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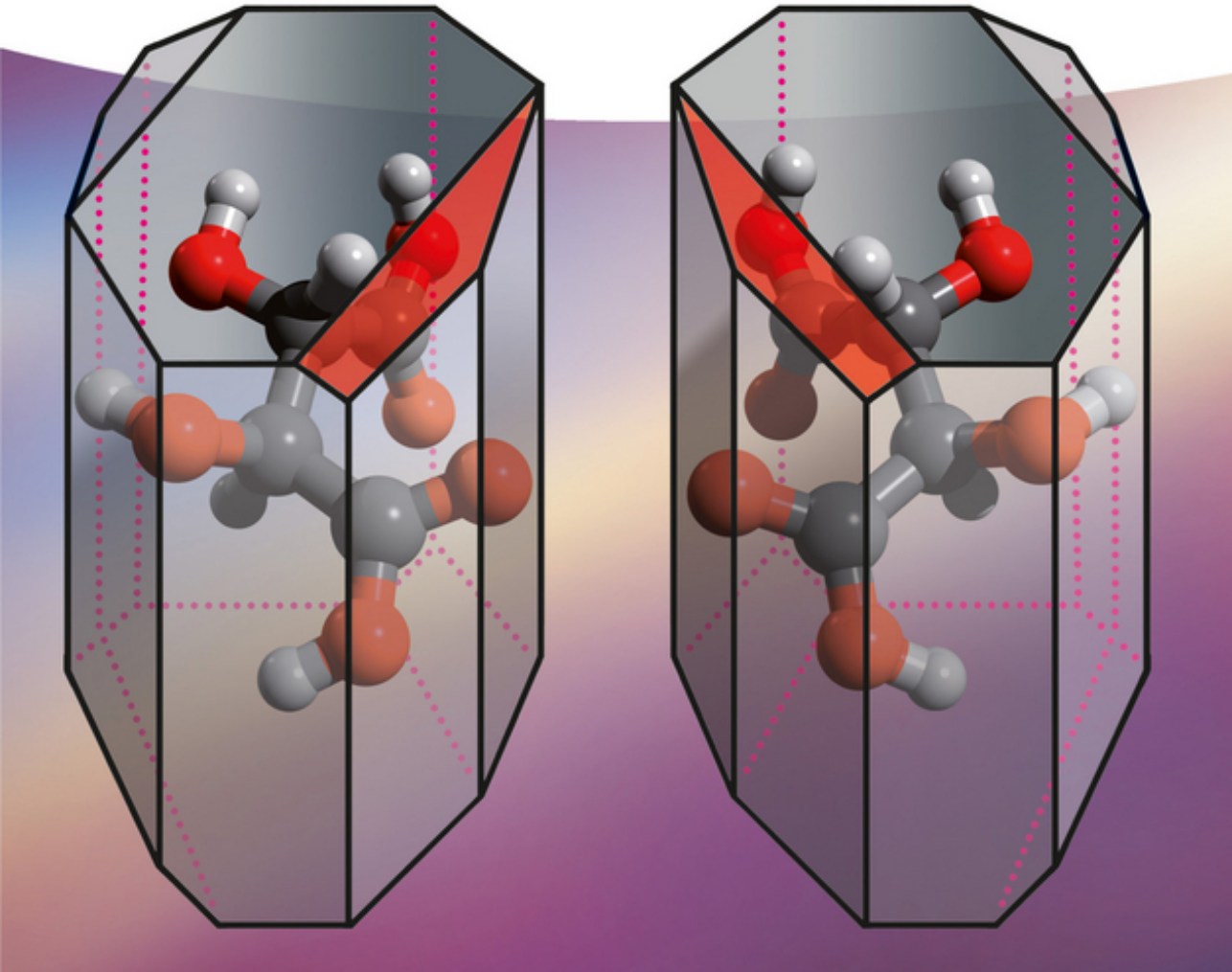
László Poppe and Mihály Nógrádi

Stereochemistry and Stereoselective Synthesis

An Introduction



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This book is accompanied by a companion website:

www.wiley.com/go/poppe/stereochemistry

The website includes animations about the software developer.

Introduction

Nowadays, the development of molecular sciences brings about a revolutionary change of our world, life, and culture as once did the industrial revolution laying the foundations of our modern world. This molecular revolution, one of the milestones of which was the elucidation of the structure of the hitherto largest known natural compound, the human genome, extends in a dimension hitherto unheard of our knowledge of both ourselves and the universe. A key element of this molecular revolution is chemistry, and within it organic chemistry, contributing a lion's share in the twentieth and twenty-first centuries to the significant achievements of biology, medical, material, and environment sciences.

