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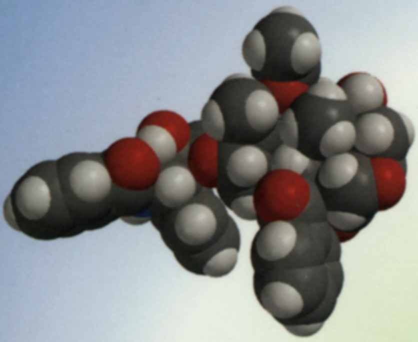

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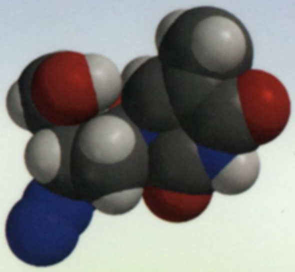

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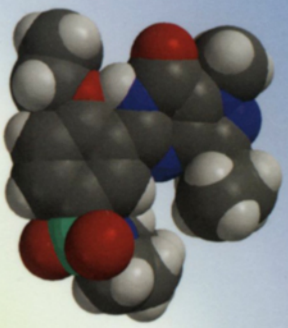

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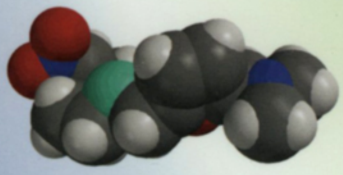
MOLECULES AND MEDICINE



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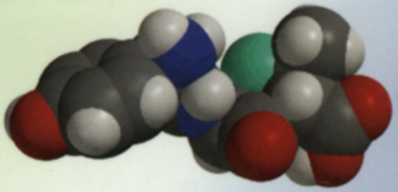

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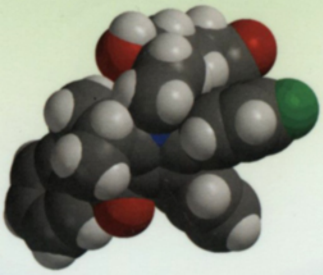

Atorvastatin (Lipitor)

E.J. Corey • Barbara Czakó • László Kürti

MOLECULES
AND
MEDICINE

BICENTENNIAL
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MOLECULES AND MEDICINE

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PREFACE

This book is intended for a broad readership, starting with curious and thoughtful college undergraduates and, reaching beyond, to professionals and researchers in the life sciences and medicine. It is hoped that it will also be useful to the educated lay person with an interest in health and medicine.

An effort has been made to integrate chemistry, biology, drug discovery and medicine in a way that is clear and self-explanatory. Heavy use has been made of chemical structures, since they provide a fundamental key to the language of life and the human activities that flow from it. Our age has seen the rapid evolution of molecular medicine as a critical part of the broader fields of health care and the biochemical basis of human disease. The understanding of human illness at the molecular level has brought, and will bring, great benefit to mankind.

There is a price to be paid in any attempt to understand molecular medicine, because that comprehension requires an ability to decipher chemical structures, which many have regarded as too onerous. One purpose of this book is to demonstrate that an adequate understanding of chemical structures is easily within the reach of most educated people, and well worth the effort. Pages 4-31 of this book aim to provide the insights and background required to appreciate the architecture of therapeutic molecules and their target proteins, as they parade though the subsequent pages of this book.

"*Molecules and Medicine*" delves into the discovery, application and mode of action of well over one hundred of the most significant molecules now in use in modern medicine. It is limited to *centamolecules*, i.e. molecules with molecular weights in the hundreds (several hundred times more than a hydrogen atom). The important and rapidly developing area of macromolecular therapy, which involves *much larger molecules* (macromolecules), such as biologically active proteins and monoclonal antibodies, is a different story, and another book.

We have tried to minimize the amount of prior knowledge required of the reader by providing much background information, both chemical and biomedical. An effort has also been made to be concise as well as clear. A large amount of material has been compressed into a small space for each therapeutic agent. Generally, each medicine is allotted just one page. One advantage of this modular arrangement is that it facilitates the reading of the book in small installments and also its use as a reference work. The therapeutic agents in this book are arranged in sections according to the type of medical condition they treat.

There are also numerous sections in the book that provide biomedical background. For instance, there are two-page to eight-page summaries of topics such as inflammation, metabolic syndrome, immunology, drug resistance, cancer and neurotransmission. These are placed at strategic locations throughout the book.

The structural representations of proteins in this book are in the public domain and may be downloaded from http://www.pdb.org.

In the process of writing this book we have come to appreciate ever more keenly the enormous amount of human talent and effort that has enabled the extraordinary advances in molecular medicine since its advent several decades ago. To the countless chemists, physicians, biologists, educators and other professionals who have participated in this venture we extend our gratitude and thanks. This book is a tribute to them all.

The writing of this work has also been motivated by the realization that the advance of molecular medicine can be even more remarkable during the coming decades of this century, if a steady flow of dedicated and able young people into all the key areas of research in the life sciences can be maintained. If this book plays just a minor part in enhancing progress in molecular medicine and human well-being, our small effort will have been amply rewarded.

A NOTE ON THE USE OF THIS BOOK

Structures of Molecules and Proteins

Those who are not familiar with the notation used to describe the structures of organic compounds will profit from a close reading of pages 4-22 of this book. Others can read through this part quickly and proceed to the next section (pages 26-31) that reviews the notation used in the book for the structures of proteins.

The coordinates for each of the protein structures shown in the book are in the public domain and can be accessed electronically.

Accessing X-Ray Crystal Structure Data Files Online – The Protein Data Bank

All the crystal structure files can be downloaded from http://www.pdb.org by entering the four-character PDB ID that is indicated in red at the bottom of the page where the protein is displayed or in the reference section. For example, on page 63 in the entry for sitagliptin (Januvia™), the X-ray crystal structure of sitagliptin bound to the target protein DPP-4 is displayed. The access code (PDB ID) for this crystal structure appears below the picture as **1X70** along with the corresponding reference.

Graphic Rendering of X-Ray Crystal Structure Data Using PyMol

The renderings of the X-ray crystal structure data were developed by the authors using the software PyMol v0.99 (DeLanoScientific LLC, http://www.delanoscientific.com). For a description of the Protein Data Bank, *see*:

H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne: The Protein Data Bank. *Nucleic Acids Research*, *28,* 235-242 (**2000**).

Organization and References

The discussion of each of the therapeutic agents in the book is limited to one page, and, consequently, much in the way of detail has been omitted. For this reason, a number of up-to-date references on other aspects of each agent are given both at the bottom of the appropriate page and at the end of each section. The page numbers on which detailed references are listed for each therapeutic agent are highlighted in green at the bottom of the pages. Additional information on the pharmacology and properties of each medicinal agent can be found in:

Goodman & Gilman's The Pharmacological Basis of Therapeutics. Laurence L. Brunton, John S. Lazo and Keith L. Parker (Editors); (McGrawHill, 11th Edition, **2006**).

