2 **States of Matter**

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Understand the nature of the intra- and intermolecular forces that are involved in stabilizing molecular and physical structures.
2. Understand the differences in these forces and their relevance to different types molecules.
3. Discuss supercritical states to illustrate the utility of supercritical fluids for crystallization and microparticulate formulations.
4. Appreciate the differences in the strengths of the intermolecular forces that are responsible for the stability of structures in the different states of matter.
5. Perform calculations involving the ideal gas law, molecular weights, vapor pressure, boiling points, kinetic molecular theory, van der Waals real gases, the Clausius–Clapeyron equation, heats of fusion and melting points, and the phase rule equations.
6. Understand the properties of the different states of matter.
7. Describe the pharmaceutical relevance of the different states of matter to drug delivery systems by reference to specific examples given in the text boxes.
8. Describe the solid state, crystallinity, solvates, and polymorphism.
9. Describe and discuss key techniques utilized to characterize solids.
10. Recognize and elucidate the relationship between differential scanning calorimetry, thermogravimetric, Karl Fisher, and sorption analyses in determining polymorphic versus solvate detection.
11. Understand phase equilibria and phase transitions between the three main states of matter.
12. Understand the phase rule and its application to different systems containing multiple components.

Binding Forces Between Molecules

For molecules to exist as aggregates in gases, liquids, and solids, *inter*molecular forces must exist. An understanding of intermolecular forces is important in the study of pharmaceutical systems and follows logically from a detailed discussion of *intra*molecular bonding energies. Like *intra*molecular bonding energies found in covalent bonds, *inter*molecular bonding is largely governed by electron orbital interactions. The key difference is that covalency is not established in the*inter*molecular state. Cohesion, or the attraction of like molecules, and adhesion, or the attraction of unlike molecules, are manifestations of intermolecular forces. Repulsion is a reaction between two molecules that forces them apart. For molecules to interact, these forces must be balanced in an energetically favored arrangement. Briefly, the term energetically favored is used to describe the intermolecular distances and intramolecular conformations where the energy of the interaction is maximized on the basis of the balancing of attractive and repulsive forces. At this point, if the molecules are moved slightly in any direction, the stability of the interaction will change by either a decrease in attraction (when moving the molecules away from one another) or an increase in repulsion (when moving the molecules toward one another).

Knowledge of these forces and their balance (equilibrium) is important for understanding not only the properties of gases, liquids, and solids, but also interfacial phenomena, flocculation in suspensions, stabilization of emulsions, compaction of powders in capsules, dispersion of powders or liquid droplets in aerosols, and the compression of granules to form tablets. With the rapid increase in biotechnology-derived products, it is important to keep in mind that these same properties are strongly involved in influencing biomolecular (e.g., proteins, DNA) secondary, tertiary, and quaternary structures, and that these properties have a profound influence on the stability of these products during production, formulation, and storage. Further discussion of biomolecular products will be limited in this text, but correlations hold between small-molecule and the larger biomolecular therapeutic agents due to the universality of the physical principles of chemistry.

Repulsive and Attractive Forces

When molecules interact, both repulsive and attractive forces operate. As two atoms or molecules are brought closer together, the opposite charges and binding forces in the two molecules are closer together than the similar charges and forces, causing the molecules to attract one another. The negatively charged electron clouds of the molecules largely govern the balance (equilibrium) of forces between the two molecules. When the molecules are brought so close that the outer charge clouds touch, they repel each other like rigid elastic bodies.

Thus, attractive forces are necessary for molecules to cohere, whereas repulsive forces act to prevent the molecules from interpenetrating and annihilating each other.

Moelwyn-Hughes1 pointed to the analogy between human behavior and molecular phenomena: Just as the actions of humans are often influenced by a conflict of loyalties, so too is molecular behavior governed by attractive and repulsive forces.

Repulsion is due to the interpenetration of the electronic clouds of molecules and increases exponentially with a decrease in distance between the molecules. At a certain equilibrium distance, about (3-4) × 10^{-8} cm (3–4 Å), the repulsive and attractive forces are equal. At this position, the potential energy of the two molecules is a minimum and the system is most stable (Fig. 2-1). This principle of minimum potential energy applies not only to molecules but also to atoms and to large objects as well. The effect of repulsion on the intermolecular three-dimensional structure of a molecule is well illustrated in considering the conformation of the two terminal methyl groups in butane, where they are energetically favored in the *trans*conformation because of a minimization of the repulsive forces. It is important to note that the arrangement of the atoms in a particular stereoisomer gives the *configuration* of a molecule. On the other hand, *conformation* refers to the different arrangements of atoms resulting from rotations about single bonds.

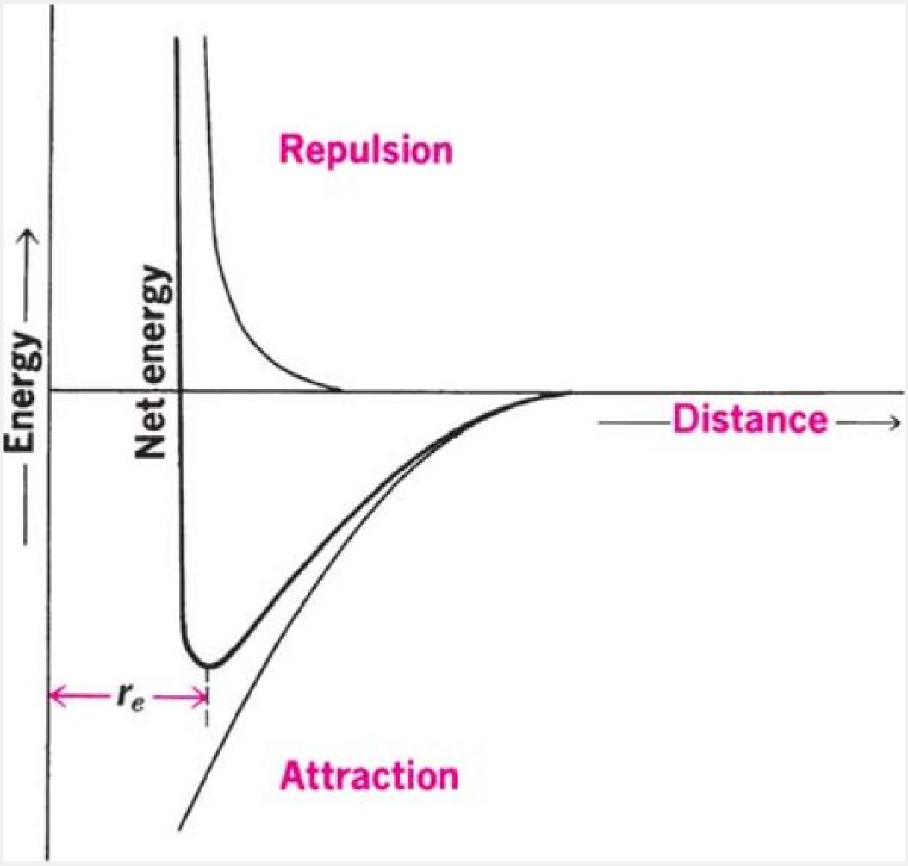
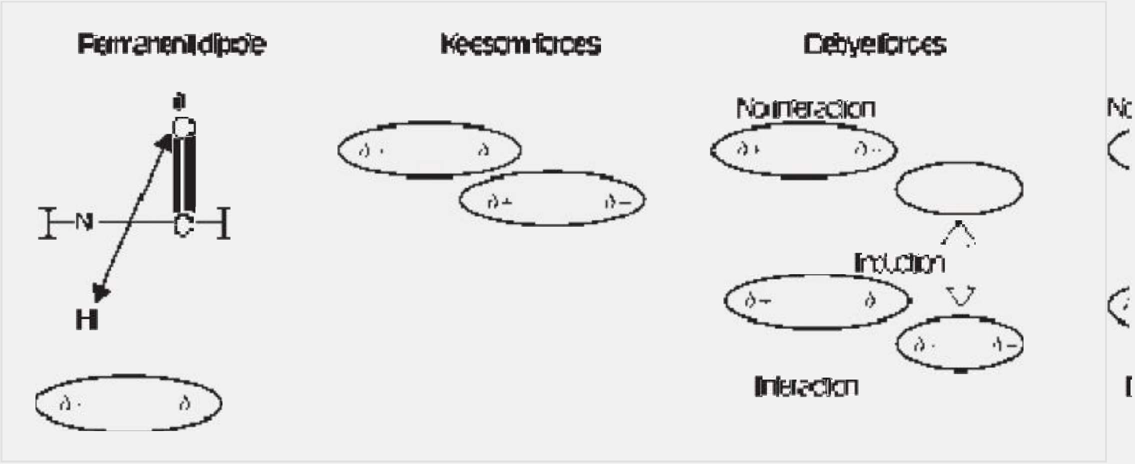


Fig. 2-1. Repulsive and attractive energies and net energy as a function of the distance between molecules. Note that a minimum occurs in the net energy because of the different character of the attraction and repulsion curves.

The various types of *attractive* intermolecular forces are discussed in the following subsections.