Similar to other sciences, organic chemistry plays a key role in our knowledge of the universe, and within chemistry a special place is allotted to the study of organic molecules. Apart from the potential of synthetic organic chemistry to construct molecules to be found in nature, it is capable to construct molecules not produced in nature.

A key problem of organic synthesis is selectivity, and within this domain stereoselectivity, a capacity to prepare selectively just one of the possible stereoisomeric structures. The importance of stereochemistry has been recognized in the very early period of organic chemistry: J. B. Biot observed in 1815 that certain organic compounds and their solutions rotate the plane of planar polarized light. L. Pasteur (1948) separated (resolved) the optically inactive tartaric acid to two optically active forms and made one of the most important hypotheses in stereochemistry, namely that the two forms are related as mirror images. J. A. LeBel and J. J. van't Hoff (1874) recognized the tetrahedral bond structure of carbon and that this structure enables, in the case of four different ligands, the existence of two nonidentical mirror image structures (enantiomers). H. E. Fischer after having identified and synthesized most of the 16 possible stereoisomeric forms of aldohexoses (1891) suggested a representation of three-dimensional structures in two dimensions, while M. A. Rosanoff (1905) proposed the conventional absolute configuration of D-(+)-glyceraldehyde.

Stereochemistry and stereoselective synthesis received a significant impetus in the middle of the past century when J. M. Bijvoet (1951) determined the actual absolute configuration of (+)-tartaric sodium rubidium salt with the aid of anomalous scattering in X-ray diffraction.

The relevance of stereochemical studies was recognized by awarding a series of Nobel Prizes. The foundation of modern stereochemistry was laid down in the monograph of M. S. Newman (1956). D. H. R. Barton and O. Hassel were awarded the Nobel Prize (1969) for conformational studies, while V. Prelog and J. W. Cornforth (1975) for analyzing the stereochemistry of enzyme-catalyzed reactions. Nobel-Prize-winning studies were carried out by D. J. Cram, J. M. Lehn, and C. J. Pedersen (1987) of selective interactions in supramolecular systems; W. S. Knowles, R. Noyori, and B. Sharpless (2001) for elaborating stereoselective synthetic methods.

The practical importance of stereochemistry is accentuated by the fact that nowadays almost exclusively enantiopure drugs can be registered and the inactive enantiomers are regarded as "contaminants." It is therefore not surprising that manufacturing enantiopure compounds is a multibillion dollar business increasing about 10% per year. Accordingly, development of stereoselective methodology of manufacturing and analyzing pure enantiomers is becoming a central issue for the pharmaceutical, pesticide, cosmetic, and even of household chemical industry.

To write a textbook on any field of science is always challenging, especially about stereochemistry and stereoselective methodology, which is now in extremely fast development. The present work is intended to serve not only students of chemistry but also a wider circle of readers, namely to those whose main interest is outside stereochemistry or even organic chemistry, but who wish to have an overview about the problems, the scope, and potentials of this highly interesting field of chemistry. We hope to find among our potential readers biochemists, polymer chemists, pharmacologists, pharmacists, biologists, and workers in other branches of biosciences.

Part I
Basic Concepts at the Molecular Level

The inherent difficulty of correlating structure with properties is that structure is a concept at the molecular (*microscopic*) level, while properties are in general "*macroscopic*" manifestations. Difficulties of comparing the two levels can be attributed to two factors: the quantity of material and the time required for the determination of properties.

This part deals with the basic concepts of stereochemistry focusing at the molecular (*microscopic*) level.

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1
Structure and Properties

A general opinion of chemists adopted by textbooks is that in chemistry, structure[1)] is a central concept: the key to everything. Properties[2)] of a given substance depend on the number and nature of its constituting atoms and their mode of connection (*connectedness*). It is less obvious but quite important that looking at structural formula, a well-versed chemist should be able to deduce many properties of a substance. In order to exploit this possibility, in this chapter, we are going to define some basic principles associated with structure and properties. After having defined the concept of structure, we will proceed to discuss correlations of structure and properties, with special emphasis on the spatial features of structure and properties derived from changes thereof. First of all, we will discuss properties derived from the spatial structure of typical organic compounds; but for the sake of completeness, the stereochemical features of inorganic compounds will be dealt briefly as well.