Other recent texts that provide much useful background information are:

(1) L. Stryer et al. *Biochemistry*, (W.H. Freeman, 6th Edition, **2007**)

(2) B. Alberts et al. *Molecular Biology of the Cell* (Garland Science, 4th Edition, **2002**)

(3) Weinberg, R.A. The Biology of Cancer (Garland Science, **2007**)

(4) *The Merck Manual of Diagnosis and Therapy.* M.H. Beers and R.S. Porter (Editors). (Merck & Co., 18th Edition, **2006**)

The references that appear in this book can serve as a portal to a great deal of information on the chemistry, biology and medicine relevant to the therapeutic agent and disease area. Additional material can be located by appropriate database- and internet searching (e.g., using SciFinder Scholar™, MEDLINE™ or Google™).

A **glossary** and an **index** appear at the end of the book.

Online Reader Feedback for the Authors

There is a website for this book maintained by the authors, the address for which is:

http://moleculesandmedicine.info/

Readers can use this website to provide comments or feedback on "*Molecules and Medicine*". The website will also contain certain useful updates. The authors invite the views of non-scientists who have read pages 4-31.

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PART I.

INTRODUCTION

We live in a troubled, but wonderful time. It is our good fortune to witness and benefit from scientific advances that would have been literally unimaginable to our grandparents. However, there are dark clouds on the horizon. The rate of growth of scientific knowledge has been so great as to outstrip the ability of our society to assimilate it, the capacity of the educational system to teach it properly, and the wisdom of government adequately to sustain and apply it. There is widespread indifference to science among the young. Even medical science, which touches the lives of us all, is generally left to the practitioners. Whatever the reason for this disparity between the importance of science and the lack of general public understanding, it is important to address it.

In this book we try to take a few steps in this direction. Specifically, the pages to follow tell the tales of many molecules that can qualify as miracles of modernity. These relatively small, highly-structured clusters of atoms, the principal therapeutic agents of modern medicine, can perform in a way that would have been considered miraculous to our ancestors. Such "miracle molecules" can save countless human lives, prolong human life, alleviate pain and suffering, control cells, tissues and organs millions of times their size, and bring enormous material gains through commercial sales of billions of dollars per year. Such molecules also can serve as tools to probe the molecular nature of life processes and disease states and pave the way for the discovery of other effective medicines.

The molecules at the core of this book have been carefully selected from several thousand therapeutic agents that have been used in medicine at one time or another. The development of each of them, arduous and costly though it might have been, represents an enormously valuable investment with very large and ongoing benefits. In the course of discovering all these wonderfully useful molecules, we have learned more about the discovery process itself and have developed an ever expanding set of new discovery tools. The invention of these new platforms for innovation is being powered by dramatic advances in technology, computing and the underlying chemical and biomedical sciences.

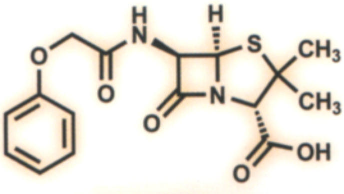
The very next section of this book provides a step-by-step introduction to the understanding of the architecture of organic molecules and the general principles that govern structures of molecules. In addition, we explore the fundamental forces that hold molecules together and that allow them to recognize and bind to one another. The affinity of molecules for one another is central to the biological activity of therapeutic agents and to life itself. The section on how to read the chemical diagrams of small molecules is followed by another tutorial on understanding much larger structures, the proteins of life.

It seems quite possible that, in the next century or so, effective treatments for most illnesses will emerge. Disease, premature death, suffering and pain may no longer be a part of the human condition. Humans will as a matter of course live out a full and healthy lifespan, and then depart with grace and dignity. The famous poem of Lady Gio in "The Tale of the Heike" describes the life process and its end in an eloquent and happy way:

> *Grasses of the plain,*
> *Springing up and withering,*
> *They all fare alike.*
> *Indeed the lot of all things*
> *Is but to wait for autumn.*

An impossible dream? Perhaps, but the immense effort required will be well worthwhile, because the gain will be incalculable. The achievements of modern science and technology provide both encouragement and inspiration.

For instance, we are now able to trace our universe back some 14 billion years to an unbelievably hot object, with a temperature of about 10^{32} Kelvin (10 followed by 32 zeros), and more than a million times smaller than the period at the end of this sentence. From this inferno of exceedingly small and simple objects, the first elements, hydrogen and helium, formed about a million years later, to be followed by all the other objects of the universe – the chemical elements, stars and galaxies, and an unknown collection of other forms of matter and energy, and finally the earth and life upon it. Surely, a time will come when our knowledge of life, intelligence, disease and health will dwarf that of the present.



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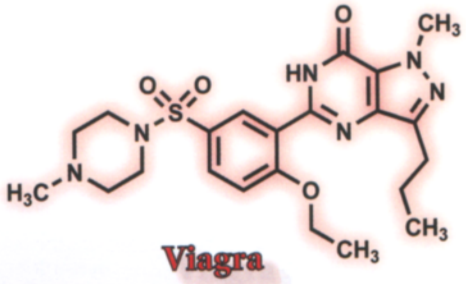
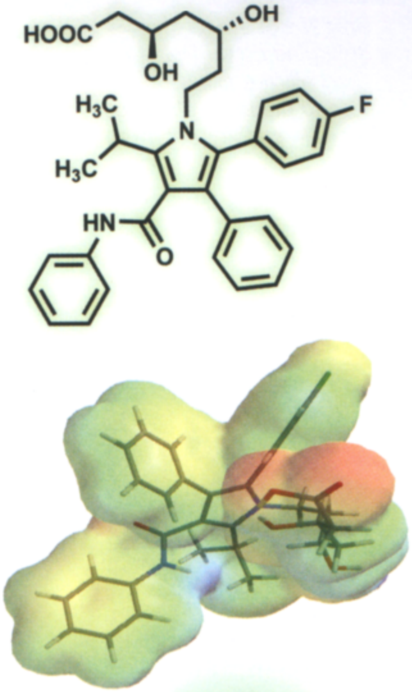
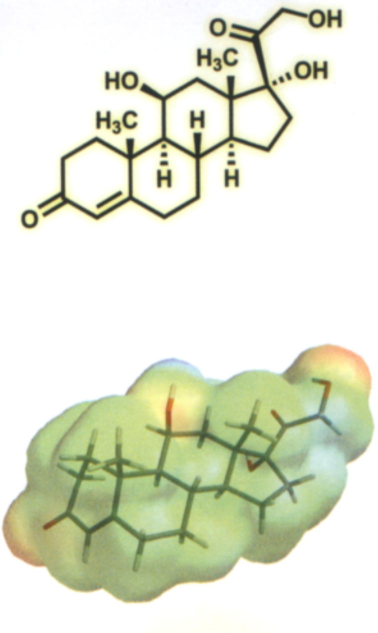


Viagra

MIRACLE MOLECULES



Lipitor



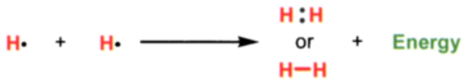
Cortisol

UNDERSTANDING STRUCTURAL DIAGRAMS OF ORGANIC MOLECULES

Introduction. Some Sample Molecules

The Simplest Molecule, H_2

Hydrogen, the simplest element, has atomic number *one* because it contains just *one* proton in the nucleus and *one* electron that surrounds it. A hydrogen atom is so reactive that it will *totally* combine with another hydrogen atom to form the simplest molecule, H_2. This process, the simplest of all chemical reactions, takes place extremely rapidly and with the release of much energy because the energy content of H_2 is much less than two isolated hydrogen atoms. The chemical equation for the reaction is:



$$H\cdot + H\cdot \longrightarrow \overset{H:H}{\underset{H-H}{\text{or}}} + \text{Energy}$$

Equation 1. Two hydrogen atoms combine to form one hydrogen molecule (H-H) with the evolution of energy.

