BIOCHEMICAL MECHANISMS

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biochemical mechanisms

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preface

Biochemistry has now reached a stage in its development that requires a knowledge of mechanistic chemical principles. Many excellent books are available which contain this background material, but these often do not fill the special needs of the biochemist. Acidity functions in strong acid solution, for example, are of no interest in the study of reactions at physiological pH values.

The use of structure variations to determine mechanisms is explained fully in books dealing with physical organic chemistry. This method has been extremely valuable in understanding organic mechanisms, but is of less value to the biochemist who deals with enzymes with great substrate specificities.

Biochemical mechanisms are a specialized branch of mechanistic chemistry. Enzyme reactions occur through transition states that are held in very definite fixed positions. This allows mechanisms that are less likely in usual solution chemistry. Acidic and basic catalysts such as carboxyl groups and amino groups are available at exactly the correct position; therefore the entropy of activation is of less hindrance in enzymic reactions than in solution chemistry. In addition the biochemist is interested in inorganic as well as organic mechanisms, and the two must be correlated. Finally the biochemist wants concrete examples of mechanisms in biochemical systems, and the methods that were used to determine these mechanisms. These specialized problems require a specialized book on biochemical mechanisms, which I have tried to provide.

The book is divided into two parts. The first part reviews general mechanistic principles of organic and inorganic chemistry that are of value to biochemistry. This includes a review of orbital and other fairly basic concepts in order to facilitate the discussion of mechanisms in the second section.

The second part treats specific biochemical mechanisms. This part is divided into various type reactions. The mechanism of the reaction as known in solution chemistry is discussed in terms of principles that may apply to the biochemical reaction. Next the mechanisms of action of any model enzymes are described, and finally the enzymic reaction is compared with model reactions.

No attempt is made to include the mechanisms of purely physiological processes such as absorption, secretion, muscle contraction, or nerve action. Our knowledge has not advanced to a state where it seems possible to explain these processes from a reaction mechanism point of view. The reader should be warned that many of the mechanisms given in this book are highly speculative. Any book on biochemical mechanisms would necessarily be so at this date. The purpose in speculating on mechanisms is only to encourage research; mechanisms should not gain in stature merely because they are in print.

I wish to acknowledge the inspiration of F. H. Westheimer. Dr. Westheimer has so many ideas that after spending a year with him it is difficult to give specific credit to those here which are rightfully his.

I wish to thank my wife, Marie Ingraham, for proofreading and repeated retypings of the manuscript.

LLOYD L. INGRAHAM

Davis, California
November, 1961

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part one

ATOMIC ORBITALS

Electrons have the interesting characteristic of showing the properties of both particles and waves. The fact that electrons may be considered as standing waves in a potential field means that they may only have certain frequencies or energies in a given potential field. A guitar string, for example, may vibrate with a given frequency or energy and harmonics of this frequency but is not allowed to vibrate at frequencies at random. This restriction on energy means that the electrons around a nucleus must exist in definite energy levels.

The wave motion of an electron can be expressed by the wave equation

$$\frac{\partial^2\psi}{\partial x^2} + \frac{\partial^2\psi}{\partial y^2} + \frac{\partial^2\psi}{\partial z^2} + \frac{8\pi^2 m}{h^2}(E - V)\psi = 0$$

which relates the amplitude ψ of the waves at any position (x, y, z) to the mass of the electron m, the total energy of the electron E, and the potential energy V. The symbol h is Planck's constant. This is a differential equation, and solutions of amplitude ψ as a function of x, y, and z are possible for only certain values of E, which is the mathematical reason for the restrictions in energy levels. If we consider an electron in a hydrogen atom, V is the coulombic potential energy between the positively charged nucleus and the electron. Many solutions are possible for the equation describing an electron in a hydrogen atom, but all may be summarized in a rather complex general solution in terms of the coordinates, several constants, and three numbers n, l, and m. The particular solutions are obtained by substituting certain integral values for n, l, and m. Not all values are possible, and the values used for one constant depend on the value given to the other constant. These constants are called quantum numbers. The *principal* quantum number, n, determines the size of the orbit; the *orbital* quantum number, l, determines the shape of the orbit; and the *magnetic* quantum number, m, determines the special orientation of the orbit. In addition, the electron itself has a magnetic spin of $\frac{1}{2}$ or $-\frac{1}{2}$ of a Bohr magneton depending upon its orientation, measured by the spin quantum number s. The four quantum numbers, n, l, m, and s completely describe an electron.