1.1
The Covalent Bond and the Octet Rule

The covalent nature of the chemical bond, assuming a shared pair of electrons, was first proposed by G. N. Lewis in 1916 [1]. According to this concept, by sharing two electrons, two hydrogen atoms can establish a stable bond by forming a closed shell of electrons similar to that of the noble gas helium (Figure 1.1).

In the ***Lewis* structures,** electrons are symbolized by dots. The amount of energy required to dissociate a hydrogen molecule to two hydrogen atoms is called the bond dissociation (or bond) energy. In the case of H_2, this is quite high: 435 kJ mol^{-1}.

1) Under *structure*, chemists often understand a single state of a single molecule; therefore, at this level, structure is a *microscopic* concept (to be discussed in more detail later).
2) *Properties* of a material are generally defined not on the basis of a given state of a single molecular structure but on an assembly of a large number of molecules, on a timescale relatively long compared to the timescale of molecular events, and therefore these properties are generally *macroscopic* concepts.

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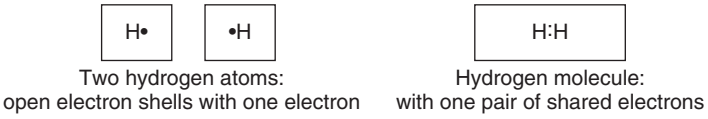


Figure 1.1 Formation of the covalent bond of the hydrogen molecule.

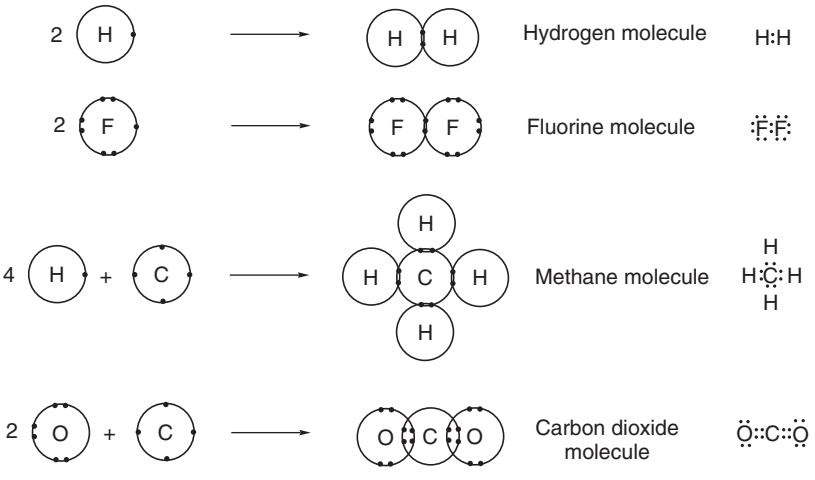


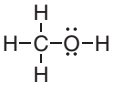
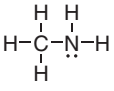
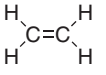
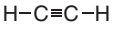
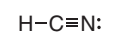
Figure 1.2 Covalent bonds in some simple molecules (*Lewis* representation).

While with hydrogen molecule the number of electrons present in the valence forming shell is limited to two, in the *Lewis* model, molecules composed from elements of the second row (Li, Be, B, C, N. O, F, and Ne) in the valence shells contain eight (shared and unshared) electrons. Most organic compounds follow the octet rule: on formation of their compounds, electrons are taken up, and elements are shared or removed in a way that they should assume a stable structure involving eight valence electrons. When in compounds of carbon, nitrogen, oxygen, and fluorine, the octet rule is valid, their electron configuration is analogous to that of the noble gas neon. *Lewis* representation of some simple molecules is shown in Figure 1.2.

Such structures showing the distribution of electrons (*Lewis* structures) are useful aids for understanding covalent bond formation, but it is simpler to use the s.c. ***Kekulé* formulas**.[3)] The latter are derived from *Lewis* formulas by replacing a shared pair of electrons with a line connecting the corresponding atomic symbols. Nonbonding electrons are shown by dots. Examples for **structural formulas** drawn according to this principle are shown in Table 1.1. As a further

3) Based on the work of A. M. Butlerov, A. Couper, and F. A. Kekulé but at variance with their original formulas, bonds between elements are shown by lines (Kekulé formulas).

Table 1.1 Lewis and Kekulé formulas of some simple molecules.