In equation 1, the dots represent electrons. The chemical bond that holds H_2 together is designated by a double dot, or simply, by a line between the hydrogens. Because the electrons are shared equally, the molecule is nonpolar. This type of two-electron bond is called a covalent single bond. Although an electron has a mass, it is very small ($9\text{x}10^{-28}$ g, at rest), and behaves like a wave. In addition, because of the Heisenberg uncertainty principle, its position and momentum cannot both be known precisely. Its location is best described in a probabilistic way as a cloud-like representation (Figure 1).

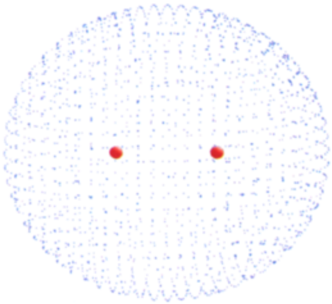


Figure 1. Approximate representation of the spatial distribution of electrons in an H_2 molecule about the nuclei (red spheres). The outer layer of dots encloses about 90% of the total electron cloud.

Helium, a Chemically Inert Element

Helium (He), atomic number *two*, has *two* protons in the nucleus and *two* surrounding electrons. The atom is stable chemically because it neither combines with itself nor reacts with other elements. The reason for this inertness is that two is the maximum number of electrons that can be accommodated in the available orbital. This orbital allows the electrons to distribute themselves like a cloud with spherical symmetry about the nucleus. This orbital is called the 1*s* orbital. The other orbitals of He are so high in energy that they are not accessible for chemical bonding with any atom or chemical fragment. Helium is the simplest of the inert elements. These elements share the feature of having the full complement of electrons in the available orbitals.

Nature of the Chemical Bond in H_2

In H_2, each H contributes a 1*s atomic orbital* (AO), leading to the formation of two *molecular orbitals* (MO's), one of lower energy than the AO and the other of higher energy. The two electrons of H_2 can occupy the lower energy MO, and so H_2 is stabilized relative to two H atoms, as the diagram in Figure 2 illustrates.

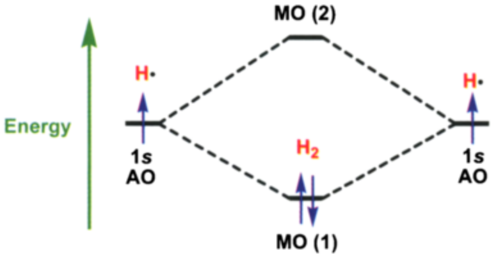


Figure 2. Energy diagram for the combination of two H atom 1*s* AO's to form two MO's of diatomic H_2. The electrons occupy the lower, bonding MO(1) and are shown as blue arrows. MO(2) is an orbital that is not occupied by electrons because of its high energy. MOs can hold only two electrons. These electrons must have opposite spins.

One simple way of thinking about the electron in the H atom is to consider it like a cloud of gas around the nucleus that is kept in place by the electrostatic attraction between the negative electron and the positively charged proton. Once H_2 is formed, the two electrons of H_2 become delocalized over a greater volume around the two-proton axis of the diatomic molecule, which leads to great stability. For a simple analogy, recall that the rapid expansion of a gas lowers its temperature (i.e., energy content). Conversely, compression of a gas raises its temperature/energy content.

The energy of the H_2 molecule is at a minimum when the nuclei are separated by 0.75×10^{-8} cm or 0.75 Angströms (Å). That bond length is determined by a balance between two factors:

(1) there is electrostatic repulsion between the two positively charged nuclear protons which tends to keep them apart and

(2) the electronic stabilization that results from formation of a molecular orbital, increases with the interpenetration (or overlap) of the individual atomic orbitals, an effect that draws the nuclei closer.

In general, chemical bonds between two atoms have characteristic bond lengths (d_0), which result from the balancing of these two effects. A typical graph of the stabilizing energy of a bond as a function of bond length is shown in Figure 3.

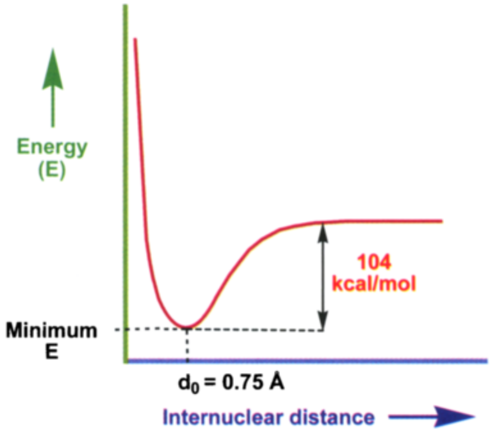


Figure 3. Energy of two hydrogens as a function of internuclear distance.

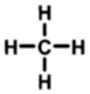
A large amount of energy is required to break the H–H bond of H_2 – 104 kcal/mol – (a mol is defined as 6.02×10^{23} atoms, Avogadro's number). In the pure state the H_2 molecule can be heated to 500 °C without any decomposition.

The bonding diagram for H_2 allows us to explain why H_2 does not react with another H atom to form H_3 as a stable molecule. The bonding orbital MO(1) of H_2 is filled since no more than two electrons can occupy a MO. No significant bonding can be attained by combining MO(2) of H_2 with the AO of the H atom.

Most of the molecules in this book contain hydrogen. In every case each hydrogen forms one *and only one* electron-pair bond with its partner leading us to the first rule:

Rule #1: ***H forms just one electron-pair bond – called a covalent single bond.***

This rule is useful in deriving the actual structures of molecules. Thus, the formula of water, H_2O, and Rule #1 lead to the structure H–O–H, rather than O–H–H, or something else. Similarly, since methane has the composition CH_4, we can draw the structure:



$$\begin{array}{ccc} & H & \\ & | & \\ H- & C & -H \\ & | & \\ & H & \end{array}$$

Three Depictions of H_2

There are a number of alternative ways of representing H_2. In addition to a line drawing H–H, we can use a ball-and-stick drawing or a space-filling diagram, as follows:

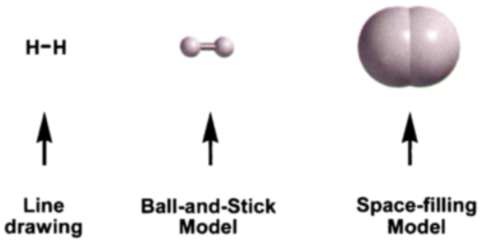


Figure 4. Three different representations of the hydrogen molecule.

