad [1.2]$$

Since the product pV is constant, at constant temperature, the expression pV/T is also a constant characteristic of the nature and mass of the gas:

$$pV/T = \text{cte.} \qquad [1.3]$$

This last equation was confirmed by the experiments of Charles who showed that a constant pressure results in the volume of a fixed mass of any gas being directly proportional to the temperature on the Kelvin scale, defined as T = 273,15 + t, where t represents the temperature on the Celsius scale (Figure 1.3.1):



The equation of the stright line plotted on the experimental data is:

$$V = Vo + (Vo / 273)t = \\ = Vo\ (1 + t / 273) = \\ = Vo\ (T / 273)$$

Defining T = 273 + t

Figure 1.3.1. The volume is proportional to temperature. The proportionality constant, Vo, is linearly dependent on the mass of gas.

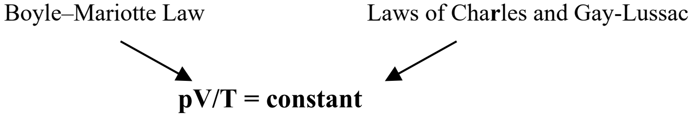
$$V = (cte/p)\ T.$$

The last expression, in combination with Dalton's theory leads to the equation that defines the ideal gas model (See Figure 1.3.2):

$$pV = n\ RT. \qquad [1.4]$$

Equation [1.4] has a universal character. The product pV / T has a constant value for the same number of molecules of every gaseous species. This observation, together with the atomic theory, forms the basis of the kinetic theory of gases, according to which the gas molecules are in continuous motion, without interactions. They have only translation energy, and thus determine the temperature and the total energy of the system. From these assumptions, the ideal gas equation [1.4] can be deduced. This equation, in turn, allows the calculation of the molecular mass of a gas, after measuring the volume occupied by a mass of gas at fixed values of pressure and temperature.

IDEAL GAS



The result is that the constant is linearly dependent on the gas mass: $pV/T = b \times m$.

From Dalton’s theory: $m = N \times M$, and $pV/T = b \times N \times M$, where N is the number of molecules and M stands for the mass of one molecule. Then $pV/TN = b \times M$.

V is proportional to N. Consequently, at constant value of p and T, $b \times M$ must be a constant, $b \times M = k$.

According to the latter, $pV/T = k \times N = k \times N_A \times n = n \times R$, where R stands for the gas constant and n represents the number of moles.

$$\mathbf{pV = nRT}$$

Figure 1.3.2.

1.4 The Periodic Table and Initial Atomic Theories

The atomic theory of Dalton, Avogadro’s hypothesis and the ideal gas equation made up the framework of theories within which relative atomic masses could be measured (with respect to the mass of the hydrogen atom or 1/12 the mass of the carbon atom) for every atom of gaseous species. Two equal volumes of gaseous substances, at the same p and T, contain the same number of molecules. Consequently:

(Mass of one volume of gas X)/(mass of one volume of a reference gas, R) = M_X/M_R

where M_X and M_R stand for the molecular masses of X and R respectively. The molecular mass of an oxygen molecule relative to one hydrogen molecule is 16, or 32 with respect to the hydrogen atom. The present reference is 1/12 the atomic mass of the isotope 12 of C. With respect to this reference, the atomic mass of hydrogen would be 1.008. Molecular masses were already known in 1818 by Berzelius. Nevertheless, they were not considered seriously until 1860, thanks to the efforts of Cannizzaro. The atomic masses of non-gaseous elements could then be obtained from the chemical composition (percentage by weight) of different compounds. When, in the middle of 19th century, chemical elements were ordered according to increasing atomic mass, the initial ordering of elements was obtained, constituting the experimental basis of the successive periodic tables. When Mendeleyev published his periodic table (1869), 63 chemical elements were already tabulated (Figure 1.4.1).

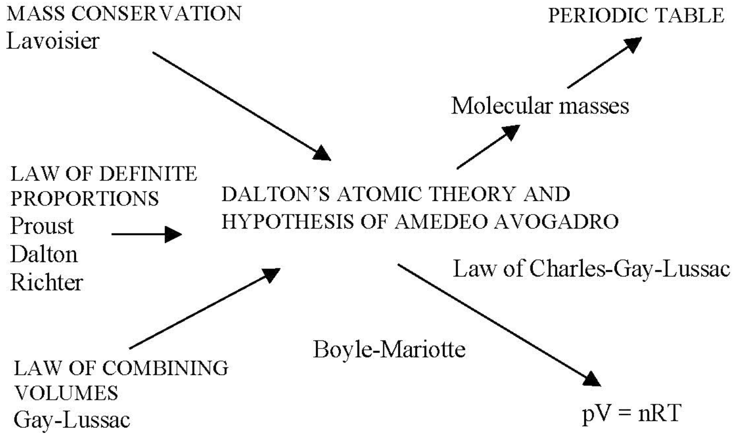


Figure 1.4.1.