Key Concept
Van Der Waals Forces



van der Waal interactions are weak forces that involve the dispersion of charge across a molecule called a dipole. In a permanent dipole, as illustrated by the peptide bond, the electronegative oxygen draws the pair of electrons in the carbon–oxygen double bond closer to the oxygen nucleus. The bond then becomes polarized due to the fact that the oxygen atom is strongly pulling the nitrogen lone pair of electrons toward the carbon atom, thus creating a partial double bond. Finally, to compensate for valency, the nucleus of the nitrogen atom pulls the electron pair involved in the nitrogen–hydrogen bond closer to itself and creates a partial positive charge on the hydrogen. This greatly affects protein structure, which is beyond the scope of this discussion. In Keesom forces, the permanent dipoles interact with one another in an ionlike fashion. However, because the charges are partial, the strength of bonding is much weaker. Debye forces show the ability of a permanent dipole to polarize charge in a neighboring molecule. In London forces, two neighboring neutral molecules, for example, aliphatic hydrocarbons, induce partial charge distributions. If one conceptualizes the aliphatic chains in the lipid core of a membrane like a biologic membrane or a liposome, one can imagine the neighboring chains in the interior as inducing a network of these partial charges that helps hold the interior intact. Without this polarization, the membrane interior would be destabilized and lipid bilayers might break down. Therefore, London forces give rise to the fluidity and cohesiveness of the membrane under normal physiologic conditions.

Van der Waals Forces

Van der Waals forces relate to nonionic interactions between molecules, yet they involve charge–charge interactions (see Key Concept Box on van der Waals Forces). In organic chemistry, numerous reactions like nucleophilic substitutions are introduced where one molecule may carry a partial positive charge and be attractive for interaction with a partially negatively charged nucleophilic reactant. These partial charges can be permanent or be induced by neighboring groups, and they reflect the polarity of the molecule. The converse can be true for electrophilic reactants. The presence of these polarities in molecules can be similar to those observed with a magnet. For example, dipolar molecules frequently tend to align themselves with their neighbors so that the negative pole of one molecule points toward the positive pole of the next. Thus, large groups of molecules may be associated through weak attractions known as *dipole–dipole* or Keesom forces. Permanent dipoles are capable of inducing an electric dipole in nonpolar molecules (which are easily polarizable) to produce *dipole-induced dipole*, or Debye, interactions, and nonpolar molecules can induce polarity in one another by *induced dipole-induced dipole*, or London, attractions. This latter force deserves additional comment here.

The weak electrostatic force by which nonpolar molecules such as hydrogen gas, carbon tetrachloride, and benzene attract one another was first recognized by London in 1930. The *dispersion* or London force is sufficient to bring about the condensation of nonpolar gas molecules so as to form liquids and solids when molecules are brought quite close to one another. In all three types of van der Waals forces, the potential energy of attraction varies inversely with the distance of separation, r, raised to the sixth power, r^6. The potential energy of repulsion changes more rapidly with distance, as shown in Figure 2-1. This accounts for the potential energy minimum and the resultant equilibrium distance of separation, r_e. A good conceptual analogy to illustrate this point is the interaction of opposite poles of magnets (Fig. 2-2). If two magnets of the same size are slid on a table so that the opposite poles completely overlap, the resultant interaction is attractive and the most energetically favored configuration (Fig. 2-2a). If the magnets are slid further so that the poles of each slide into like-pole regions of the other (Fig. 2-2b), this leads to repulsion and a force that pushes the magnetic poles back to the energetically favored configuration (Fig. 2-2a). However, it must be noted that attractive (opposite-pole overlap) and repulsive (same-pole overlap) forces coexist. If the same-charged poles are slid into the proximity of one another, the resultant force is complete repulsion (Fig. 2-2c).

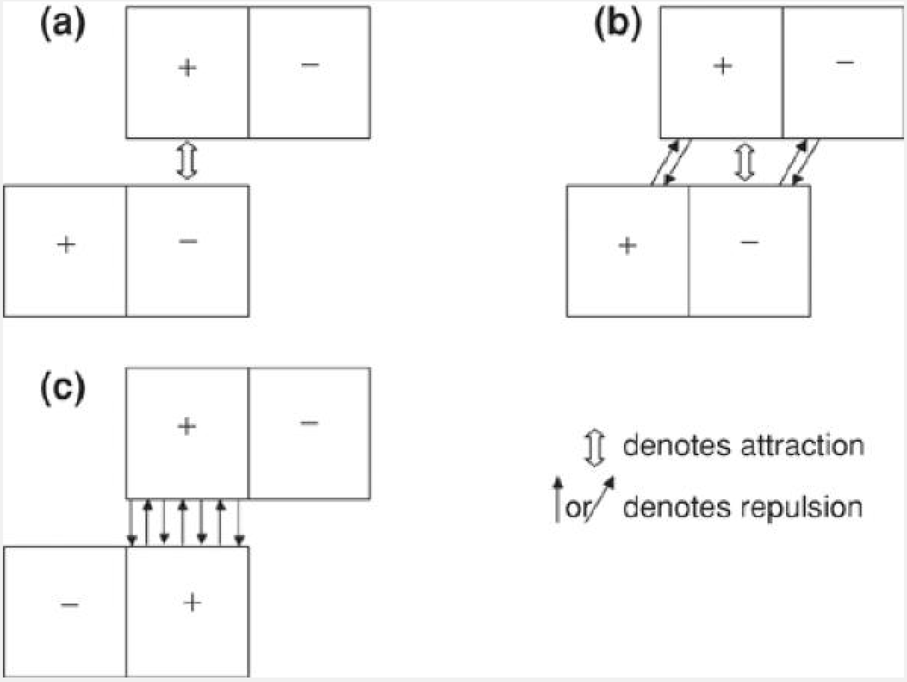


Fig. 2-2. (*a*) The attractive, (*b*) partially repulsive, and (*c*) fully repulsive interactions of two magnets being brought together.

These several classes of interactions, known as van der Waals forces* and listed in Table 2-1, are associated with the condensation of gases, the solubility of some drugs, the formation of some metal complexes and molecular addition compounds, and certain biologic processes and drug actions. The energies associated with primary valence bonds are included for comparison.

Orbital Overlap

An important *dipole–dipole* force is the interaction between pi-electron orbitals in systems. For example, aromatic–aromatic interactions can occur when the double-bonded pi-orbitals from the two rings overlap (Fig. 2-3).2 Aromatic rings are dipolar in nature, having a partial negative charge in the pi-orbital electron cloud above and below the ring and partial positive charges residing at the equatorial hydrogens, as illustrated in Figure 2-3a. Therefore, a dipole–dipole interaction can occur between two aromatic molecules. In fact, at certain geometries aromatic–aromatic interaction can stabilize *inter*-and/or *intra*molecular interactions (Fig. 2-3b and c), with the highest energy interactions occurring when the rings are nearly perpendicular to one another.2 This phenomena has been largely studied in proteins, where stacking of 50% to 60% of the aromatic side chains can often add stabilizing energy to secondary and tertiary structure (*inter*molecular) and may even participate in stabilizing quaternary interactions (*intra*molecular). Aromatic stacking can also occur in the solid state, and was first identified as a stabilizing force in the structure of small organic crystals.

It is important to point out that due to the nature of these interactions, repulsion is also very plausible and can be destabilizing if the balancing attractive force is changed. Finally, lone pairs of electrons on atoms like oxygen can also interact with aromatic pi orbitals and lead to attractive or repulsive interactions. These interactions are dipole–dipole in nature and they are introduced to highlight their importance. Students seeking additional information on this subject should read the excellent review by Meyer et al.3

Table 2-1 Intermolecular Forces and Valence Bonds

Bond Type	Bond Energy (approximately) (kcal/mole)
Van der Waals forces and other intermolecular attractions	
Dipole–dipole interaction, orientation effect, or Keesom force	
Dipole-induced dipole interaction, induction effect, or Debye force	1–10
Induced dipole–induced dipole interaction, dispersion effect, or London force	
Ion–dipole interaction	
Hydrogen bonds: O—H· · ·O	6
C—H· · ·O	2–3
O—H· · ·N	4–7
N—H· · ·O	2–3
F—H· · ·F	7
Primary valence bonds	
Electrovalent, ionic, heteropolar	100–200
Covalent, homopolar	50–150

Ion–Dipole and Ion-Induced Dipole Forces

In addition to the dipolar interactions known as van der Waals forces, other attractions occur between polar or nonpolar molecules and ions. These types of interactions account in part for the solubility of ionic crystalline substances in water; the cation, for example, attracts the relatively negative oxygen atom of water and the anion attracts the hydrogen atoms of the dipolar water molecules. Ion-induced dipole forces are presumably involved in the formation of the iodide complex,

$$I_2 + K^+I^- = K^+I_3^- \qquad (2\text{–}1)$$

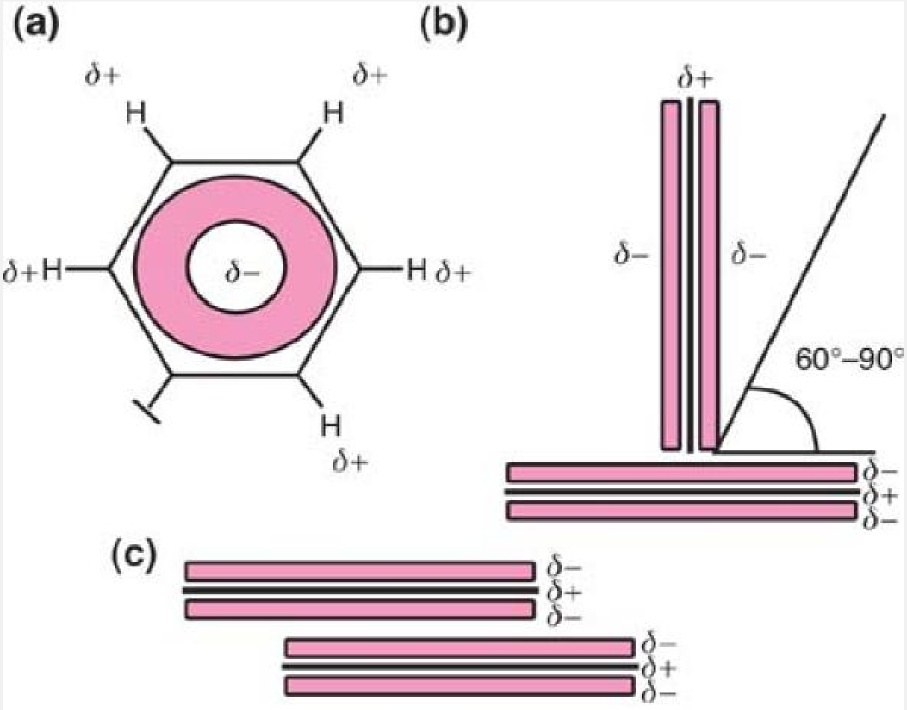


Fig. 2-3. Schematic depicting (*a*) the dipolar nature of an aromatic ring, (*b*) its preferred angle for aromatic–aromatic interactions between 60° and 90°, and (*c*) the less preferred planar interaction of aromatic rings. Although typically found in proteins, these interactions can stabilize states of matter as well. See the excellent review on this subject with respect to biologic recognition by Meyer et al.3

Reaction **(**2-1**)** accounts for the solubility of iodine in a solution of potassium iodide. This effect can clearly influence the solubility of a solute and may be important in the dissolution process.