The space-filling representation contains additional information because it tells us about the shape and size of a molecule. These features are exceedingly important in determining how two molecules can fit together or interact and also how close they can get. With molecules, as with macroscopic objects, two things cannot occupy the same space at the same time.

Bonding in Carbon Compounds

Carbon, the element with atomic number *six* has *six* protons in the nucleus and *six* electrons surrounding it. *Two* of these fill the low energy 1*s* orbital and play no role in chemical bonding. The remaining *four* electrons can form bonds utilizing a spherical 2*s* orbital and three dumbbell-shaped, mutually perpendicular 2*p* orbitals, the shapes of which are illustrated in Figure 5. The boundary of each dumbbell encloses about 90% of the total electron cloud. The three *p* orbitals are usually designated as 2p_x, 2p_y and 2p_z because they can be placed along the axes of a rectilinear coordinate system. The sum of the electron densities for all three 2*p* orbitals is a *spherical* cloud of larger diameter than the 2*s* orbital.

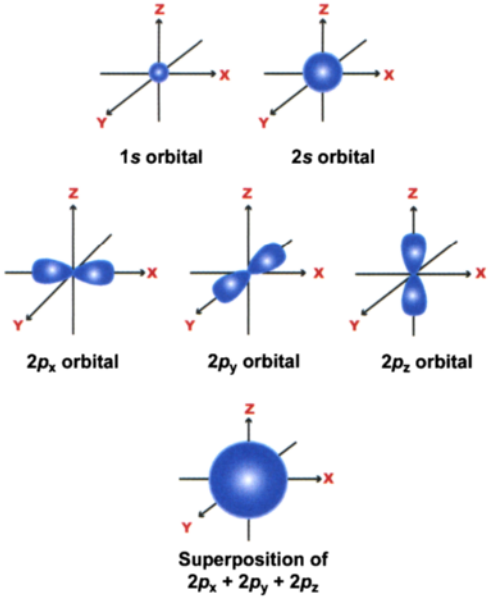


Figure 5. Representation of *s* and *p* atomic orbitals. The boundary of each sphere and dumbbell encloses about 90% of the total electron cloud.

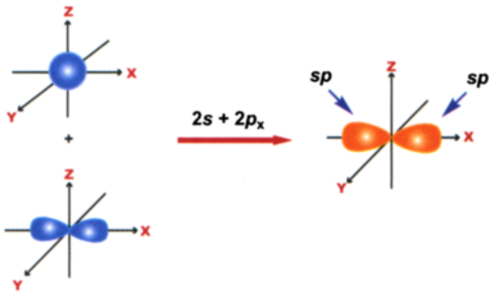


Figure 6. Combination of one 2*s* and one 2p_x atomic orbital (AO) to form two *sp* hybrid orbitals.

The 2*s* orbital can mix with three 2*p* orbitals to form hybrid atomic orbitals in *three* different ways. A sequence for generating the three different 2*s*/2*p* hybrids is shown in Figures 6-8. The number of hybrid orbitals always equals the number of AOs from which they derive.

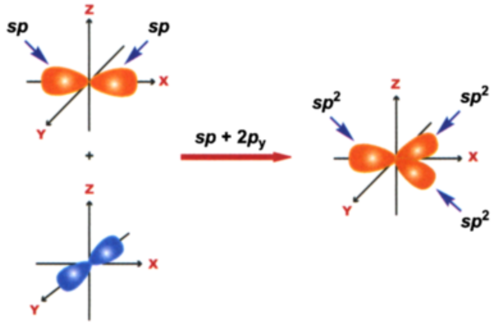


Figure 7. Combination of two *sp* hybrid orbitals and a 2p_y atomic orbital to form three sp^2 hybrid orbitals.

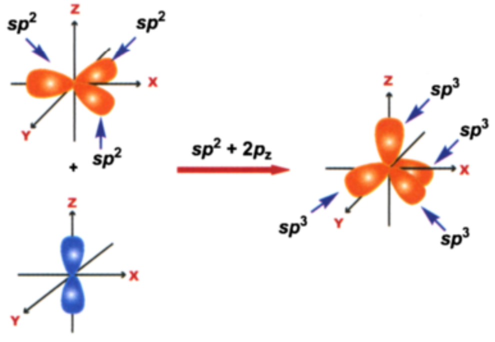
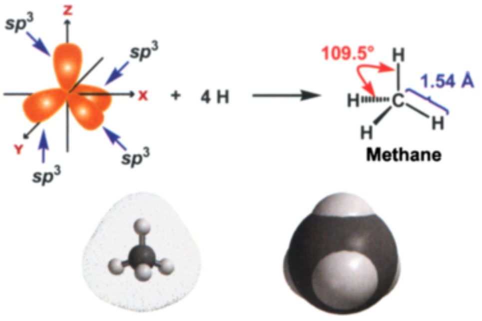


Figure 8. Combination of three sp^2 hybrid orbitals and a 2p_y orbital to form four sp^3 hybrid orbitals.

Hybrid Orbitals for Tetracoordinate Carbon

If all three of the 2*p* orbitals and the 2*s* orbital are hybridized, a set of 4 equivalent orbitals results, the axes of which are directed at the vertices of a tetrahedron (Figure 9a). This arrangement is used in forming methane and other compounds having four atoms attached to carbon (tetracoordinate carbon). The attachment of four hydrogen atoms (4 H) to a carbon atom results in the formation of four electron-pair bonds and the complete filling of the 4 bonding MOs by eight electrons (4 from C and 4 from H).



Ball-and-Stick Model **Space-filling Model**

Figure 9a. Formation of methane from four sp^3 hybrid orbitals of carbon and four 1*s* orbitals of hydrogen.

The angle between any two of the C–H bonds in methane is 109.5°, the angle between the center of a tetrahedron and any two of the vertices (Figure 9b). The internuclear distance of each C–H bond is 1.54×10^{-8} cm or 1.54 angströms (Å). A second useful bonding rule emerges from these facts.

Rule #2: ***Carbon (C) can bond to a maximum of four atoms (tetracoordination). The preferred angle between any two of the bonds is 109.5°. Tetracoordinate carbon utilizes sp^3 hybrid orbitals.***

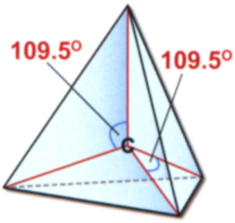


Figure 9b. The angle between the center of a tetrahedron and any two of its vertices is 109.5°.

Deviation of the bond angles at an sp^3-hybridized carbon atom from the preferred value of 109.5° leads to a higher energy (i.e., less stable) structure. The destabilization increases to a value of about 6 kcal/mol for an angle of 90°. This destabilization, called *angle strain*, influences the chemistry and properties of a compound.

Carbon forms strong bonds to most atoms, including H, oxygen (O), nitrogen (N), chlorine (Cl), and by no means least, to itself. Thus, methane is just the first in a large family of compounds of carbon and hydrogen (hydrocarbons). That family includes the straight-chain saturated hydrocarbons, the first five members of which are shown in Figure 10.