Name	Molecular formula	*Lewis* formula	*Kekulé* formula
Water	H_2O		
Ammonia	H_3N		
Methane	CH_4		
Methanol	CH_4O		
Methylamine	CH_5N		
Ethene	C_2H_4		
Formaldehyde	CH_2O		
Acetylene	C_2H_2		
Hydrogen cyanide	CHN		

simplification of *Kekulé* formulas, nonbonding electrons are not shown since these can be readily calculated following the octet rule.

As illustrated in Table 1.1 by ethene, formaldehyde, acetylene, and hydrogen cyanide, atoms may share more than one pair of electrons forming in this way **multiple bonds**. Compounds of boron, such as BH_3 or BF_3, are exceptional in a way that the valence shell of boron is not filled up with electrons as would be required by the octet rule. Accordingly, these compounds have a high affinity to electrons and are very reactive.

Valence is the number of those valence electrons, which must be taken up or shed that the valence shell should attain the octet state (Table 1.2). In their covalent compounds, the number of bonds adjoined to an atom is equal to the valence of the given atom. Valences listed in Table 1.2 are typical of atoms common in organic compounds.

Table 1.2 Valence states of selected elements common in organic compounds.

Atom	H	C	N	O	F	Cl	Br	I
Valence	1	4	3	2	1	1	1	1

1.2 Representation of Chemical Structures

For the representation of simpler compounds, condensed *Kekulé* formulas are suitable; but this is a cumbersome way to represent more complex compounds. Thus, cyclic compounds are best represented by further simplified, s.c. **linear formulas**. Application of linear formulas is exemplified by formulas for cycloalkanes (Figure 1.3).

Linear formulas are also convenient to depict open chain compounds (Figure 1.4).

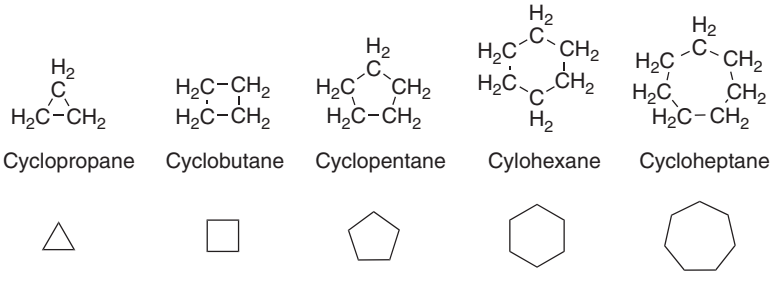


Figure 1.3 Representation of cycloalkanes by linear formulas.

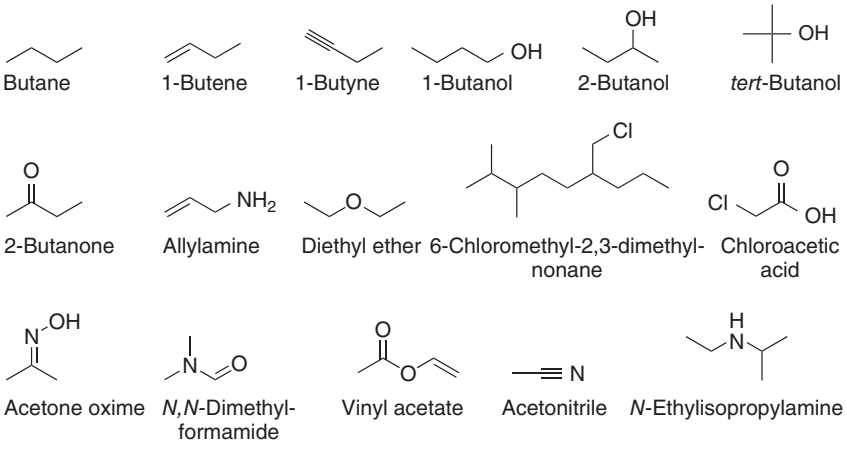


Figure 1.4 Representation of open-chain compounds with linear formulas.