Ion–Ion Interactions

Another important interaction that involves charge is the ion–ion interaction. An ionic, electrovalent bond between two counter ions is the strongest bonding interaction and can persist over the longest distance. However, weaker ion–ion interactions, in particular salt formations, exist and influence pharmaceutical systems. This section focuses on those weaker ion–ion interactions. The ion–ion interactions of salts and salt forms have been widely discussed in prerequisite general chemistry and organic chemistry courses that utilize this text, but they will briefly be reviewed here.

It is well established that ions form because of valency changes in an atom. At neutrality, the number of protons and the number of electrons in the atom are equal. Imbalance in the ratio of protons to neutrons gives rise to a change in charge state, and the valency will dictate whether the species is cationic or anionic. Ion–ion interactions are normally viewed from the standpoint of attractive forces: A cation on one compound will interact with an anion on another compound, giving rise to an*inter*molecular association. Ion–ion interactions can also be repulsive when two ions of like charge are brought closely together. The repulsion between the like charges arises from electron cloud overlap, which causes the *inter*molecular distances to increase, resulting in an energetically favored dispersion of the molecules. The illustration of the magnetic poles in Figure 2-2 offers an excellent corollary for the understanding of the attractive cationic (positive pole) and anionic (negative pole) interactions (panel A), as well as the need for proper distance to an energetically favored electrovalent interaction (panels A and B), and the

repulsive forces that may occur between like charges (panels B and C). Ion–ion interactions may be *inter*molecular (e.g., a hydrochloride salt of a drug) or*intra*molecular (e.g., a salt-bridge interaction between counter ions in proteins).

Clearly, the strength of ion–ion interactions will vary according to the balancing of attractive and repulsive forces between the cation- and anion-containing species. It is important to keep in mind that ion–ion interactions are considerably stronger than many of the forces described in this section and can even be stronger than covalent bonding when an ionic bond is formed. The strength of ion–ion interactions has a profound effect on several physical properties of pharmaceutical agents including salt-form selection, solid-crystalline habit, solubility, dissolution, pH and p *K* determination, and solution stability.

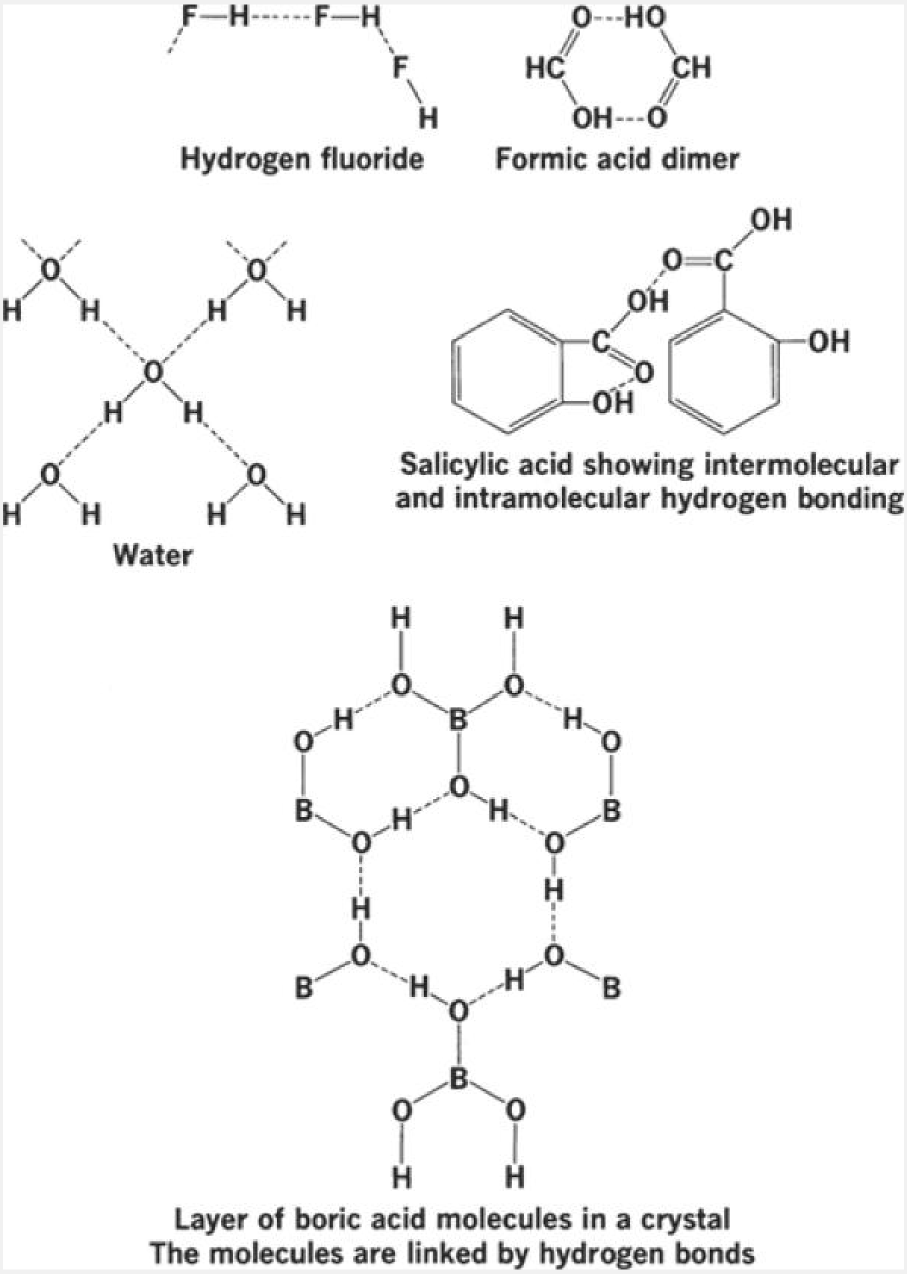
Hydrogen Bonds

The interaction between a molecule containing a hydrogen atom and a strongly electronegative atom such as fluorine, oxygen, or nitrogen is of particular interest. Because of the small size of the hydrogen atom and its large electrostatic field, it can move in close to an electronegative atom and form an electrostatic type of union known as a *hydrogen bond* or *hydrogen bridge*. Such a bond, discovered by Latimer and Rodebush4 in 1920, exists in ice and in liquid water; it accounts for many of the unusual properties of water including its high dielectric constant, abnormally low vapor pressure, and high boiling point. The structure of ice is an open but well ordered three-dimensional array of regular tetrahedra with oxygen in the center of each tetrahedron and hydrogen atoms at the four corners. The hydrogens are not exactly midway between the oxygens, as may be observed in Figure 2-4. Roughly one sixth of the hydrogen bonds of ice are broken when water passes into the liquid state, and essentially all the bridges are destroyed when it vaporizes. Hydrogen bonds can also exist between alcohol molecules, carboxylic acids, aldehydes, esters, and polypeptides.

The hydrogen bonds of formic acid and acetic acid are sufficiently strong to yield *dimers* (two molecules attached together), which can exist even in the vapor state. Hydrogen fluoride in the vapor state exists as a hydrogen-bonded polymer $(F—H \ldots)_n$, where n can have a value as large as 6. This is largely due to the high electronegativity of the fluorine atom interacting with the positively charged, electropositive hydrogen atom (analogous to an ion–ion interaction). Several structures involving hydrogen bonds are shown in Figure 2-4. The dashed lines represent the hydrogen bridges. It will be noticed that *intra*- as well as *inter*molecular hydrogen bonds may occur (as in salicylic acid).

Bond Energies

Bond energies serve as a measure of the strength of bonds. Hydrogen bonds are relatively weak, having a bond energy of about 2 to 8 kcal/mole as compared with a value of about 50 to 100 kcal for the covalent bond and well over 100 kcal for the ionic bond. The metallic bond, representing a third type of primary valence, will be mentioned in connection with crystalline solids.



Hydrogen fluoride

Formic acid dimer

Water

Salicylic acid showing intermolecular and intramolecular hydrogen bonding

Layer of boric acid molecules in a crystal
The molecules are linked by hydrogen bonds

Fig. 2-4. Representative hydrogen-bonded structures.