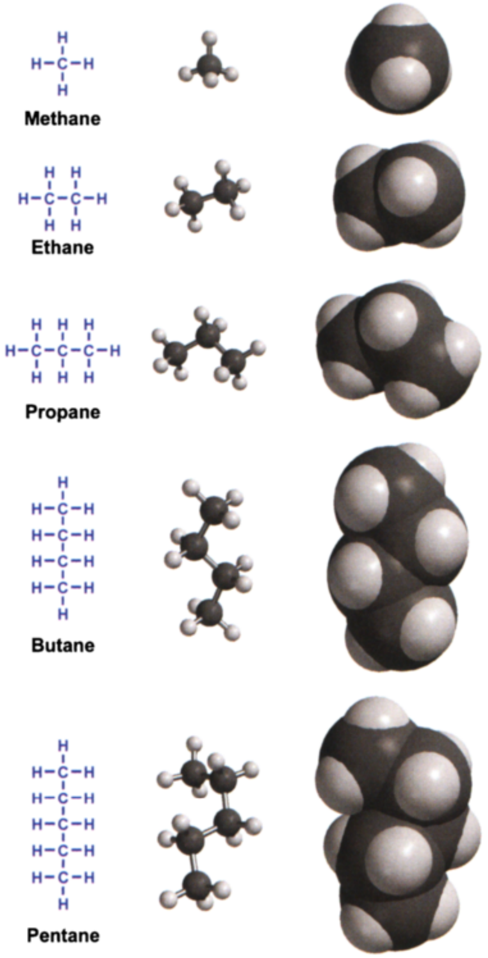


Figure 10. The simplest straight-chain hydrocarbons.

Branching of Carbon Chains

Carbon chains can also be branched.

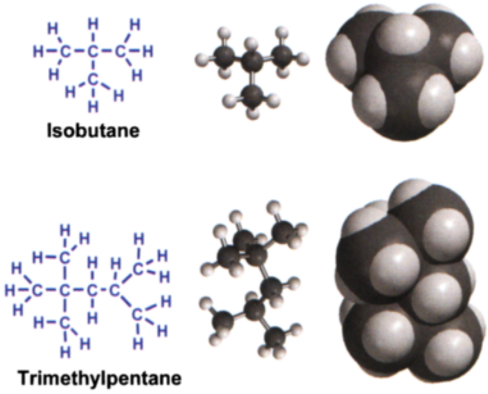


Figure 11a. Two simple branched hydrocarbons, isobutane and trimethylpentane.

There is a simpler notation for depicting the structures of carbon compounds in which the hydrogens are omitted. This shorthand notation leaves it to the reader to add the number of hydrogens corresponding to tetracoordination (Figure 11b).

Figure 11b. Simplified notation of carbon compounds in which the hydrogens are omitted.

Cyclic Structures

Carbon can form rings by bonding with itself in a cycle as well as chains. The simplest members of the family of cyclic hydrocarbons are shown in Figure 12.

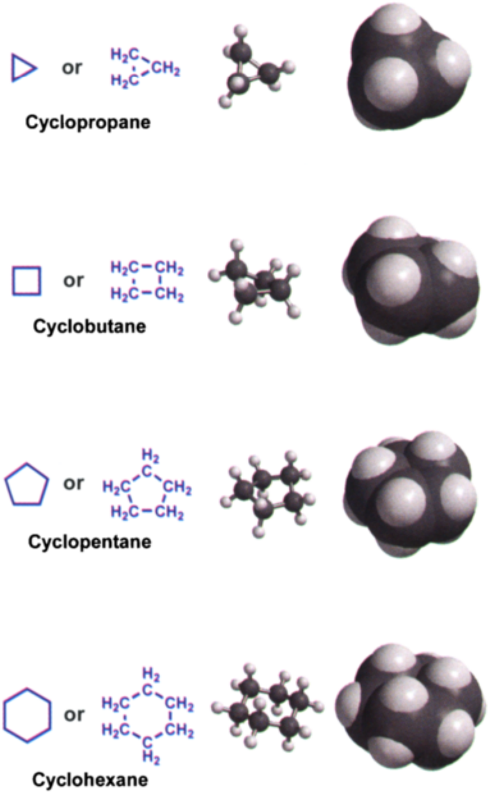


Figure 12. The first four members of cyclic hydrocarbons: cyclopropane, cyclobutane, cyclopentane and cyclohexane.

Tricoordinate Carbon Compounds. The Double Bond

Carbon can form compounds in which *three atoms* are linked to it using hybrid orbitals generated from the combination of the 2*s* atomic orbital with two of the 2*p* atomic orbitals. The orbitals of trigonally hybridized carbon are shown in Figure 13.

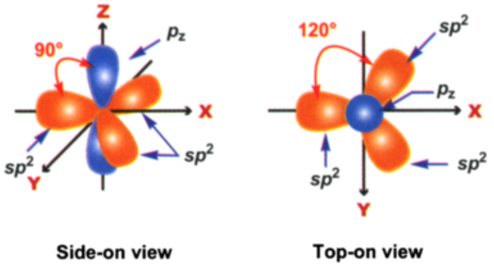


Figure 13. Side-on and Top-on views of the orbitals of a trigonally hybridized (sp^2-hybridized) carbon atom.

Two of the simplest carbon compounds that involve tricoordinate (trigonally hybridized) carbon atoms are formaldehyde ($H_2C=O$) and ethylene ($H_2C=CH_2$). These are planar molecules that contain a double bond to carbon as well as single (electron-pair) bonds to the hydrogens (Figure 14).

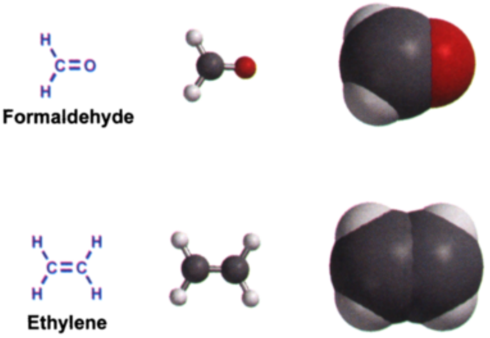


Figure 14. Formaldehyde and ethylene contain trigonally hybridized carbon.

Bonding to tricoordinate carbon utilizes three sp^2 hybrid orbitals and the remaining 2*p* AO. These orbitals allow the derivation of the correct geometry of molecules with tricoordinate carbon. For example, the planar structure of ethylene results because overlap of the *p*-orbitals is maximum when they are parallel, as shown in Figure 15a.

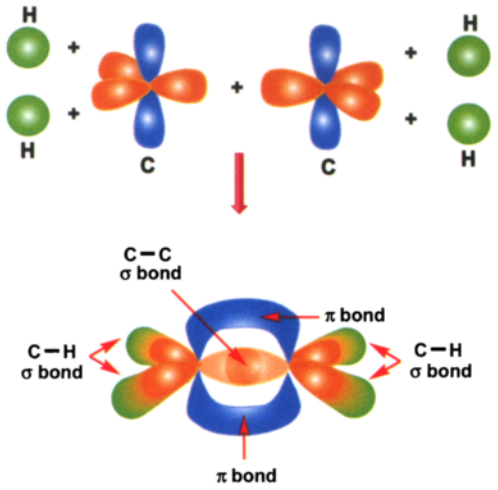


Figure 15a. Formation of ethylene by the combination of two carbon atoms and four hydrogen atoms.