No two electrons in the same atom can have the same values for these four quantum numbers. The principal quantum number, n, can have positive integral values 1, 2, 3, 4, etc. The orbital quantum number, l, can have integral values including zero between zero and $n - 1$. The magnetic quantum number, m, can have both positive and negative values, including zero, between and including $-l$ and l. The spin quantum number, s, can have only values of $\pm\frac{1}{2}$. The quantum numbers of the ten electrons in the $n = 1$ and $n = 2$ levels are shown below. Notice that no two electrons have the same four quantum numbers.

n	l	m	s	*Designation*
1	0	0	$\frac{1}{2}$	1*s*
1	0	0	$-\frac{1}{2}$	1*s*
2	0	0	$\frac{1}{2}$	2*s*
2	0	0	$-\frac{1}{2}$	2*s*
2	1	-1	$\frac{1}{2}$	2*p*
2	1	-1	$-\frac{1}{2}$	2*p*
2	1	0	$\frac{1}{2}$	2*p*
2	1	0	$-\frac{1}{2}$	2*p*
2	1	1	$\frac{1}{2}$	2*p*
2	1	1	$-\frac{1}{2}$	2*p*

An orbital is described by the quantum numbers n, l, and m, so that an orbital may contain two electrons, one with $s = \frac{1}{2}$ and the other with $s = -\frac{1}{2}$. Orbitals with $l = 0, 1, 2, 3$ and 4, are designated by the symbols *s*, *p*, *d*, *f* and *g*, respectively. After *f* the letters are in alphabetical order. A 2*s* orbital means $n = 2$ and $l = 0$, and a 4*p* orbital means $p = 4$ and $l = 1$. From the table above it is evident that there is only one 1*s* orbital and only one 2*s* orbital but there are three 2*p* orbitals. Further extrapolation will show that there are five 3*d* orbitals. All of these orbitals (*s*, *p*, *d*, *f*, *g*, etc.) are solutions of the wave equation and determine the amplitude of the wave at any position. No physical meaning can be attached to the orbital other than the concept of wave amplitude. Nevertheless, orbitals are a valuable concept that will prove useful in later discussions of enzyme mechanisms. The value of the orbital varies with the direction and distance from the nucleus. The equations for two typical wave functions or orbitals are shown below:

n	l	m	*Orbital*
1	0	0	$\psi_{1s} = \dfrac{1}{\sqrt{\pi}}\left(\dfrac{Z}{a_0}\right)^{3/2} e^{-\rho}$
2	1	0	$\psi_{2pz} = \dfrac{1}{4\sqrt{2\pi}}\left(\dfrac{Z}{a_0}\right)^{3/2} \rho e^{-\rho/2} \cos\theta$

The symbol Z stands for the nuclear charge, a_0 is a constant, and $\rho = r/a_0$.

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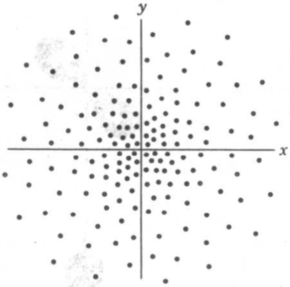
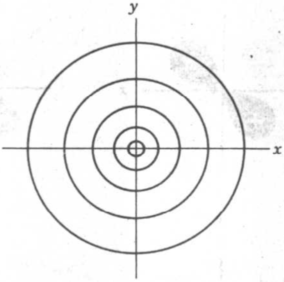
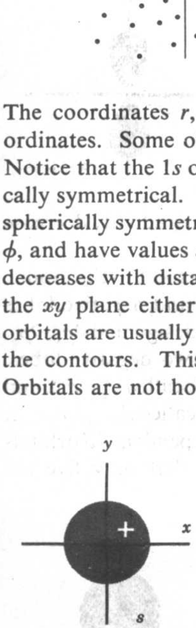
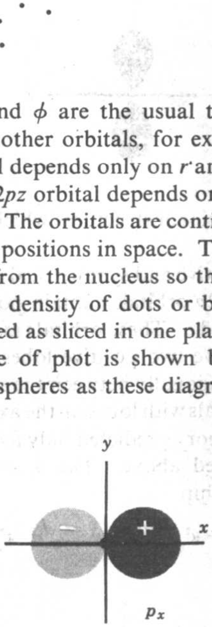
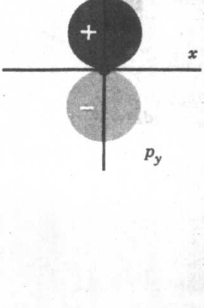