The energies associated with intermolecular bond forces of several compounds are shown in Table 2-2. It will be observed that the total interaction energies between molecules are contributed by a combination of orientation, induction, and dispersion effects. The nature of the molecules determines which of these factors is most influential in the attraction. In water, a highly polar substance, the orientation or dipole–dipole interaction predominates over the other two forces, and solubility of drugs in water is influenced mainly by the orientation energy or dipole interaction. In hydrogen chloride, a molecule with about 20% ionic character, the orientation effect is still significant, but the dispersion force contributes a large share to the total interaction energy between molecules. Hydrogen iodide is predominantly covalent, with its intermolecular attraction supplied primarily by the London or dispersion force.

Table 2-2 Energies Associated with Molecular and Ionic Interactions

	Interaction (kcal/mole)			
Compound	**Orientation**	**Induction**	**Dispersion**	**Total Energy**
H_2O	8.69	0.46	2.15	11.30
HCl	0.79	0.24	4.02	5.05
HI	0.006	0.027	6.18	6.21
$NaCl$	—	—	3.0	183

The ionic crystal sodium chloride is included in Table 2-2 for comparison to show that its stability, as reflected in its large total energy, is much greater than that of molecular aggregates, and yet the dispersion force exists in such ionic compounds even as it does in molecules.

States of Matter

Gases, liquids, and crystalline solids are the three primary states of matter or phases. The molecules, atoms, and ions in the solid state are held in close proximity by intermolecular, interatomic, or ionic forces. The atoms in the solid can oscillate only about fixed positions. As the temperature of a solid substance is raised, the atoms acquire sufficient energy to disrupt the ordered arrangement of the lattice and pass into the liquid form. Finally, when sufficient energy is supplied, the atoms or molecules pass into the gaseous state. Solids with high vapor pressures, such as iodine and camphor, can pass directly from the solid to the gaseous state without melting at room temperature. This process is known as *sublimation*, and the reverse process, that is, condensation to the solid state, may be referred to as*deposition*. Sublimation will not be discussed in detail here but is very important in the freeze-drying process, as briefly detailed in the Key Concept Box on Sublimation in Freeze Drying (Lyophilization).

Key Concept

Sublimation in Freeze Drying (Lyophilization)

Freeze drying (lyophilization) is widely used in the pharmaceutical industry for the manufacturing of heat-sensitive drugs. Freeze drying is the most common commercial approach to making a sterilized powder. This is particularly true for injectable formulations, where a suspended drug might undergo rapid degradation in solution, and thus a dried powder is preferred. Many protein formulations are also prepared as freeze-dried powders to prevent chemical and physical instability processes that more rapidly occur in a solution state than in the solid state. As is implied by its name, freeze drying is a process where a drug suspended in water is frozen and then dried by a sublimation process. The following processes are usually followed in freeze drying: (*a*) The drug is formulated in a sterile buffer formulation and placed in a vial (it is important to note that there are different types of glass available and these types may have differing effects on solution stability; (*b*) a slotted stopper is partially inserted into the vial, with the stopper being raised above the vial so that air can get in and out of the vial; (*c*) the vials are loaded onto trays and placed in a lyophilizer, which begins the initial freezing; (*d*) upon completion of the primary freeze, which is conducted at a low temperature, vacuum is applied and the water sublimes into vapor and is removed from the system, leaving a powder with a high water content (the residual water is more tightly bound to the solid powder); (*e*) the temperature is raised (but still maintaining a frozen state) to add more energy to the system, and a secondary freeze-drying cycle is performed under vacuum to pull off more of the tightly bound water; and (*f*) the stoppers are then compressed into the vials to seal them and the powders are left remaining in a vacuum-sealed container with no air exchange. These vials are subsequently sealed with a metal cap that is crimped into place. It is important to note that there is often residual water left in the powders upon completion of lyophilization. In addition, if the caps were not air tight, humidity could enter the vial and cause the powders to absorb atmospheric water (the measurement of the ability of a powder/solid material to absorb water is called its hygroscopicity), which could lead to greater instability. Some lyophilized powders are so hygroscopic that they will absorb enough water to form a solution; this is called deliquescence and is common in lyophilized powders. Finally, because the water is removed by sublimation and the compound is not crystalized out, the residual powder is commonly amorphous.

Certain molecules frequently exhibit a fourth phase, more properly termed a *mesophase* (Greek *mesos*, middle), which lies between the liquid and crystalline states. This so-called *liquid crystalline* state is discussed later. Supercritical fluids are also considered a mesophase, in this case a state of matter that exists under high pressure and temperature and has properties that are intermediate between those of liquids and gases. Supercritical fluids will also be discussed later because of their increased utilization in pharmaceutical agent processing.

The Gaseous State

Owing to vigorous and rapid motion and resultant collisions, gas molecules travel in random paths and collide not only with one another but also with the walls of the container in which they are confined. Hence, they exert a *pressure*—a force per unit area—expressed in dynes/cm^2. Pressure is also recorded in atmospheres or in millimeters of mercury because of the use of the barometer in pressure measurement. Another important characteristic of a gas, its *volume*, is usually expressed in liters or cubic centimeters (1 cm^3 = 1 mL). The temperature involved in the gas equations is given according the absolute or Kelvin scale. Zero degrees on the centigrade scale is equal to 273.15 Kelvin (K).

The Ideal Gas Law

The student may recall from general chemistry that the gas laws formulated by Boyle, Charles, and Gay-Lussac refer to an ideal situation where no intermolecular interactions exist and collisions are perfectly elastic, and thus no energy is exchanged upon collision. Ideality allows for certain assumptions to be made to derive these laws. Boyle's law relates the volume and pressure of a given mass of gas at constant temperature,

$$P \propto \frac{1}{V}$$

or

$$PV = k \qquad (2\text{–}2)$$

The law of Gay-Lussac and Charles states that the volume and absolute temperature of a given mass of gas at constant pressure are directly proportional,

$$V \propto T$$

$$V = kT \qquad (2\text{–}3)$$

These equations can be combined to obtain the familiar relationship

$$\frac{P_1 V_1}{T_1} = \frac{P_2 V_2}{T_2} \qquad (2\text{–}4)$$

In equation (2-4), P_1, V_1, and T_1 are the values under one set of conditions and P_2, V_2, and T_2 the values under another set.

Example 2-1

The Effect of Pressure Changes on the Volume of an Ideal Gas

In the assay of ethyl nitrite spirit, the nitric oxide gas that is liberated from a definite quantity of spirit and collected in a gas burette occupies a volume of 30.0 mL at a temperature of 20°C and a pressure of 740 mm Hg. Assuming the gas is ideal, what is the volume at 0°C and 760 mm Hg? Write

$$\frac{740 \times 30.0}{273 + 20} = \frac{760 \times V_2}{273}$$
$$V_2 = 27.2 \text{ mL}$$

From equation (2-4) it is seen that *PV/T* under one set of conditions is equal to *PV/T* under another set, and so on. Thus, one reasons that although *P*, *V*, and *T*change, the ratio *PV/T* is constant and can be expressed mathematically as

$$\frac{PV}{T} = R$$

or

$$PV = RT \qquad (2\text{–}5)$$

in which *R* is the constant value for the *PV/T* ratio of an ideal gas. This equation is correct only for 1 mole (i.e., 1 g molecular weight) of gas; for *n* moles it becomes

$$PV = nRT \qquad (2\text{–}6)$$

Equation (2-6) is known as the *general ideal gas law*, and because it relates the specific conditions or state, that is, the pressure, volume, and temperature of a given mass of gas, it is called the *equation of state* of an ideal gas. Real gases do not interact without energy exchange, and therefore do not follow the laws of Boyle and of Gay-Lussac and Charles as ideal gases are assumed to do. This deviation will be considered in a later section.

The *molar gas constant R* is highly important in physical chemical science; it appears in a number of relationships in electrochemistry, solution theory, colloid chemistry, and other fields in addition to its appearance in the gas laws. To obtain a numerical value for *R*, let us proceed as follows. If 1 mole of an ideal gas is chosen, its volume under standard conditions of temperature and pressure (i.e., at 0°C and 760 mm Hg) has been found by experiment to be 22.414 liters. Substituting this value in equation (2-6), we obtain

$$1 \text{ atm} \times 22.414 \text{ liters} = 1 \text{ mole} \times R \times 273.16 \text{ K}$$
$$R = 0.08205 \text{ liter atm/mole K}$$

The molar gas constant can also be given in energy units by expressing the pressure in dynes/cm^2 (1 atm = 1.0133 × 10^6 dynes/cm^2) and the volume in the corresponding units of cm^3 (22.414 liters = 22,414 cm^3). Then

$$R = \frac{PV}{T} = \frac{(1.0133 \times 10^6) \times 22.414}{273.16}$$
$$= 8.314 \times 10^6 \text{ erg/mole K}$$

or, because 1 joule = 10^7 ergs,

$$R = 8.314 \text{ joules/mole K}$$

The constant can also be expressed in cal/mole deg, employing the equivalent 1 cal = 4.184 joules:

$$R = \frac{8.314 \text{ joules/mole deg}}{4.184 \text{ joules/cal}} = 1.987 \text{ cal/mole deg}$$

One must be particularly careful to use the value of *R* commensurate with the appropriate units under consideration in each problem. In gas law problems, *R* is usually expressed in liter atm/mole deg, whereas in thermodynamic calculations it usually appears in the units of cal/mole deg or joule/mole deg.