The linkage between the two carbons of ethylene is called a double bond because it involves four electrons. The double bond can be represented by two lines, as in the drawing in Figure 14, or by σ and π bonds as shown in Figure 15a. The π bond, formed by the side-by-side combination of two parallel *p* atomic orbitals (shown in blue in Figure 15a), has two lobes, one above and one below the molecular plane. The σ bond, formed by the combination of two colinear sp^2 orbitals, is symmetric about the C-C axis (axial symmetry).

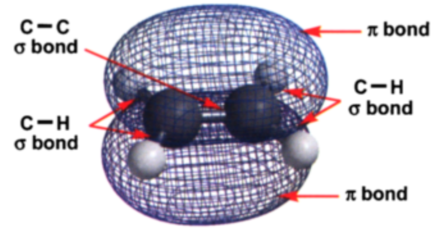


Figure 15b. π-Bond of ethylene.

Rule #3: ***Tricoordinate carbon is connected to each of the three attached atoms in a planar arrangement. The bonding involves three in-plane hybrid sp^2 orbitals and an orthogonal p atomic orbital.***

Dicoordinate Carbon Compounds. The Triple Bond.

Dicoordinate carbon compounds utilize two *sp* orbitals formed from the hybridization of the 2*s* orbital with one 2*p* orbital, and also the remaining two 2*p* orbitals. The orbitals for this type of carbon are shown in Figure 16; note that the angle between the two *sp* orbitals is 180°. The p_y and p_z orbitals that are not involved in hybridization remain unchanged.

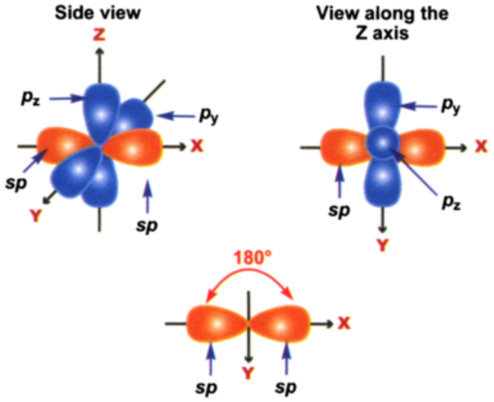


Figure 16. Two views of the orbitals of a dicoordinate (*sp*-hybridized) carbon atom.

Two simple examples of dicoordinate carbon compounds are hydrogen cyanide and acetylene, both of which possess triple bonds and linear geometry because of the 180° angle between the *sp* orbitals of carbon (Figure 17).

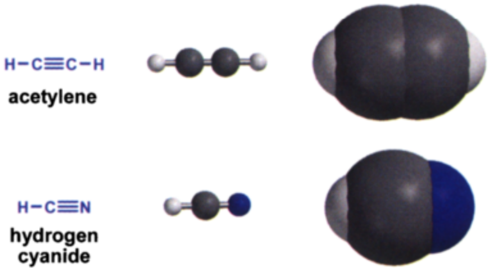


Figure 17. The two simplest dicoordinate carbon compounds, acetylene and hydrogen cyanide.

The triple bond consists of six electrons; two of these are in an axially symmetric MO formed from the combination of two *sp* AOs. The remaining 4 electrons are in two bonding π-MOs formed from overlap of the four 2*p* AOs.

The linear structure of acetylene follows from the use of the *sp* hybrid orbitals and *p* orbitals of each carbon and two H 1*s* orbitals to assemble the molecule, as shown in Figure 18a.

An electron cloud representation of the two π bonds of acetylene is shown in Figure 18b. These two π-bonds and the *sp*-*sp* σ bond of acetylene hold six electrons and constitute a C-C triple bond.

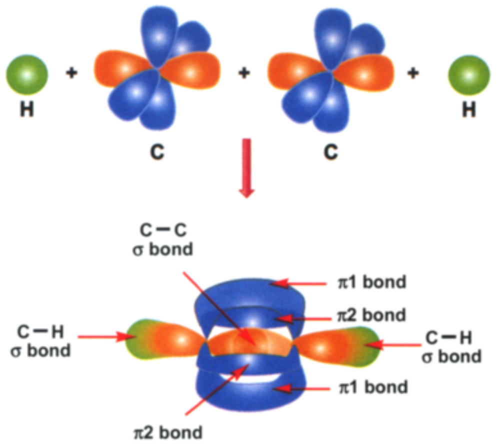


Figure 18a. Formation of acetylene by the combination of two *sp*-hybridized carbon atoms and two hydrogen atoms.

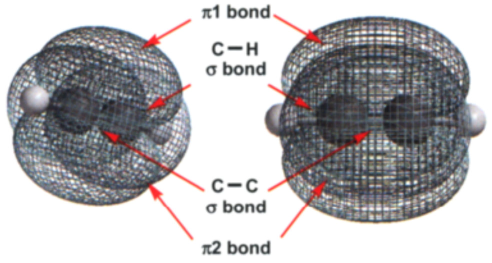


Figure 18b. The two π-bonds of acetylene.

Rule #4: ***Dicoordinate carbon forms bonds to the two attached atoms in a colinear arrangement. The bonding involves two colinear sp orbitals and two p atomic orbitals at carbon.***

Carbon dioxide (CO_2) is another linear molecule in which carbon is *sp*-hybridized (Figure 19).

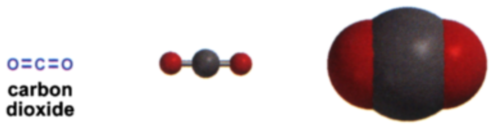
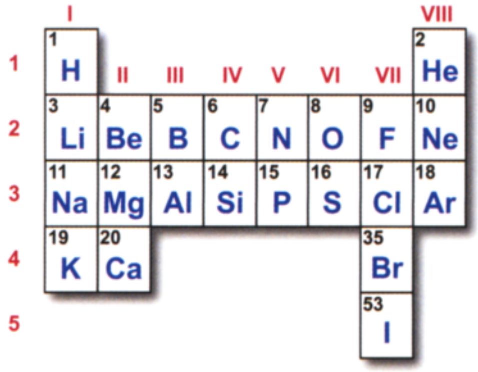


Figure 19. Structure and shape of carbon dioxide.

The Common Chemical Elements in Living Systems

Most of the common elements that make life possible fall within the first three rows of the Periodic Table of Elements. These are shown in Figure 20 along with the corresponding atomic numbers. The atomic number of an atom is identical to the number of protons in the nucleus or the number of orbiting electrons.



	I	II	III	IV	V	VI	VII	VIII
1	1 H							2 He
2	3 Li	4 Be	5 B	6 C	7 N	8 O	9 F	10 Ne
3	11 Na	12 Mg	13 Al	14 Si	15 P	16 S	17 Cl	18 Ar
4	19 K	20 Ca					35 Br	
5							53 I	

Figure 20. A portion of the Periodic Table of Elements.