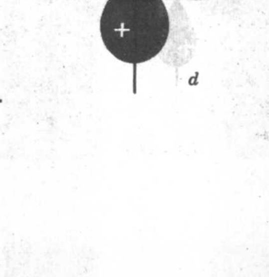


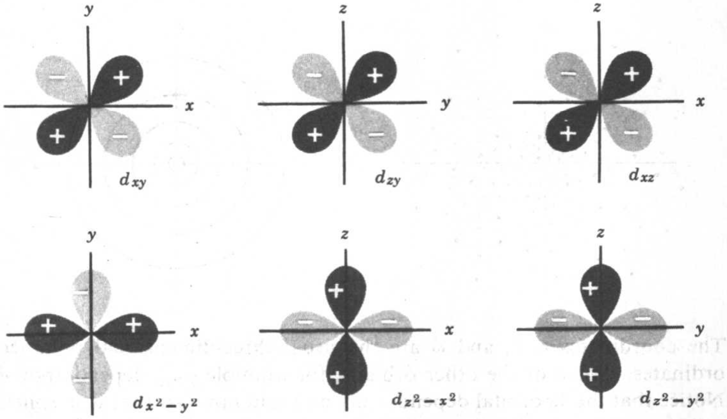
The coordinates r, θ, and ϕ are the usual three-dimensional polar coordinates. Some of the other orbitals, for example ψ_{2p_z}, depend upon ϕ. Notice that the 1*s* orbital depends only on r and not θ so that it is spherically symmetrical. The 2*pz* orbital depends on θ, so that this orbital is not spherically symmetrical. The orbitals are continuous functions of r, θ, and ϕ, and have values at all positions in space. The amplitude of a 1*s* orbital decreases with distance from the nucleus so that it should be described in the xy plane either by a density of dots or by contour lines. However, orbitals are usually plotted as sliced in one plane and only showing one of the contours. This type of plot is shown below for various orbitals. Orbitals are not hollow spheres as these diagrams would indicate but are







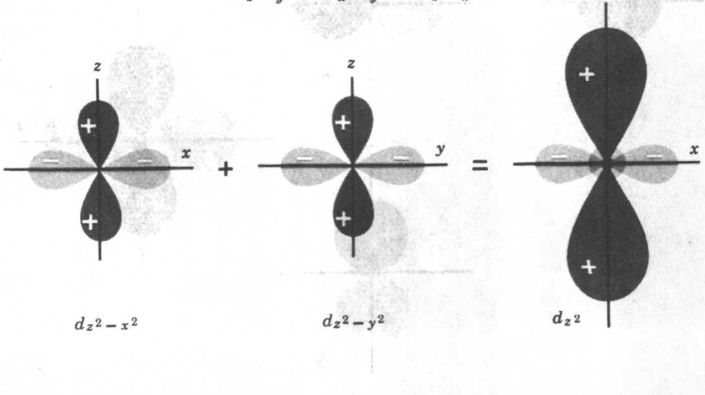




actually diffuse three-dimensional structures which only gradually decrease in value through space.

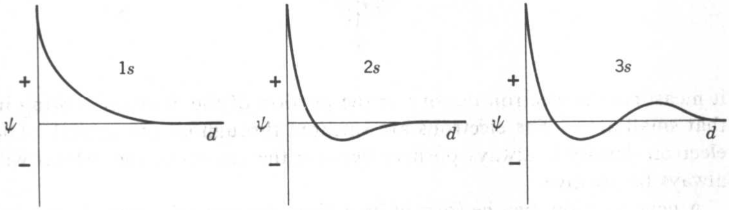
The 2*s* orbitals are all positive and symmetrical with respect to the atomic nucleus, whereas the three 2*p* orbitals contain positive and negative lobes along the three axes, x, y, and z. These orbitals may be designated $2p_x$, $2p_y$, and $2p_z$. The *d* orbitals have two positive lobes and two negative lobes. The *d* orbitals with lobes diagonally between the axis are called d_{xy}, d_{yz}, and d_{xz} respectively. The *d* orbitals with lobes on the axis are called $d_{x^2-y^2}$, $d_{z^2-x^2}$, and $d_{z^2-y^2}$ respectively. Theory predicted only five independent 3*d* orbitals and six have been described above. The answer is that only five are independent. The relationship