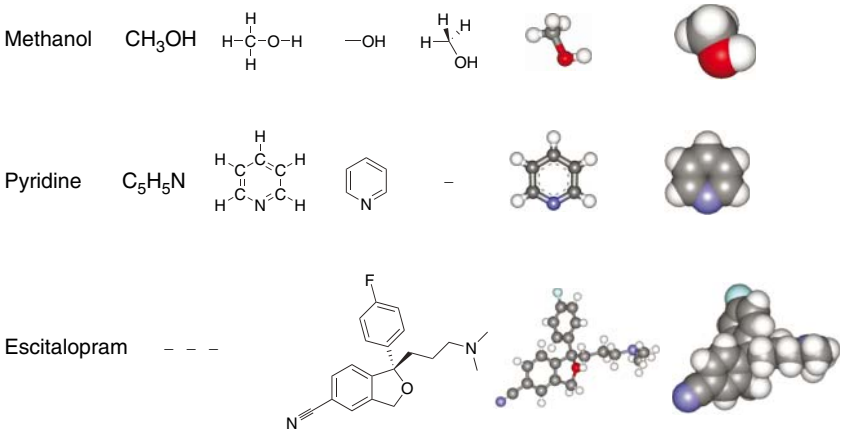


Figure 1.5 Various modes of representation for methanol, pyridine, and the antidepressant escitalopram.

When drawing linear formulas, for simplicity, symbols of carbon atoms, the pairs of electrons, and hydrogen atoms attached to carbons are omitted. Accordingly, all end points, breaking points, and points of branching represent a carbon atom. Multiple bonds are shown by an appropriate number of parallel lines. Heavy atoms other than carbon are shown by their atomic symbols together with the hydrogen atoms attached.

Additional ways of representation are shown in Figure 1.5 by the example of methanol, pyridine, and the antidepressant escitalopram. Representations include the following:

- **A**: Name (trivial or systematic)
- **B**: Condensed formulas (generally suitable for printing in a single line)
- **C**: *Kekulé* formulas (showing all the atoms and bonds)
- **D**: Linear formulas (hydrogens omitted, breaking, branching, and end points represent carbon atoms; heavy atoms are shown with the hydrogen attached)
- **E**: **Stereoformulas**[4] (depicting the spatial orientation of bonds)
- **F**: Ball and stick model (often used to depict X-ray structures or computed models)
- **G**: Space-filling model (approaches the electron distribution).

Figure 1.5 well demonstrates that for smaller open-chain organic compounds (e.g., methanol), it is the condensed or *Kekulé* formula that is the most appropriate for the demonstration of the two-dimensional features of the structure. In case of smaller cyclic compounds (e.g., pyridine), the linear formulas are most often used. To depict more complex structures (e.g., escitalopram), condensed

4) The details of the use of stereo formulas are exactly defined by IUPAC recommendations [2]. Easily perceptible stereo formulas have only become generally used in the second half of the twentieth century. Earlier, various other representations were used.

or *Kekulé* representations are practically useless, and therefore a combination of linear and stereo representation is recommended. The complete stereostructure of molecules can be best depicted by a simplified representation of 3D structures. In Figure 1.5, two possible modes of representation of molecular models that is, ball and stick and space-filling models are shown.[5] As can be seen with more complex molecules, space-filling models refer to their overall shape, while the details of the structure are less apparent.

1.3 Description of Chemical Structure

Chapters of the rules of International Union of Pure and Applied Chemistry (IUPAC) for naming compounds [3] do not give a precise definition of what should be understood under "chemical structure." Therefore, we define in a general way as **chemical structure** as it is understood by crystallographers: chemical structure is an accurate description of the spatial arrangement of the constituting atoms (atomic nuclei) in space.

The exact spatial arrangement of atoms can be described, for instance, by their **Cartesian coordinates**.[6] From a structural point of view, however, it is not the absolute position and orientation of the molecule that is decisive; therefore, it is often more useful to describe the relative position of atoms by s.c. **internal coordinates**[7] (Figure 1.6). Internal coordinates for the description of molecules are the bond lengths (r), the bond angles (α), and the torsion angles (ω).[8]

For the description of molecules containing two atoms (**I**), besides defining the type of atoms (A, B), it is sufficient to give the bond length as a single internal coordinate. In organic molecules, the value of **bond lengths** varies in a relatively narrow range (Table 1.3).

The structure of a triatomic molecule (**II**) is characterized by the type of atoms (A, B, and C), two bond lengths (r_1 and r_2), and one **bond angle** (α).[9] In real triatomic molecules, bond lengths and bond angles depend on the type of constituting atoms, their hybridization state, and the order of the bonds (Figure 1.7).

It is apparent from Figure 1.7 that in triatomic molecules, bond angles vary in a wide range. The molecules of hydrogen sulfide and water form an angular

5) Computer programs suitable to visualize chemical structures offer further possibilities (e.g., wire models, ball and stick models, covering surfaces according to various properties and combinations thereof).

6) A molecule containing n atoms can have a maximum of $3n - 6$ internal degrees of freedom and can be described by $3n - 6$ Cartesian coordinates. Use of Cartesian coordinates also defines its absolute position, and therefore their use is uncomfortable.