Some Simple Compounds of Hydrogen and Non-Carbon Elements

All the elements shown in Figure 20 combine with hydrogen, with the exception of the inert gases He, Ne and Ar. Some examples of the simplest of these are the following (Figure 21).

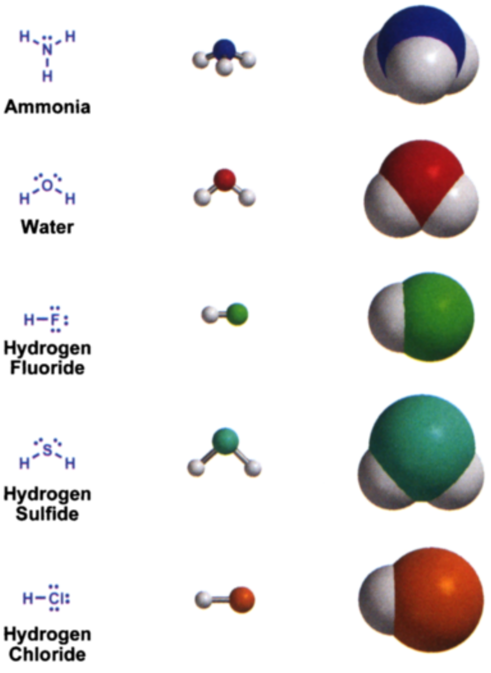


Figure 21. Simple compounds of hydrogen and non-carbon elements.

The dot pairs in the above structures represent electrons in the outer valence shell that are not needed in bonding. The structure of water, for example, involves an sp^3 hybridized oxygen atom connected to two hydrogen atoms. The single bonds to the hydrogens use up two out of the six available electrons of an O atom. The remaining four oxygen electrons are located in the remaining (nonbonding) sp^3 orbitals. Since the four sp^3 orbitals are filled by eight electrons, no further electrons, for instance from a hydrogen atom (H·), can be added. (*Reminder:* each orbital can hold only two electrons.)

Carbon Bonding to Elements Other than Hydrogen

Carbon can also bond to most of the elements, for instance replacing hydrogen in the compounds shown in Figure 21.

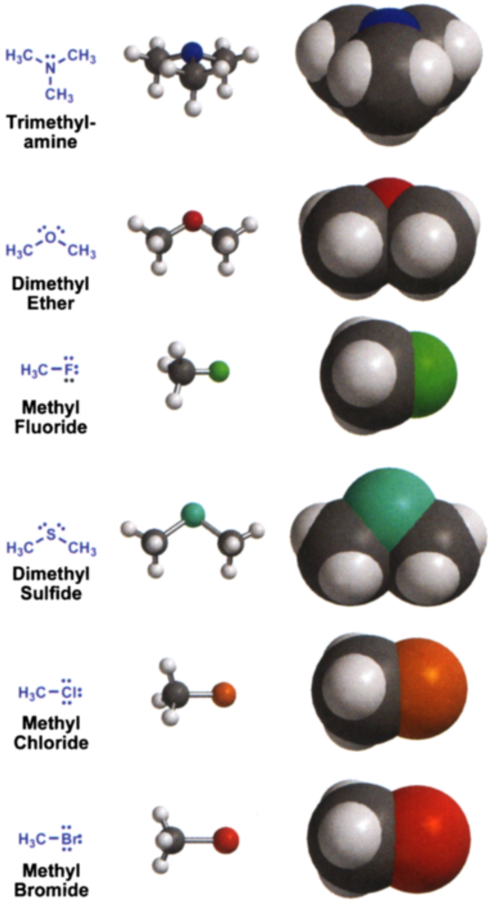


Figure 22. Simple compounds of carbon with non-carbon elements.

Rule #5: ***Carbon can bond to itself to form either straight or branched chains or rings. Carbon can also bond to many other atoms.***

Ionic Bonds

The metallic elements at the left of the Periodic Table lose an electron very readily and tend to form positively-charged ions (cations), rather than covalently bonded compounds. The elements F, Cl, Br and I at the right of the Periodic Table, in contrast, have high electron affinity and readily accept an electron to form negative ions (anions). In the case of fluoride ion (F^-) the available orbitals are filled, as with the inert gas neon (Ne) with which it is isoelectronic (i.e., both F^- and Ne have a total of 8 outer shell electrons). The bonding between sodium and chlorine, for example, is essentially electrostatic, and the bond is described as ionic in character. It is the extreme of the covalent bond of H_2 which involves no charge separation. Sodium chloride (NaCl, salt) in solid form is a crystalline structure containing Na^+ and Cl^- ions in an indefinitely repeating lattice in which each Na^+ is surrounded by 6 Cl^-, and vice versa. It is so stable that the melting point of salt is about 800 °C. The energy that holds Na^+Cl^- in the crystal lattice is 187 kcal/mol, much greater than the H–H covalent bond energy (104 kcal/mol).

Bonds of Intermediate Polarity

Hydrogen chloride (HCl) is a gas at room temperature, in contrast to the ionic solid sodium chloride. The bonding in H-Cl is best described as a covalent bond with appreciable (but far from full) ionic character or charge separation. The electron pair between H and Cl is not shared equally. It is a polarized molecule with more electron density at the Cl end and less at the H end (Figure 23).

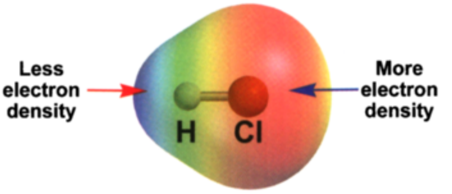


Figure 23. The electron density around HCl. In this computer-generated electron-density map, the blue color represents the lowest electron density whereas the red color represents the highest electron density.

In aqueous solution HCl ionizes to form a hydrated proton and a hydrated chloride ion. Thus, it is a strong acid.

$$HCl + H_2O \longrightarrow HOH_2^+(H_2O)_n + Cl^-(H_2O)_n$$

Equation 2. Dissociation of HCl in water.

The polarization of the bond in gaseous hydrogen chloride, often indicated using the notation $H^{\delta+}$–$Cl^{\delta-}$, is a consequence of greater electron affinity of a chlorine atom as compared to a hydrogen atom. Expressed in another way, chlorine is more strongly electron-attracting than hydrogen.

Polarization of covalent bonds is very common. Four examples are shown in Figure 24.

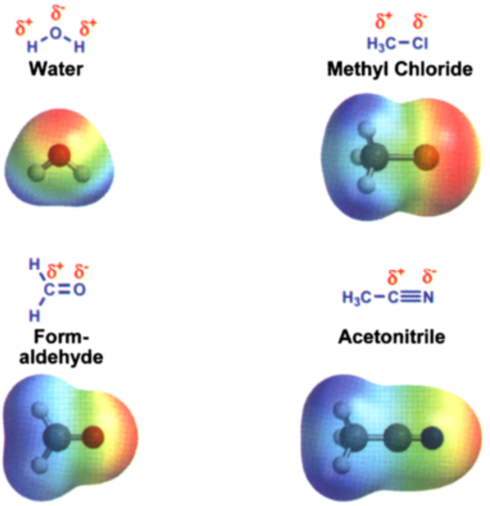


Figure 24. Electron density maps of four simple compounds. The highest electron density is shown in red whereas the lowest electron density is shown in blue.