Example 2-2

Calculation of Volume Using the Ideal Gas Law

What is the volume of 2 moles of an ideal gas at 25°C and 780 mm Hg?

$$(780 \text{ mm}/760 \text{ mm atm}^{-1}) \times V$$
$$= 2 \text{ moles} \times (0.08205 \text{ liter atm/mole deg}) \times 298 \text{ K}$$
$$V = 47.65 \text{ liters}$$

Molecular Weight

The approximate molecular weight of a gas can be determined by use of the ideal gas law. The number of moles of gas *n* is

P.24

replaced by its equivalent *g/M*, in which *g* is the number of grams of gas and *M* is the molecular weight:

$$PV = \frac{g}{M}RT \qquad (2\text{–}7)$$

or

$$M = \frac{gRT}{PV} \qquad (2\text{–}8)$$

Example 2-3

Molecular Weight Determination by the Ideal Gas Law

If 0.30 g of ethyl alcohol in the vapor state occupies 200 mL at a pressure of 1 atm and a temperature of 100°C, what is the molecular weight of ethyl alcohol? Assume that the vapor behaves as an ideal gas. Write

$$M = \frac{0.30 \times 0.082 \times 373}{1 \times 0.2}$$
$$M = 46.0 \text{ g/mole}$$

The two methods most commonly used to determine the molecular weight of easily vaporized liquids such as alcohol and chloroform are the *Regnault* and *Victor Meyer* methods. In the latter method, the liquid is weighed in a glass bulb; it is then vaporized and the volume is determined at a definite temperature and barometric pressure. The values are finally substituted in equation **(**2-8**)** to obtain the molecular weight.

Kinetic Molecular Theory

The equations presented in the previous section have been formulated from experimental considerations where the conditions are close to ideality. The theory that was developed to explain the behavior of gases and to lend additional support to the validity of the gas laws is called the *kinetic molecular theory*. Here are some of the more important statements of the theory:

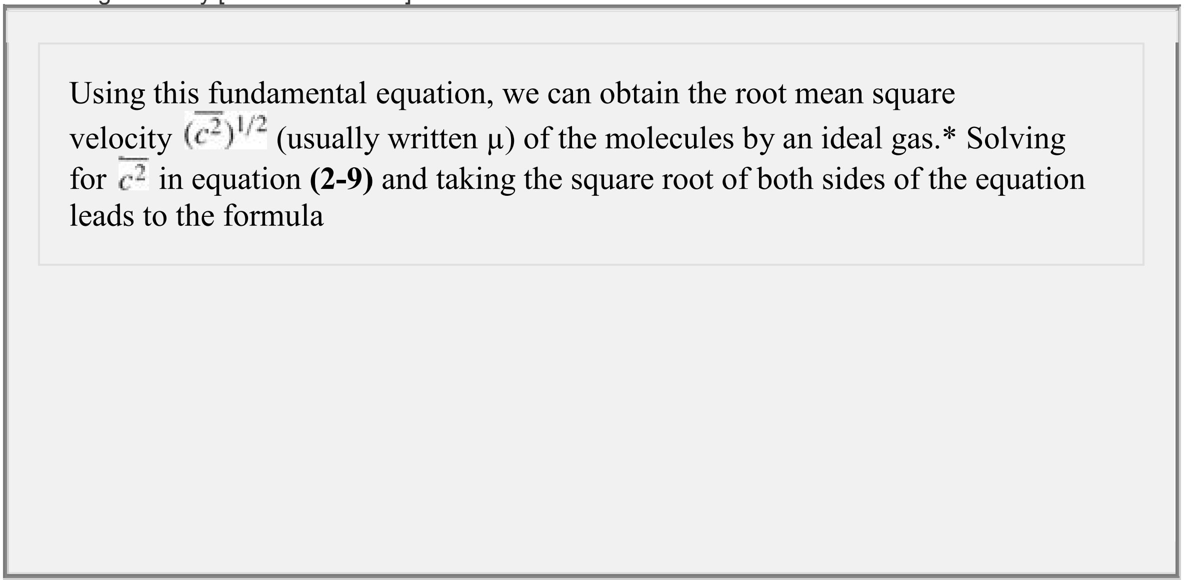
1. Gases are composed of particles called atoms or *molecules*, the total volume of which is so small as to be negligible in relation to the volume of the space in which the molecules are confined. This condition is approximated in actual gases only at low pressures and high temperatures, in which case the molecules of the gas are far apart.
2. The particles of the gas do not attract one another, but instead move with complete independence; again, this statement applies only at low pressures.
3. The particles exhibit continuous random motion owing to their kinetic energy. The average kinetic energy, *E*, is directly proportional to the absolute temperature of the gas, or $E = (3/_2)RT$.

4. The molecules exhibit perfect elasticity; that is, there is no net loss of speed or transfer of energy after they collide with one another and with the molecules in the walls of the confining vessel, which latter effect accounts for the gas pressure. Although the net velocity, and therefore the average kinetic energy, does not change on collision, the speed and energy of the individual molecules may differ widely at any instant. More simply stated, the net velocity can be an average velocity of many molecules; thus, a distribution of individual molecular velocities can be present in the system.

From these and other postulates, the following *fundamental kinetic equation* is derived:

$$PV = \frac{1}{3} nm\overline{c^2} \qquad (2\text{–}9)$$

where *P* is the pressure and *V* the volume occupied by any number *n* of molecules of mass *m* having an average velocity [C with bar above].



Using this fundamental equation, we can obtain the root mean square velocity $(\overline{c^2})^{1/2}$ (usually written μ) of the molecules by an ideal gas.* Solving for $\overline{c^2}$ in equation **(2-9)** and taking the square root of both sides of the equation leads to the formula

$$\mu = \sqrt{\frac{3RV}{nm}} \qquad (2\text{–}10)$$

Restricting this case to 1 mole of gas, we find that *PV* becomes equal to *RT* from the equation of state **(**2-5**)**, *n* becomes Avogadro's number N_A, and N_A multiplied by the mass of one molecule becomes the molecular weight *M*. The root mean square velocity is therefore given by

$$\mu = \sqrt{\frac{3RT}{M}} \qquad (2\text{–}11)$$

Example 2-4
Calculation of Root Mean Square Velocity

What is the root mean square velocity of oxygen (molecular weight, 32.0) at 25°C (298 K)?

$$\mu = \sqrt{\frac{3 \times 8.314 \times 10^7 \times 298}{32}} = 4.82 \times 10^4 \text{cm/sec}$$

Because the term *nm/V* is equal to density, we can write equation **(**2-10**)** as

$$\mu = \sqrt{\frac{3P}{d}} \qquad (2\text{–}12)$$

Remembering that density is defined as a mass per unit volume, we see that the rate of diffusion of a gas is inversely proportional to the square root of its density. Such a relation confirms the early findings of Graham, who showed that a lighter gas diffuses more rapidly through a porous membrane than does a heavier one.

P.25

The van der Waals Equation for Real Gases

The fundamental kinetic equation (2-9) is found to compare with the ideal gas equation because the kinetic theory is based on the assumptions of the ideal state. However, real gases are not composed of infinitely small and perfectly elastic nonattracting spheres. Instead, they are composed of molecules of a finite volume that tend to attract one another. These factors affect the volume and pressure terms in the ideal equation so that certain refinements must be incorporated if equation (2-5) is to provide results that check with experiment. A number of such expressions have been suggested, the *van der Waals equation* being the best known of these. For 1 mole of gas, the van der Waals equation is written as

$$\left(P + \frac{a}{V^2}\right)(V - b) = RT \qquad (2\text{–}13)$$

For the more general case of *n* moles of gas in a container of volume *V*, equation (2-13) becomes

$$\left(P + \frac{an^2}{V^2}\right)(V - nb) = nRT \qquad (2\text{–}14)$$

The term a/V^2 accounts for the *internal pressure* per mole resulting from the intermolecular forces of attraction between the molecules; *b* accounts for the incompressibility of the molecules, that is, the *excluded volume*, which is about four times the molecular volume. This relationship holds true for all gases; however, the influence of nonideality is greater when the gas is compressed. Polar liquids have high internal pressures and serve as solvents only for substances of similar internal pressures. Nonpolar molecules have low internal pressures and are not able to overcome the powerful cohesive forces of the polar solvent molecules. Mineral oil is immiscible with water for this reason.

When the volume of a gas is large, the molecules are well dispersed. Under these conditions, a/V^2 and *b* become insignificant with respect to *P* and *V*, respectively. Under these conditions, the van der Waals equation for 1 mole of gas reduces to the ideal gas equation, *PV* = *RT*, and at low pressures, real gases behave in an ideal manner. The values of *a* and *b* have been determined for a number of gases. Some of these are listed in Table 2-3. The weak van der Waals forces of attraction, expressed by the constant *a*, are those referred to in Table 2-1.