7) A molecule containing n atoms can have a maximum of $3n - 6$ internal degrees of freedom and can be described by $3n - 6$ internal coordinates. Internal coordinates reflect to local bonds and symmetries; they can be composed by linear combinations of Cartesian coordinates.

8) Bond angles are often denoted by the symbol Θ. In polymer chemistry, it is usual to denote bond angles as τ, while the symbol Θ is for torsion angles.

9) Bond angles are sometimes called valence angles.

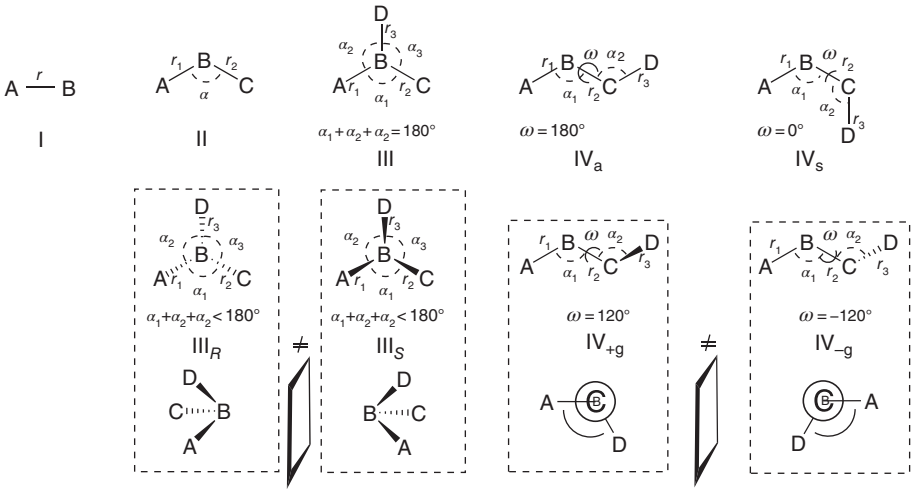


Figure 1.6 Characterization of molecules consisting of two, three, and four atoms with internal coordinates.

Table 1.3 Characteristic values of bond lengths commonly occurring in organic compounds.

	C–C	C=C	C≡C	C–H	C–O	C=O	C–N	C–S	C–F	C–Cl	C–Br	C–I
pm	154	133	120	109	143	122	147	182	135	176	192	212
Å	1.54	1.33	1.20	1.09	1.43	1.22	1.47	1.82	1.35	1.76	1.92	2.12

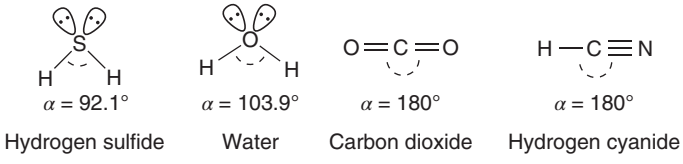


Figure 1.7 Bond angles in selected triatomic molecules.

structure owing to the presence of two nonbonding pairs of electrons in an approximately tetrahedral arrangement. (The difference in the bond angles is caused by the different strengths of repulsion between the pairs of electrons.) On the other hand, hydrogen cyanide and carbon dioxide are linear due to the *sp* hybridization state of the central atom. In bond angles between atoms of given types, the value of bond angles varies in a narrow range and therefore when discussing structures, organic chemists take them as constant.

Molecules consisting of four atoms (A, B, C, and D) present a new situation (Figure 1.6). If the fourth atom (D) is attached to the central atom (B) of the chain formed by the other three, we are dealing with a branched structure (Figure 1.6, **III, III**$_R$, and **III**$_S$). When the four atoms (A, B, C, and D) are coplanar (the sum of

the three bond angles α_1, α_2, and α_3 is 180°), the structure is planar (**III**). When, however, the sum of the three bond angles α_1, α_2, and α_3 is less than 180°, pyramidal structures ($\mathbf{III}_R$ and $\mathbf{III}_S$) are formed. It can be seen that while the internal coordinates of the two structures (α_1, α_2, and α_3) are identical, the structures themselves are nonidentical.