The periodic variation in the properties displayed by the elements ordered according to their atomic mass suggested that that variation might be a consequence of the internal structure of the atoms. In other words, the periodic character showed by matter could be the direct consequence of some periodicity in the internal atomic structure.

The initial theories and models of atomic structure emerged from the experimental evidence which supported the idea that atoms are not indivisible. The experiments of Volta and Faraday showed that, by the action of electricity, chemical substances were decomposed into components having opposite sign charges. Experiments in vacuum tubes carried out in

England at the end of the 19th century suggested the existence of particles with a negative charge that had a charge to mass relationship which was independent of the nature of the gas and the electrodes. These particles were called electrons. Particles with opposite charge were also found which showed a charge to mass relationship that was dependent on the gas's nature. These particles had a mass almost two thousand times the mass of electrons and were called protons.

Finally, spectroscopy techniques supplied the rest of the experimental evidence on which the initial atomic models were sustained. When the light emitted by a gas sample exposed to a very high voltage (a hydrogen lamp) is analysed after dispersion by a prism, only radiation of definite values of frequency is found. There is no continuous emission. It seems that excited atoms inside the lamp emit radiation of only definite values of wavelength. By the end of the 19th century, spectroscopists had observed certain regularities in the radiation wavelengths. In the particular case of hydrogen, series of spectral lines were found, indicating values of wavelength given by the expression:

$$1/\lambda = R\,(1/n_i^2 - 1/n_j^2) \qquad n_j > n_i \qquad [1.5]$$

where R was a constant with the dimension of the inverse of the wavelength, while ni and nj were natural numbers: ni defining the series and nj, the lines within each series.

In 1904, Joseph John Thomson presented the first hypothesis concerning the atomic structure. In his model, the atom was like a sphere with a positive electric charge onto which much smaller particles with negative charge were glued. The first model resembling our present ideas on the structure of the atom was that of Rutherford in 1911. It was based on experiments made by Rutherford himself. Making a-particles go through thin films of gold, he concluded that most of an atom's volume was empty. The main difference with respect to the model of Thomson was that, according to Rutherford, the electrons were orbiting at long distances around the nucleus composed of the positively charged protons. Indeed, the number of electrons surrounding the nucleus must be the same as the number of protons.

The models of Thomson and Rutherford satisfied the electrochemistry experiments of Faraday as well as those made on vacuum tubes and lead them to postulate the existence of electrons and protons. They did not explain, however, the experimental results found by spectroscopists showing the non-continuous emission of light by excited atoms. Finally, Bohr proposed a model in which the electrons were orbiting the nucleus describing only some allowed orbits (those for which the angular momentum was a multiple of a numerical constant), therefore explaining the apparent quantization of the energy emitted by the excited atoms. The Bohr model had an extraordinary impact, mainly after explaining quantitatively the spectroscopic experiments. However, it could not explain many other observations concerning more complex atoms. Of course, it cannot explain any experiment concerning molecules and has today fallen out of use.

1.5 The Hydrogen Atom and the Schrödinger Equation

The atomic model we use today to describe the molecular structure is that supplied by quantum mechanics. Newton's laws are the basis of classical mechanics. Newton's first law is the inertial law, initially proposed by Galileo. The third law is the action–reaction law. According to the second law, the quotient between the force acting on a body and the acceleration it acquires is a constant, equal to the body's mass:

$$m = F/(d^2 x/d t^2). \tag{1.6}$$

To obtain x as a function of time we must integrate twice:

$$x = (F/m)\, t^2 / 2 + v_0 t + x_0. \tag{1.7}$$

Therefore, provided we know the force acting on a body, as well as its initial position and velocity, we can obtain the position, x, of the particle as a function of time. Position, velocity and force define the state of our system, the body. Classical mechanics can then predict its time evolution.

In quantum mechanics the state of a particle (or body) is a mathematical function, which is known as the state function of the particle. It is a function of the coordinates of the particles (3N coordinates for an N particles system) and also, in general, is a function of time. This function lacks a physical meaning by itself.