Table 2-3 The Van Der Waals Constants for some Gases

Gas	*a* (liter^2 atm/mole^2)	*b* (liter/mole)
H_2	0.244	0.0266
O_2	1.360	0.0318
CH_4	2.253	0.0428
H_2O	5.464	0.0305
Cl_2	6.493	0.0562

$CHCl_3$	15.17	0.1022

Example 2-5

Application of the van der Waals Equation

A 0.193-mole sample of ether was confined in a 7.35-liter vessel at 295 K. Calculate the pressure produced using (*a*) the ideal gas equation and (*b*) the van der Waals equation. The van der Waals *a* value for ether is 17.38 liter^2 atm/mole^2; the *b* value is 0.1344 liter/mole. To solve for pressure, the van der Waals equation can be rearranged as follows:

$$P = \frac{nRT}{V - nb} - \frac{an^2}{V^2}$$

(*a*)

$$\begin{aligned} P &= \frac{0.193 \text{ mole} \times 0.0821 \text{ liter atm/deg mole} \times 295 \text{ deg}}{7.35 \text{ liter}} \\ &= 0.636 \text{ atm} \end{aligned}$$

(*b*)

$$\begin{aligned} P &= \frac{0.193 \text{ mole} \times 0.0821 \text{ liter atm/deg mole} \times 295 \text{ deg}}{7.35 \text{ liter} - (0.193 \text{ mole}) \times (0.1344 \text{ liter/mole})} \\ &\quad - \frac{17.38 \text{ liter}^2 \text{ atm/mole}^2 \, (0.193 \text{ mole})^2}{(7.35 \text{ liter})^2} \\ &= 0.626 \text{ atm} \end{aligned}$$

Example 2-6

Calculation of the van der Waals Constants

Calculate the pressure of 0.5 mole of CO_2 gas in a fire extinguisher of 1-liter capacity at 27°C using the ideal gas equation and the van der Waals equation. The van der Waals constants can be calculated from the critical temperature T_c and the critical pressure P_c (see the section Liquefaction of Gases for definitions):

$$a = \frac{27 R^2 T_c^{\,2}}{64 P_c} \quad \text{and} \quad b = \frac{RT_c}{8P_c}$$

The critical temperature and critical pressure of CO_2 are 31.0°C and 72.9 atm, respectively. Using the ideal gas equation, we obtain

$$P = \frac{nRT}{V} = \frac{0.5\ \text{mole} \times 0.0821\ \text{liter atm/deg mole} \times 300.15\ \text{deg}}{1\ \text{liter}}$$

$$= 12.32\ \text{atm}$$

Using the van der Waals equation, we obtain

$$a = \frac{27 \times (0.0821\ \text{liter atm/deg mole})^2 \times (304.15\ \text{deg})^2}{64 \times 72.9\ \text{atm}}$$

$$= 3.608\ \text{liter}^2\ \text{atm/mole}^2$$

$$b = \frac{(0.0821\ \text{liter atm/deg mole}) \times 304.15\ \text{deg}}{8 \times 72.9\ \text{atm}}$$

$$= 0.0428\ \text{liter/mole}$$

$$P = \frac{nRT}{V - nb} - \frac{an^2}{V^2}$$

$$= \frac{(0.5\ \text{mole} \times 0.821\ \text{liter atm/deg mole}) \times 300.15\ \text{deg}}{1\ \text{liter} - (0.5\ \text{mole} \times 0.0428821\ \text{liter/mole})}$$

$$- \frac{(3.608\ \text{liter}^2\ \text{atm/mole}^2) \times 0.5\ \text{mole}^2}{(1\ \text{liter})^2}$$

$$= 11.69\ \text{atm}$$

Although it is beyond the scope of this text, it should be mentioned that to account for nonideality, the concept of fugacity was introduced by Lewis.5 In general chemistry, the student learns about the concept of chemical potential. At equilibrium in an ideal homogeneous closed system, intermolecular interactions are considered to be nonexistent. However, in real gaseous states and in multiple-component systems, intermolecular interactions occur. Without going into great detail, one can say that these interactions can influence the chemical potential and cause deviations from the ideal state. These deviations reflect the activities of the component(s) within the system. Simply put, fugacity is a measurement of the activity associated with nonideal interactions. For further details pertaining to fugacity and its effects on gases, the student is directed to any introductory physical chemistry text.

The Liquid State

Liquefaction of Gases

When a gas is cooled, it loses some of its kinetic energy in the form of heat, and the velocity of the molecules decreases. If pressure is applied to the gas, the molecules are brought within the sphere of the van der Waals interaction forces and pass into the liquid state. Because of these forces, liquids are considerably denser than gases and occupy a definite volume. The transitions from a gas to a liquid and from a liquid to a solid depend not only on the temperature but also on the pressure to which the substance is subjected.

If the temperature is elevated sufficiently, a value is reached above which it is impossible to liquefy a gas irrespective of the pressure applied. This temperature, above which a liquid can no longer exist, is known as the *critical temperature*. The pressure required to liquefy a gas at its critical temperature is the *critical pressure*, which is also the highest vapor pressure that the liquid can have. The further a gas is cooled below its critical temperature, the less pressure is required to liquefy it. Based on this principle, all known gases have been liquefied. Supercritical fluids, where excessive temperature and pressure are applied, do exist as a separate/intermediate phase and will be discussed briefly later in this chapter. The critical temperature of water is 374°C, or 647 K, and its critical pressure is 218 atm, whereas the corresponding values for helium are 5.2 K and 2.26 atm. The critical temperature serves as a rough measure of the attractive forces between molecules because at temperatures above the critical value, the molecules possess sufficient kinetic energy so that no amount of pressure can bring them within the range of attractive forces that cause the atoms or molecules to “stick” together. The high critical values for water result from the strong dipolar forces between the molecules and particularly the hydrogen bonding that exists. Conversely, only the weak London force attracts helium molecules, and, consequently, this element must be cooled to the extremely low temperature of 5.2 K before it can be liquefied. Above this critical temperature, helium remains a gas no matter what the pressure.

Methods of Achieving Liquefaction

One of the most obvious ways to liquefy a gas is to subject it to intense cold by the use of freezing mixtures. Other methods depend on the cooling effect produced in a gas as it expands. Thus, suppose we allow an ideal gas to expand so rapidly that no heat enters the system. Such an expansion, termed an *adiabatic* expansion, can be achieved by carrying out the process in a Dewar, or vacuum, flask, which effectively insulates the contents of the flask from the external environment. The work done to bring about expansion therefore must come from the gas itself at the expense of its own heat energy content (collision frequency). As a result, the temperature of the gas falls. If this procedure is repeated a sufficient number of times, the total drop in temperature may be sufficient to cause liquefaction of the gas.

A cooling effect is also observed when a highly compressed *nonideal* gas expands into a region of low pressure. In this case, the drop in temperature results from the energy expended in overcoming the cohesive forces of attraction between the molecules. This cooling effect is known as the *Joule–Thomson effect* and differs from the cooling produced in adiabatic expansion, in which the gas does external work. To bring about liquefaction by the Joule–Thomson effect, it may be necessary to precool the gas before allowing it to expand. Liquid oxygen and liquid air are obtained by methods based on this effect.

Aerosols

Gases can be liquefied under high pressures in a closed chamber as long as the chamber is maintained below the critical temperature. When the pressure is reduced, the molecules expand and the liquid reverts to a gas. This reversible change of state is the basic principle involved in the preparation of pharmaceutical aerosols. In such products, a drug is dissolved or suspended in a *propellant*, a material that is liquid under the pressure conditions existing inside the container but that forms a gas under normal atmospheric conditions. The container is so designed that, by depressing a valve, some of the drug–propellant mixture is expelled owing to the excess pressure inside the container. If the drug is nonvolatile, it forms a fine spray as it leaves the valve orifice; at the same time, the liquid propellant vaporizes off.

Chlorofluorocarbons and hydrofluorocarbons have traditionally been utilized as propellants in these products because of their physicochemical properties. However, in the face of increasing environmental concerns (ozone depletion) and legislation like the Clean Air Act, the use of chlorofluorocarbons and hydrofluorocarbons is tightly regulated. This has led researchers to identify additional propellants, which has led to the increased use of other gases such as nitrogen and carbon dioxide. However, considerable effort is being focused on finding better propellant systems. By varying the proportions of the various propellants, it is possible to produce pressures within the container ranging from 1 to 6 atm at room

temperature. Alternate fluorocarbon propellants that do not deplete the ozone layer of the atmosphere are under investigation.6

The containers are filled either by cooling the propellant and drug to a low temperature within the container, which is then sealed with the valve, or by sealing the drug in the container at room temperature and then forcing the required amount of propellant into the container under pressure. In both cases, when the product is at room temperature, part of the propellant is in the gaseous state and exerts the pressure necessary to extrude the drug, whereas the remainder is in the liquid state and provides a solution or suspension vehicle for the drug.

The formulation of pharmaceuticals as aerosols is continually increasing because the method frequently offers distinct advantages over some of the more conventional methods of formulation. Thus, antiseptic materials can be sprayed onto abraded skin with a minimum of discomfort to the patient. One product, ethyl chloride, cools sufficiently on expansion so that when sprayed on the skin, it freezes the tissue and produces a local anesthesia. This procedure is sometimes used in minor surgical operations.

More significant is the increased efficiency often observed and the facility with which medication can be introduced into body cavities and passages. These and other aspects of aerosols have been considered by various researchers.7’8 Byron and Clark9a studied drug absorption from inhalation aerosols and provided a rather complete analysis of the problem. The United States Pharmacopeia (USP)[9b] includes a discussion of metered-dose inhalation products and provides standards and test procedures (USP). The identification of biotechnology-derived products has also dramatically increased the utilization of aerosolized formulations.10 Proteins, DNA, oligopeptides, and nucleotides all demonstrate poor oral bioavailability due to the harsh environment of the gastrointestinal tract and their relatively large size and rapid metabolism. The pulmonary and nasal routes of administration enable higher rates of passage into systemic circulation than does oral administration.11 It is important to point out that aerosol products are formulated under high pressure and stress limits. The physical stability of complex biomolecules may be adversely affected under these conditions (recall that pressure and temperature may influence the attractive and repulsive *inter*- and *intra*molecular forces present).