If the atoms in a molecule consisting of four atoms form a continuous chain, in addition to bond lengths (r_1, r_2, and r_3) and bond angles (α_1 and α_2), an additional type of internal coordinate, the **torsion angle** (ω),[10] has to be taken into consideration (Figure 1.6). With the variation of torsion angles, a further multiplication of structural alternatives arises (Figure 1.6, $\mathbf{IV}_S$, $\mathbf{IV}_R$, $\mathbf{IV}_{+g}$, and $\mathbf{IV}_{-g}$). While in organic molecules, as discussed before, the values of bond lengths ($r_1 \cdots r_n$) and bond angles ($\alpha_1 \cdots \alpha_n$) are relatively constant, torsion angles (ω) for single bonds can take up any value between 0° and 180°. Coplanarity of the four atoms is possible in two different ways: $\omega = 0°$ ($\mathbf{IV}_s$) or $\omega = 180°$ ($\mathbf{IV}_a$) (Figure 1.6). While in structures built up from the same kind of atoms, bond lengths and bond angles may be identical, it is apparent that owing to the difference of torsion angles, the two structures are different. Besides the two coplanar arrangements ($\mathbf{IV}_s$ and $\mathbf{IV}_a$), an infinite number of noncoplanar structures is possible with the alteration of torsion angles in the range of 0–180°. It can be seen that the arrangement of a chain of atoms A–B–C–D assuming a given torsion angle (e.g., $\omega = 120°$: $\mathbf{IV}_{+g}$) and the corresponding arrangement characterized by an identical but negative torsion angle ($\omega = -120°$: $\mathbf{IV}_{-g}$) are nonidentical mirror images.

1.4 Problems of Correlating Chemical Structure with Properties

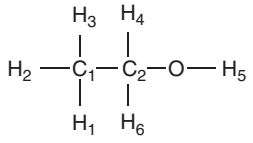
For a representation of chemical structures **bonding matrices**, describing the order of attachment of atoms and bonds (connectedness) may be useful (Figure 1.8).

Figure 1.8 clearly demonstrates that while the chemical formula of ethanol and dimethyl ether (C_2H_5O) is identical, their bonding matrices are different. We can therefore reasonably assume that these molecules are in fact different, in other words **isomers**.[11]

While acetaldehyde and "vinyl alcohol" have the same chemical formula (C_2H_4O, Figure 1.9), both their structural formulas and their bonding matrices are apparently different.

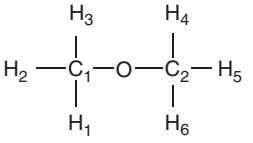
10) A torsion or dihedral angle (ω) is defined in case of a consecutive nonlinear chain of atoms A, B, C, and D as the angle formed by the planes of atoms ABC and BCD. If the plane is seen along the line BC, the torsion angle is taken as positive if the bond AB ought to be moved clockwise (in an angle <180°) to superpose bond CD. If AB ought to be rotated counterclockwise, the torsion angle is taken as negative.

11) According to their most common definition, **isomers** have the same molecular formula but are nevertheless different. This definition is inexact, since it lacks the definition of the circumstances (thermal energy level, environment, state, and time interval) under which the compounds are viable as stable entities (cf. Section 2.2.2).



Ethanol

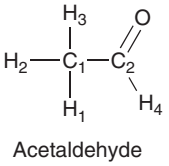
	C_1	C_2	O	H_1	H_2	H_3	H_4	H_5	H_6
C_1		1	0	1	1	1	0	0	0
C_2	1		1	0	0	0	1	0	1
O	0	0		0	0	0	0	1	0
H_1	1	0	0		0	0	0	0	0
H_2	1	0	0	0		0	0	0	0
H_3	1	0	0	0	0		0	0	0
H_4	0	1	0	0	0	0		0	0
H_5	0	0	1	0	0	0	0		0
H_6	0	1	0	0	0	0	0	0	



Dimethyl ether

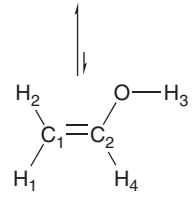
	C_1	C_2	O	H_1	H_2	H_3	H_4	H_5	H_6
C_1		0	1	1	1	1	0	0	0
C_2	0		1	0	0	0	1	1	1
O	1	1		0	0	0	0	0	0
H_1	1	0	0		0	0	0	0	0
H_2	1	0	0	0		0	0	0	0
H_3	1	0	0	0	0		0	0	0
H_4	0	1	0	0	0	0		0	0
H_5	0	1	0	0	0	0	0		0
H_6	0	1	0	0	0	0	0	0	

Figure 1.8 Kekulé formula and the bonding matrix of ethanol and dimethyl ether.