In the particular case in which the potential energy of the system is independent of time, the state function, Φ, can be obtained by solving a differential equation, the time-independent Schrödinger equation, which adopts the next form for the case of one particle moving only in one dimension:

$$-(h'^2/2m)\,(d^2\,\Phi/dx^2) + V\,(x)\Phi = E\,\Phi. \qquad [1.8]$$

In this equation h' represents the Planck's constant divided by 2π. V(x) represents the potential energy of the system. E and m stand for the total energy and the mass of the system respectively.

The expression H:

$$H \equiv -\,(h'^2/2m)\,(d^2/dx^2) + V(x) \qquad [1.9]$$

is the energy operator or the system's Hamiltonian. Using the Hamiltonian symbol, the Schrödinger equation adopts the simple form:

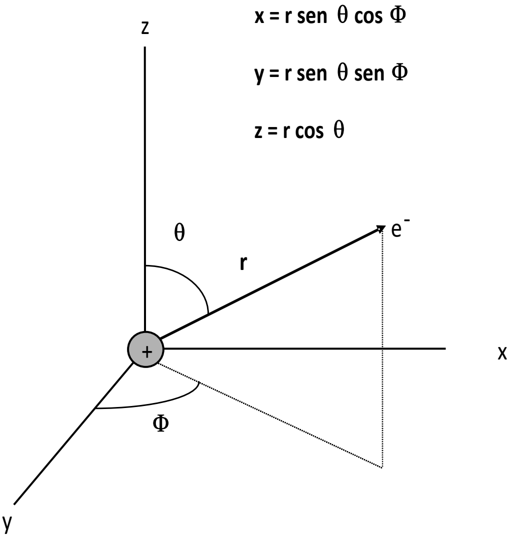
$$H\,\Phi = E\,\Phi. \qquad [1.10]$$

The hydrogen atom is a system composed of two particles: nucleus and electron. The potential energy of the system is given by $-e^2/r$, where e and r represent the electron charge and the distance between electron and nucleus respectively. As a first approximation, we can suppose that the system consists of one particle (the electron) orbiting around the nucleus, which is motionless at the origin of coordinates. The Schrödinger equation for this system is:

$$-\,h'^2/2m\;(d^2\Phi/dx^2 + d^2\Phi/dy^2 + d^2\Phi/dz^2) + (-e^2/r)\;\Phi = E\;\Phi. \qquad [1.11]$$

The stated function, Φ, is a function of the three spatial coordinates: x, y and z. Consequently, we find three partial derivatives, with respect to x, y and z. Equation [1.11] is already impressive enough. However, it can be made even more so by writing it in spherical coordinates (we will not do this here). The point is that this differential equation is solved quite easily when it is written in this type of coordinate system (Figure 1.5.1). This mathematical 'advantage' has governed the form of all results concerning the atomic model derived from the Schrödinger equation.

$$-h'^2/2\mu\,(d^2\varphi / dx^2 + d^2\varphi / dy^2 + d^2\varphi /dz^2) + (-e^2/r)\,\varphi = E\varphi$$



$$x = r \text{ sen } \theta \cos \Phi$$

$$y = r \text{ sen } \theta \text{ sen } \Phi$$

$$z = r \cos \theta$$

Figure 1.5.1. Spherical coordinates and their equivalence with Cartesian coordinates

The mathematical conditions imposed by quantum mechanics on the state function, to make it acceptable, produce three quantum numbers (corresponding to the three spatial coordinates): n, l and m. These numbers present conditional values:

$$n = 1, 2, 3\ldots$$

$$l = 0, 1, 2, \ldots n\text{-}1$$

and

$$m = - l, - (l - 1) \ldots 0 \ldots l - 1, l.$$

Each trio of quantum numbers n, l and m defines a function state of the system, which is a solution to the differential equation [1.11]. The energy of the system, however, comes defined only by the quantum number n. The energy values whose adoption is permitted by the system are those given by the next equation:

$$E = (-2\,\pi^2\, me^4/h^2)\,(1/n^2) \qquad [1.12]$$

where m and e stand for the mass and charge of the electron. h is the Planck's constant. There is a letter code for specifying the quantum numbers. Therefore, the possible state function and energy levels allowed to the hydrogen atom are (Figure 1.5.2):

n	**l**	**m**	**Function Φ**	**Energy**
1	0	0	1s	$(-2\,\pi^2\, me^4 / h^2)$
2	0	0	2s	$(-2\,\pi^2\, me^4 / h^2)/4$
2	1	-1	$2p_x$	$(-2\,\pi^2\, me^4 / h^2)/4$
2	1	0	$2p_y$	$(-2\,\pi^2\, me^4 / h^2)/4$
2	1	1	$2p_z$	$(-2\,\pi^2\, me^4 / h^2)/4$
…				