Vapor Pressure of Liquids

Translational energy of motion (kinetic energy) is not distributed evenly among molecules; some of the molecules have more energy and hence higher velocities than others at any moment. When a liquid is placed in an evacuated container at a constant temperature, the molecules with the highest energies break away from the surface of the liquid and pass into the gaseous state, and some of the molecules subsequently return to the liquid state, or condense. When the rate of condensation equals the rate of vaporization at a definite temperature, the vapor becomes saturated and a dynamic equilibrium is established. The pressure of the saturated vapor* above the liquid is then known as the *equilibrium vapor pressure*. If a manometer is fitted to an evacuated vessel containing the liquid, it is possible to obtain a record of the vapor pressure in millimeters of mercury. The presence of a gas, such as air, above the liquid decreases the rate of evaporation, but it does not affect the equilibrium pressure of the vapor.

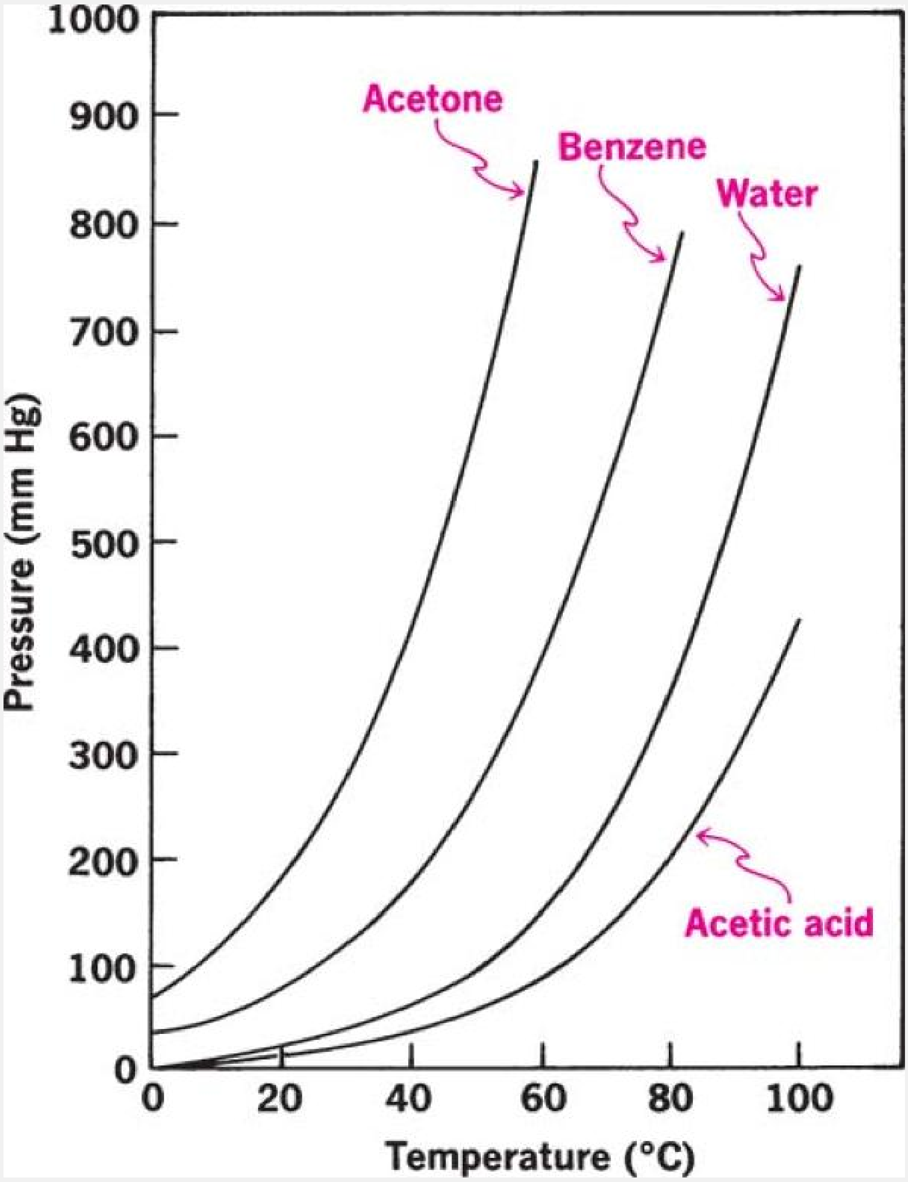


Fig. 2-5. The variation of the vapor pressure of some liquids with temperature.

As the temperature of the liquid is elevated, more molecules approach the velocity necessary for escape and pass into the gaseous state. As a result, the vapor pressure increases with rising temperature, as shown in Figure 2-5. Any point on one of the curves represents a condition in which the liquid and the vapor exist together in equilibrium. As observed in the diagram, if the temperature of any of the liquids is increased while the pressure is held constant, or if the pressure is decreased while the temperature is held constant, all the liquid will pass into the vapor state.

Clausius–Clapeyron Equation: Heat of Vaporization

The relationship between the vapor pressure and the absolute temperature of a liquid is expressed by the Clausius–Clapeyron equation (the Clapeyron and the Clausius–Clapeyron equations are derived in Chapter 3):

$$\log \frac{p_2}{p_1} = \frac{\Delta H_v (T_2 - T_1)}{2.303 R T_1 T_2} \qquad (2\text{–}15)$$

where p_1 and p_2 are the vapor pressures at absolute temperatures T_1 and T_2, and ΔH_v is the *molar heat of vaporization*, that is, the heat absorbed by 1 mole of liquid when it passes into the vapor state. Heats of vaporization vary somewhat with temperature. For example, the heat of vaporization of water is 539 cal/g at 100°C; it is 478 cal/g at 180°C, and at the critical temperature, where no distinction can be made between liquid and gas, the heat of vaporization becomes zero. Hence, the $\Delta H_v$of equation **(**2-15**)** should be recognized as an average value, and the equation should be considered strictly valid only over a narrow temperature range. The equation contains additional approximations, for it assumes that the vapor behaves as an ideal gas and that the molar volume of the liquid is negligible with respect to that of the vapor. These are important approximations in light of the nonideality of real solutions.

Example 2-7

Application of the Clausius–Clapeyron Equation

Compute the vapor pressure of water at 120°C. The vapor pressure p_1 of water at 100°C is 1 atm, and ΔH_v may be taken as 9720 cal/mole for this temperature range. Thus,

$$\log \frac{p_2}{1.0} = \frac{9720 \times (393 - 373)}{2.303 \times 1.987 \times 393 \times 373}$$

$$p_2 = 1.95 \text{ atm}$$

The Clausius–Clapeyron equation can be written in a more general form,

$$\log p = -\frac{\Delta H_v}{2.303 R} \frac{1}{T} + \text{constant} \qquad (2\text{–}16)$$

or in natural logarithms,

$$\ln p = -\frac{\Delta H_v}{R} \frac{1}{T} + \text{constant} \qquad (2\text{–}17)$$

from which it is observed that a plot of the logarithm of the vapor pressure against the reciprocal of the absolute temperature results in a straight line, enabling one to compute the heat of vaporization of the liquid from the slope of the line.

Boiling Point

If a liquid is placed in an open container and heated until the vapor pressure equals the atmospheric pressure, the vapor will form bubbles that rise rapidly through the liquid and escape into the gaseous state. The temperature at which the vapor pressure of the liquid equals the external or atmospheric pressure is known as the*boiling point*. All the absorbed heat is used to change the liquid to vapor, and the temperature does not rise until the liquid is completely vaporized. The atmospheric pressure at sea level is approximately 760 mm Hg; at higher elevations, the atmospheric pressure decreases and the boiling point is lowered. At a pressure of 700 mm Hg, water boils at 97.7°C; at 17.5 mm Hg, it boils at 20°C. The change in boiling point with pressure can be computed by using the Clausius–Clapeyron equation.

The heat that is absorbed when water vaporizes at the normal boiling point (i.e., the heat of vaporization at 100°C) is 539 cal/g or about 9720 cal/mole. For benzene, the heat of vaporization is 91.4 cal/g at the normal boiling point of 80.2°C. These quantities of heat, known as *latent heats of vaporization*, are taken up when the liquids vaporize and are liberated when the vapors condense to liquids.

The boiling point may be considered the temperature at which thermal agitation can overcome the attractive forces between the molecules of a liquid. Therefore, the boiling point of a compound, like the heat of vaporization and the vapor pressure at a definite temperature, provides a rough indication of the magnitude of the attractive forces.

The boiling points of normal hydrocarbons, simple alcohols, and carboxylic acids increase with molecular weight because the attractive van der Waals forces become greater with increasing numbers of atoms. Branching of the chain produces a less compact molecule with reduced intermolecular attraction, and a decrease in the boiling point results. In general, however, the alcohols boil at a much higher temperature than saturated hydrocarbons of the same molecular weight because of association of the alcohol molecules through hydrogen bonding. The boiling points of carboxylic acids are more abnormal still because the acids form dimers through hydrogen bonding that can persist even in the vapor state. The boiling points of straight-chain primary alcohols and carboxylic acids increase about 18°C for each additional methylene group. The rough parallel between the intermolecular forces and the boiling points or latent heats of vaporization is illustrated inTable 2-4. Nonpolar substances, the molecules of which are held together predominantly by the London force, have low boiling points and low heats of vaporization. Polar molecules, particularly those such as ethyl alcohol and water, which are associated through hydrogen bonds, exhibit high boiling points and high heats of vaporization.