$$d_{z^2-y^2} - d_{x^2-y^2} = d_{z^2-x^2}$$

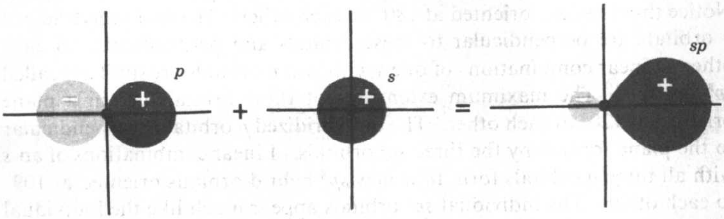


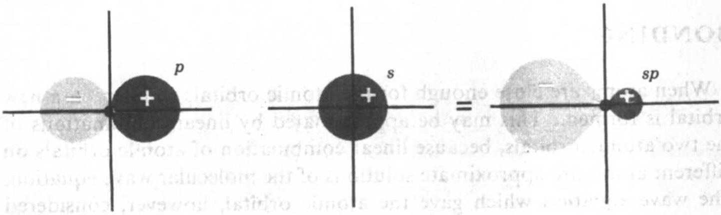
shows that the last three are linearly dependent. Usually a new orbital called d_{z^2} is formed by adding $d_{z^2-y^2}$ and $d_{z^2-x^2}$. The five orbitals are then taken as d_{xy}, d_{yz}, d_{xz}, $d_{x^2-y^2}$, and d_{z^2}. The signs of the orbitals refer only to the sign of the amplitude of the wave functions, and are not related to the spin or electron density. The *n* quantum number changes the sign of the orbital and the internal structure but not the shape, for example, 2*s* orbitals are larger than 1*s* orbitals and contain a nodal sphere of zero amplitude. The sign of the amplitude changes at this node.

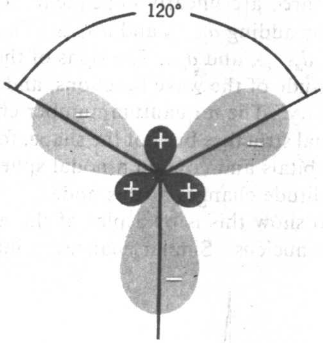
The easiest way to show this is by a plot of the amplitude against the distance, *d*, from the nucleus. Similar changes in internal structure occur with the higher *p* and *d* orbitals. Differences in internal structure, however, are not of importance in the qualitative descriptions of chemical reactions, so that internal structure will be neglected in further discussions.



The square of the orbital does have physical meaning: in any small area





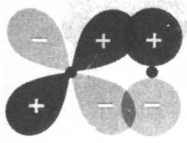


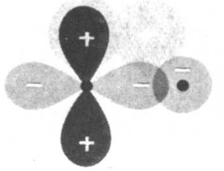
it measures the electron density or the portion of the electron existing in that small area. The electrons are smeared throughout the orbital. The electron density is always positive because the square of the orbital will always be positive.

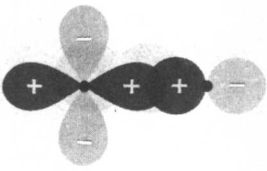
A new function may be formed by adding the two solutions, 2*s* and 2*p*, of the wave equation. This new function satisfies the wave equation and is therefore an orbital. It satisfies the wave equation because linear combinations of solutions of a differential equation are also solutions of the equation. These new orbitals, formed by adding and subtracting 2*s* and 2*p* orbitals, are called hybridized orbitals and are designated as *sp* orbitals. Notice that they are oriented at 180° to each other. The two unhybridized *p* orbitals are perpendicular to these orbitals and perpendicular to each other. Linear combinations of one *s* with two *p* orbitals are similarly called sp^2 orbitals. The maximum extensions of these orbitals are in a plane oriented at 120° to each other. The unhybridized *p* orbital is perpendicular to the plane formed by the three sp^2 orbitals. Linear combinations of an *s* with all three *p* orbitals form four new sp^3 hybrid orbitals oriented at 109° to each other. The individual sp^3 orbitals appear much like the individual sp^2 orbitals.