Figure 1.5.2. Quantum numbers

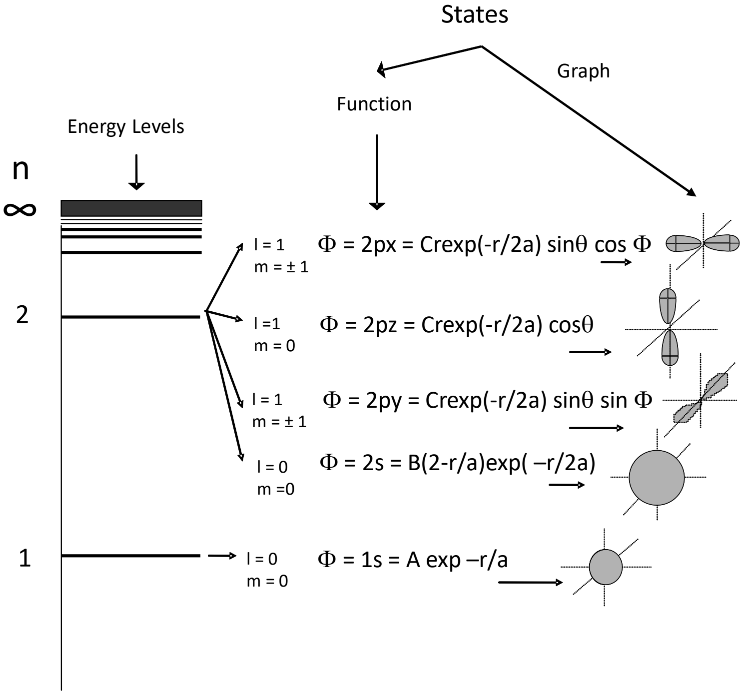


Figure 1.5.3. Some state functions and energy levels allowed to the hydrogen atom

The initial models for the hydrogen atom, such as those of Rutherford or Bohr, described the electron in orbital motion around the nucleus. The model offered by quantum mechanics rejects the use of the classical motion of particles to describe a trajectory. Instead we have the state function, Φ. This function, however, does not mean anything by itself. Nevertheless, one of the postulates of quantum mechanics establishes that if Φ is a state function, describing the state of the particle, Φ^2, is a probability density function:

$$P = \int \Phi^2 \, dV. \qquad [1.13]$$

For example, the state defined by the set of quantum numbers 1, 0, 0 is the 1s function. As can be seen in Figure 1.5.2, this function is the following exponential:

$$1s \equiv \Phi = A \exp(-r/a) \qquad [1.14]$$

where A is a constant, and a is a constant that has dimensions of r (length), and a numerical value equal to the radius of the first orbit of the Bohr atom. The probability density function will be Φ^2.

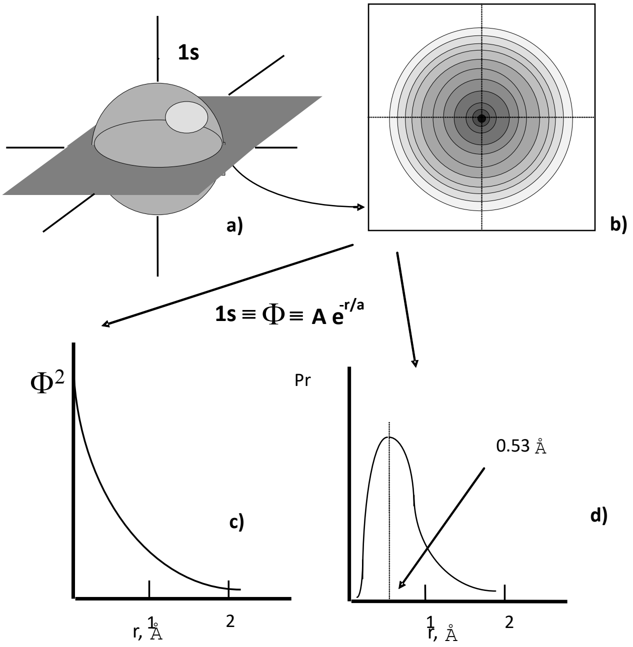


Figure 1.5.4. Φ^2 represents a function of probability density. It means that the probability of finding the electron has spherical symmetry. This is why we represent 1s by a sphere.