Molecular Polarity and Hydrogen Bonding

Oil and water do not mix because neither can dissolve the other. The former is essentially hydrocarbon-like and nonpolar, whereas water is polarized with the oxygen relatively negative and the two hydrogens positive.

The polarity of the O–H bonds in water causes the boiling point of water (100 °C) to be much higher than that, for instance, of methane (CH_4, -161 °C) which has about the same size, or ammonia (NH_3, -33 °C). The O–H bond polarity of water causes molecules of H_2O to associate with one another, primarily because of electrostatic forces, forming an extended three-dimensional network, a small part of which is shown in Figure 25.

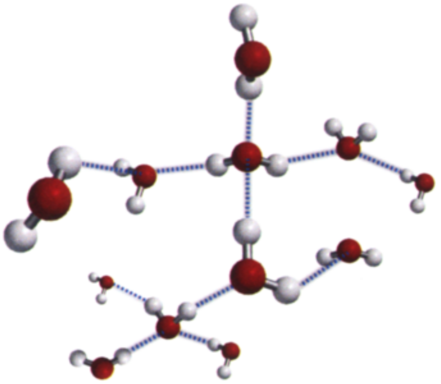


Figure 25. An extended three-dimensional network of molecules in liquid water involves "hydrogen bonds" (blue dashes) as shown.

The bonds between molecules of H_2O in the liquid – called "hydrogen bonds" – are much weaker than the H–H bond (104 kcal/mol), or the C–H bond in methane (105 kcal/mol). The bond dissociation energy of the covalent H–O bond in gaseous H_2O is about 117 kcal/mol, whereas the energy of attraction of an H in water with an O atom of a neighboring water molecule is about 6 kcal/mol. Intermolecular hydrogen bonds between water molecules in the liquid are about 90% electrostatic and 10% covalent. The hydrogen bonds in liquid water stabilize it by an energy of cohesion that is responsible for the unusually high heat of vaporization (9.7 kcal/mol, or 538 kcal/liter).

Aqueous Solvation of Ions

Another unique property of water is the existence of ionized species. In pure, neutral water, the concentration of the hydrated proton $H_3O^+(H_2O)_n$ and hydrated hydroxide ion $HO^-(H_2O)_n$ are each ca. 10^{-7} mol/liter. These species are essentially hydrogen-bonded clusters.

The polarity of water makes it a good solvent for polar ionic molecules because water can form electrostatic or hydrogen bonds to the dissolved species. For example:

$$NaCl + H_2O \longrightarrow Na^+(H_2O)_n + Cl^-(H_2O)_n$$

$$HCl + H_2O \longrightarrow H_3O^+(H_2O)_n + Cl^-(H_2O)_n$$

Equation 3. Formation of hydrated ions in water.

One of the simplest indications that solutions of NaCl or HCl in water contain ions is their high electrical conductivity. Pure water is only a weak conductor of electricity because the concentrations of the ions H_3O^+ and HO^- are only 10^{-7} mol/liter. Seawater is a much better conductor because it contains 0.1 mol/liter of Na^+ and Cl^- ions.

Solvation Energies in Water

Water is unique as a solvent.

Despite the fact that solid NaCl is bound in the crystal lattice with an energy of 187 kcal/mol, it dissolves in water to give solutions of hydrated Na^+ and Cl^-. The reason for this is that the energy of solvation of these ions in water (191 kcal/mol) overcomes the high lattice energy by 4 kcal/mol. The sum of energies of solvation by water of a proton (269 kcal/mol) and of a chloride ion (89 kcal/mol) are greater than the dissociation energy of gaseous hydrogen chloride (358 kcal/mol *vs* 103 kcal/mol), and so it is clear why HCl is both soluble in water and fully ionized. The take-home lesson is that solvation by water strongly stabilizes both positive and negative ions.

The high solvation energy of sodium chloride in water is largely electrostatic. Solvated Na^+ is surrounded by a cluster of at least six H_2O molecules with oxygen in proximity to Na^+. Solvation of Cl^- similarly involves a cluster of H_2O molecules with hydrogen in proximity to Cl^-.

Interactions Between Nonpolar Molecules

There are also attractive forces that operate between nonpolar molecules such as straight-chain hydrocarbons. These intermolecular attractions, sometimes called van der Waals forces, are very much *weaker* than covalent or ionic bonds, or even hydrogen bonds. An instructive example is the attraction between two atoms of the inert gas argon (Ar) which has been measured as ca. 0.28 kcal/mol. This attraction arises not from covalent bonding (because the atomic orbitals of Ar are filled), but from fluctuations in electron density around Ar that create transient imbalance, with one side of the atom being more negative than the other. This polarity induces an opposite distribution of charge on a nearby Ar atom, and the result is a transient attraction (Figure 26).

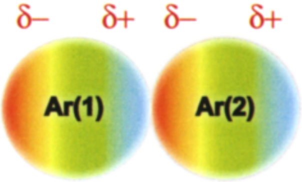


Figure 26. Electron density fluctuation in Ar(1) induces opposite electron density in Ar(2), leading to net attraction between them.

The attraction between two adjacent non-polar molecules increases in proportion to the area of contact and is usually on the order of ca. 1 kcal per square Å of close contact. One manifestation of van der Waals attraction is the steady increase in boiling point temperatures (in °C) with increasing molecular size for the series of straight-chain hydrocarbons (Figure 27).

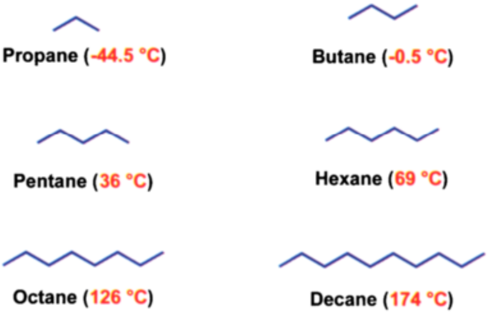

Propane (-44.5 °C)
Butane (-0.5 °C)
Pentane (36 °C)
Hexane (69 °C)
Octane (126 °C)
Decane (174 °C)

Figure 27. Boiling points (red) of straight-chain hydrocarbons (blue).

Although van der Waals attractions between molecules are weaker than hydrogen bonding or electrostatic interactions, they can become significant when two nonpolar molecular surfaces are complimentary in shape of sizeable area. These forces play a major role in determining three-dimensional protein geometry and specificity of drug action. In addition, this type of interaction is what makes it possible for gecko lizards to walk across smooth ceilings or vertical walls.

Functional Groups, Subunits Within Structures that Confer Characteristic Properties and Reactivity.

Compounds containing a carbon-carbon *double bond* within the structure show characteristic chemical behavior. For instance,