BONDING

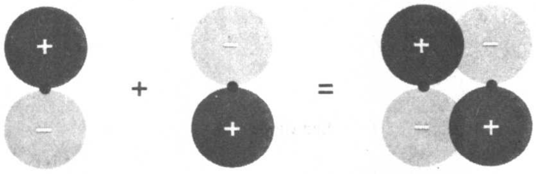
When atoms are close enough for the atomic orbitals to interact, a new orbital is formed. This may be approximated by linear combinations of the two atomic orbitals, because linear combination of atomic orbitals on different atoms are approximate solutions of the molecular wave equation. The wave equation which gave the atomic orbital, however, considered

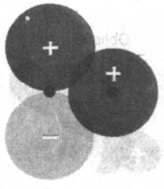


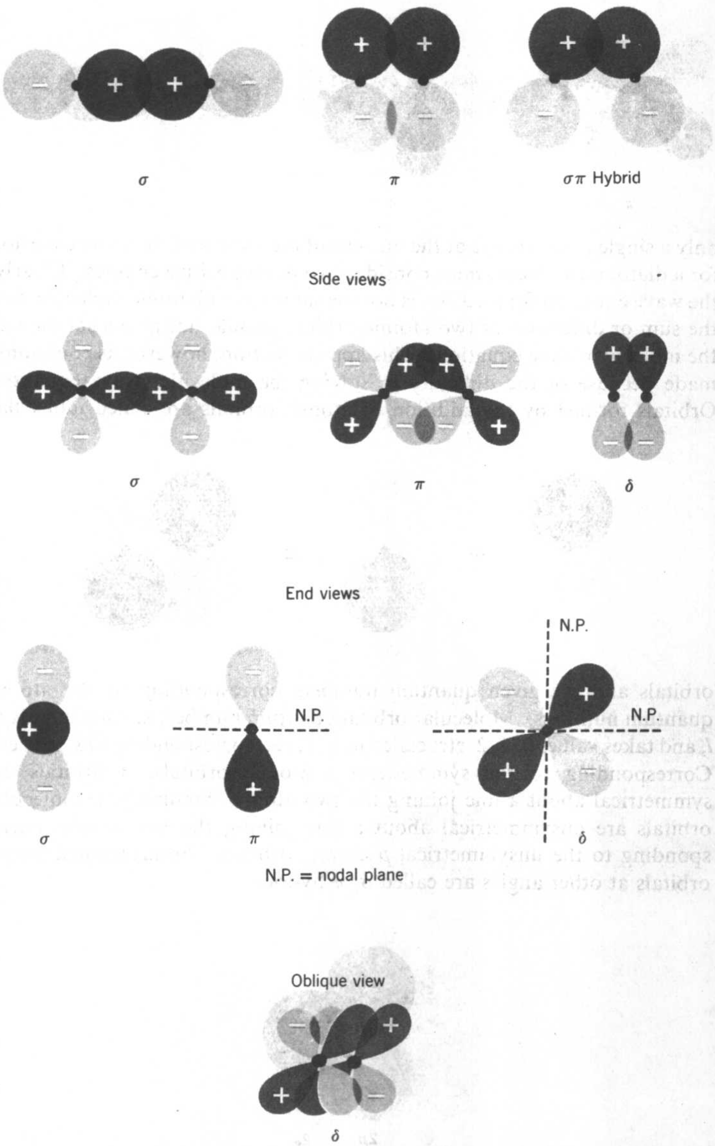




only a single point charge at the nucleus of the atom and the wave equation for a diatomic molecule must consider two point positive charges. Clearly, the wave equation for an atom is not the same for a diatomic molecule, and the sum or difference of two atomic orbitals should not give a solution to the molecular wave equation. This approximation, however, is commonly made because of the difficulty in solving the molecular wave equation. Orbitals formed by the addition of atomic orbitals are called molecular orbitals and are given quantum numbers corresponding to the atomic quantum numbers. Molecular orbital quantum number, λ, corresponds to l, and takes values 0, 1, 2, etc. called σ, π, δ, etc. corresponding to *s*, *p*, *d*, etc. Corresponding to the symmetrical *s* atomic orbitals, σ orbitals are symmetrical about a line joining the two atoms. Similarily, π molecular orbitals are unsymmetrical about a line joining the two atoms, corresponding to the unsymmetrical *p* atomic orbitals. Bonds formed from *p* orbitals at other angles are called σ, π hybrids.



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N.P. = nodal plane
Oblique view
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