Both Φ and Φ^2 are only functions of r. This means that the probability of finding the electron has spherical symmetry with respect to the nucleus. This probability depends only on the distance, r, between the electron and the nucleus (see Figure 1.5.4). According to [1.13], the probability of finding the electron somewhere in the nucleus environment can be calculated by solving this integral. It can be shown that the probability of finding the electron somewhere at a distance r from the nucleus of the hydrogen has a maximum value for a fixed value of r, as can be seen in Figure 1.5.4 and Seminar 1.5.1.

Finally, to complete this brief summary about the model of the hydrogen atom described by quantum mechanics, we must say something about spin. Electrons are particles with a negative charge. According to classical mechanics, the orbital angular momentum of this charged particle around the nucleus generates a magnetic moment similar to that used to describe the interaction between an electrical circuit and a magnetic field. In the case of electrons, however, the magnitude and orientation of the orbital angular momentum (and the corresponding magnetic moment) are quantized by quantum numbers l and m. The different orientations of the orbital angular momentum are degenerate. They possess the same energy, which depends only on the quantum number n. In the presence of a magnetic field, however, the degeneracy disappears (Zeeman effect) and the energy depends on quantum number m, as well as on n.

Elementary particles possess an additional angular momentum (and the corresponding magnetic moment), which lacks a classical analogy, although it appears naturally when relativity theory is taken into consideration. This is the spin angular momentum. In the particular case of electrons, it can be represented by a vector with two allowed orientations corresponding to two quantum numbers of spin, ms, +1/2 and – 1/2. The existence of this magnetic momentum derives from observations, in the presence of external magnetic fields, with spectroscopic instruments of very high resolution, the description of which is above our present ambition. Both angular momenta interact with each other. Therefore, the energy of the hydrogen atom depends on n, and, although almost negligibly, also on the value of l.

1.6 Atomic Structure

The Schrödinger equation for the helium atom cannot be solved because of the term of potential energy corresponding to the repulsion between the two electrons that, together with the positively charged nucleus, form the atom. Obviously, explicit solutions to the Schrödinger equation corresponding to the rest of many-electron atoms cannot be found either. Approximate solutions can be found by means of complex mathematical procedures which have configured the way we currently work with and the way we talk about atoms and molecules.

The approximate solutions (states) to the Schrödinger equation are sought one by one. Obviously the most relevant function for a chemist is that corresponding to the ground state. For example, in the case of helium, the simplest approximate state would be that resulting from ignoring the repulsion energy between the two electrons of the atom. This approach leads us to propose, as a first approximate function for the ground state of helium, the product of two hydrogen-like functions (or orbitals):

$$\Phi = (1s)\,(1s). \qquad [1.15]$$

It can be shown that when [1.15] is the state function of the system, the corresponding energy must be the sum of two hydrogen atoms, corrected by the presence of two protons in the nucleus. This approximation represents an error of about 20% with respect to the true ground state energy of the helium atom. Nevertheless, quantum mechanics offers many mathematical tools to improve the approximate function [1.15] and the corresponding energy. We say that the electronic configuration of helium is $1s^2$, which means that we are using two hydrogen-like functions to build the first approximation of the ground state of helium.

The next atom in the periodic table is Lithium. The approximate state function for the ground state might be formed by the product of three hydrogen-like functions, similar to the approximate function built for helium. However, that function would violate the Pauli exclusion principle. The statement of this principle is very abstract in mathematical terms. Nevertheless, an important consequence derived from it can be easily expressed: to construct the approximate state function, no two functions may have the same values for the four quantum numbers. Since the coincidence between the number of electrons contained by the atom, and the number of functions used to build the approximated function, it can also be said, in line with the Pauli exclusion principle, "no two electrons may have equal values for the four quantum numbers". The function $1s^3$ defines two different sets of quantum numbers (n, l, m and ms) as 1, 0, 0, 1/2 and 1, 0, 0, -1/2. The third electron would have to have a set of quantum numbers equal to one of the previous sets. In order to satisfy the Pauli principle, a different set of orbital quantum numbers must be assigned to the third electron. The one supplying the lowest energy is 2, 0, 0 and 1/2 or -1/2 for the spin quantum number. The approximate function for the ground state of Lithium is built by multiplying two hydrogen-like functions 1s by one hydrogen-like function 2s. We then say that the electronic configuration of Lithium is $1s^2\,2s$.