Acetaldehyde

	C_1	C_2	O	H_1	H_2	H_3	H_4
C_1		1	0	1	1	1	0
C_2	1		2	0	0	0	1
O	0	2		0	0	0	0
H_1	1	0	0		0	0	0
H_2	1	0	0	0		0	0
H_3	1	0	0	0	0		0
H_4	0	1	0	0	0	0	



Vinyl alcohol

	C_1	C_2	O	H_1	H_2	H_3	H_4
C_1		2	0	1	1	0	0
C_2	2		1	0	0	0	1
O	0	1		0	0	1	0
H_1	1	0	0		0	0	0
H_2	1	0	0	0		0	0
H_3	0	0	1	0	0		0
H_4	0	1	0	0	0	0	

Figure 1.9 Kekulé formulas and the bond matrices of acetaldehyde and "vinyl alcohol."

Looking at the structures, we might assume that also in this case the compounds are isomers, but in reality, the two structures cannot be separated because they form a dynamic equilibrium mixture of **tautomers** (cf. Chapter 6).[12)]

12) A relatively exact definition of **tautomers** may be that these are inseparable isomers in a dynamic equilibrium.

Examples in Figures 1.7 – 1.9 already demonstrate that without the examination of additional features, structures in themselves do not give information about the nature of differences of the entities in question. The inherent difficulty of correlating structure with properties is that structure is a concept at the molecular (*microscopic)* level, while properties are in general "*macroscopic*" manifestations. Difficulties of comparing the two levels can be attributed to two factors: the quantity of material and the time required for the determination of properties.

For the determination of the **amount of substance** (n, mol), it is necessary to know the number (N) of the units (generally atoms or molecules) constituting the substance (Figure 1.10). This can be determined based on the ***Avogadro* constant** (N_A) using the equation $N_A = N/n$. The best value of the experimentally determined value of the *Avogadro* constant is $6.022140857(74) \times 10^{23}$ units/mol [4]. This number is the link between microscopic (at the atomic or molecular level) and macroscopic level of observing natural phenomena.

In order to demonstrate the significance of **time**, it is useful to compare the timescale of molecular vibrations and rotations with the actual time needed to determine the properties of a given substance. On the molecular level, it is the former that characterizes and determines the dynamics of chemical bonds and reactions. The timescale of these motions is in the range of 10^{-10}–10^{-13} s. Femtosecond laser techniques are probably the fastest method of measurement.

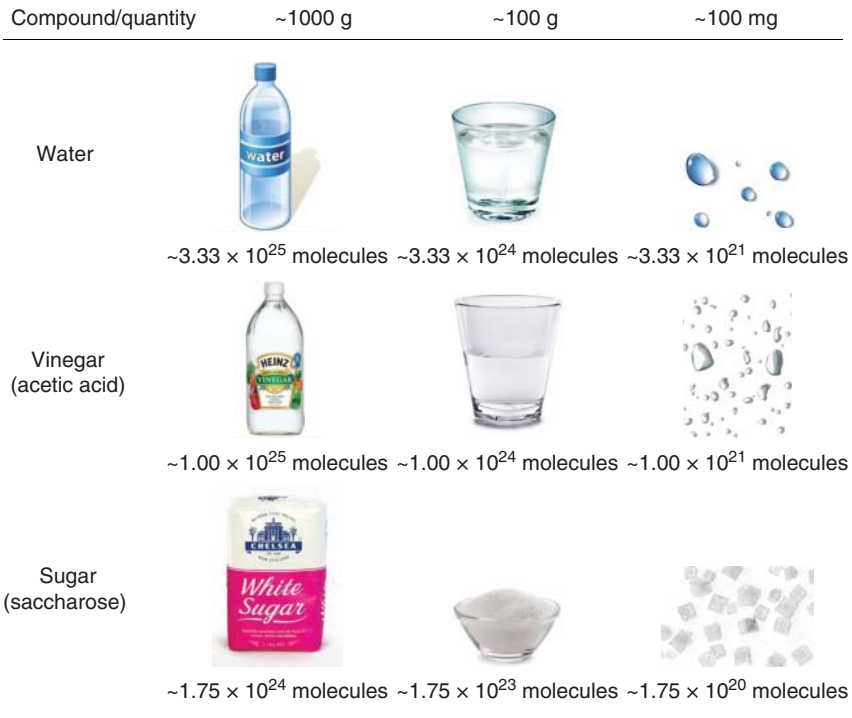


Figure 1.10 Number of molecules in a customary amount of various substances.