Table 2-4 Normal Boiling Points and Heats of Vaporization

Compound	Boiling Point (°C)	Latent Heat of Vaporization (cal/g)
Helium	-268.9	6
Nitrogen	-195.8	47.6
Propane	-42.2	102
Methyl chloride	-24.2	102
Isobutane	-10.2	88
Butane	-0.4	92
Ethyl ether	34.6	90
Carbon disulfide	46.3	85
Ethyl alcohol	78.3	204
Water	100.0	539

Solids and the Crystalline State

Crystalline Solids

The structural units of crystalline solids, such as ice, sodium chloride, and menthol, are arranged in fixed geometric patterns or lattices. Crystalline solids, unlike liquids and gases, have definite shapes and an orderly arrangement of units. Gases are easily compressed, whereas solids, like liquids, are practically incompressible. Crystalline solids show definite melting points, passing rather sharply from the solid to the liquid state. Crystallization, as is sometimes taught in organic chemistry laboratory courses, occurs by precipitation of the compound out of solution and into an ordered array. Note that there are several important variables here, including the solvent(s) used, the temperature, the pressure, the crystalline array pattern, salts (if crystallization is occurring through the formation of insoluble salt complexes that precipitate), and so on, that influence the rate and stability of the crystal (see the section Polymorphism) formation. The various crystal forms are divided into six distinct crystal systems based on symmetry. They are, together with examples of each, cubic (sodium chloride), tetragonal (urea), hexagonal (iodoform), rhombic (iodine), monoclinic (sucrose), and triclinic (boric acid). The morphology of a crystalline form is often referred to as its *habit*, where the crystal habit is defined as having the same structure but different outward appearance (or alternately, the collection of faces and their area ratios comprising the crystal).

The units that constitute the crystal structure can be atoms, molecules, or ions. The sodium chloride crystal, shown in Figure 2-6, consists of a cubic lattice of sodium ions interpenetrated by a lattice of chloride ions, the binding force of the crystal being the electrostatic attraction of the oppositely charged ions. In diamond and graphite, the lattice units consist of atoms held together by covalent bonds. Solid carbon dioxide, hydrogen chloride, and naphthalene form crystals composed of molecules as the building units. In organic compounds, the molecules are held together by van der Waals forces, Coulombic forces, and hydrogen bonding, which account for the weak binding and for the low melting points of these crystals. Aliphatic hydrocarbons crystallize with their chains lying in a parallel arrangement, whereas fatty acids crystallize in layers of dimers with the chains lying parallel or tilted at an angle with respect to the base plane. Whereas ionic and atomic crystals in general are hard and brittle and have high melting points, molecular crystals are soft and have relatively low melting points.

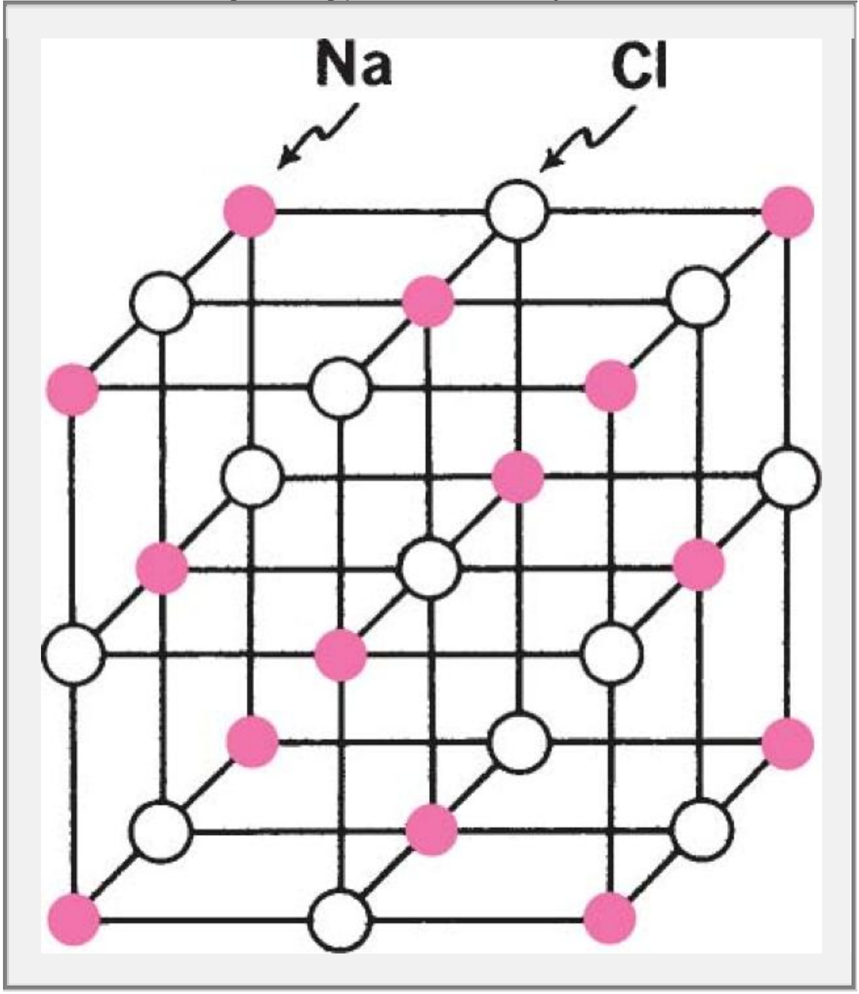


Fig. 2-6. The crystal lattice of sodium chloride.

Metallic crystals are composed of positively charged ions in a field of freely moving electrons, sometimes called the *electron gas*. Metals are good conductors of electricity because of the free movement of the electrons in the lattice. Metals may be soft or hard and have low or high melting points. The hardness and strength of metals depend in part on the kind of imperfections, or *lattice defects*, in the crystals.

Polymorphism

Some elemental substances, such as carbon and sulfur, may exist in more than one crystalline form and are said to be *allotropic*, which is a special case of*polymorphism*. Polymorphs have different stabilities and may spontaneously convert from the metastable form at a temperature to the stable form. They also exhibit different melting points, x-ray crystal and diffraction patterns (see later discussion), and solubilities, even though they are chemically identical. The differences may not always be great or even large enough to “see” by analytical methods but may sometimes be substantial. Solubility and melting points are very important in pharmaceutical processes, including dissolution and formulation, explaining the primary reason we are interested in polymorphs. The formation of polymorphs of a compound may depend upon several variables pertaining to the crystallization process, including solvent differences (the packing of a crystal might be different from a polar versus a nonpolar solvent); impurities that may favor a metastable polymorph because of specific inhibition of growth patterns; the level of supersaturation from which the material is crystallized (generally the higher the concentration above the solubility, the more chance a metastable form is seen); the temperature at which the crystallization is carried out; geometry of the covalent bonds (are the molecules rigid and planar or free and flexible?); attraction and repulsion of cations and anions (later you will see how x-ray crystallography is used to define an electron density map of a compound); fit of cations into coordinates that are energetically favorable in the crystal lattice; temperature; and pressure.

Perhaps the most common example of polymorphism is the contrast between a diamond and graphite, both of which are composed of crystalline carbon. In this case, high pressure and temperature lead to the formation of a diamond from elemental carbon. When contrasting an engagement ring with a pencil, it is quite apparent that a diamond has a distinct crystal habit from that of graphite. It should be noted that a diamond is a less stable (*metastable*) crystalline form of carbon than is graphite. Actually, the imperfections in diamonds continue to occur with time and represent the diamond converting, very slowly at the low ambient temperature and pressure, into the more stable graphite polymorph.

Nearly all long-chain organic compounds exhibit polymorphism. In fatty acids, this results from different types of attachment between the carboxyl groups of adjacent molecules, which in turn modify the angle of tilt of the chains in the crystal. The triglyceride tristearin proceeds from the low-melting metastable alpha (α) form through the beta prime (β') form and finally to the stable beta (β) form, having a high melting point. The transition cannot occur in the opposite direction.

Theobroma oil, or cacao butter, is a polymorphous natural fat. Because it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°C–36°C). Theobroma oil is capable of existing in four polymorphic forms: the unstable gamma form, melting at 18°C; the alpha form, melting at 22°C; the beta prime form, melting at 28°C; and the stable beta form, melting at 34.5°C. Riegelman12 pointed out the relationship between polymorphism and the preparation of cacao butter suppositories. If theobroma oil is heated to the point at which it is completely liquefied (about 35°C), the nuclei of the stable beta crystals are destroyed and the mass does not crystallize until it is supercooled to about 15°C. The crystals that form are the metastable gamma, alpha, and beta prime forms, and the suppositories melt at 23°C to 24°C or at ordinary room temperature. The proper method of preparation involves melting cacao butter at the lowest possible temperature, about 33°C. The mass is sufficiently fluid to pour, yet the crystal nuclei of the stable beta form are not lost. When the mass is chilled in the mold, a stable suppository, consisting of beta crystals and melting at 34.5°C, is produced.

Polymorphism has achieved significance in last decade because different polymorphs exhibit different solubilities. In the case of slightly soluble drugs, this may affect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug. Aguiar et al.13 showed that the polymorphic state of chloramphenicol palmitate has a significant influence on the biologic availability of the drug. Khalil et al.14 reported that form II of sulfameter, an antibacterial agent, was more active orally in humans than form III, although marketed pharmaceutical preparations were found to contain mainly form III. Another case is that of the AIDS drug ritonavir, which was marketed in a dissolved formulation until a previously unknown, more stable and less soluble polymorph appeared. This resulted in a voluntary recall and reformulation of the product before it could be reintroduced to the market.

Polymorphism can also be a factor in suspension technology. Cortisone acetate exists in at least five different forms, four of which are unstable in the presence of water and change to a stable form.15 Because this transformation is usually accompanied by appreciable caking of the crystals, these should all be in the form of the stable polymorph before the suspension is prepared. Heating, grinding under water, and suspension in water are all factors that affect the interconversion of the different cortisone acetate forms.16

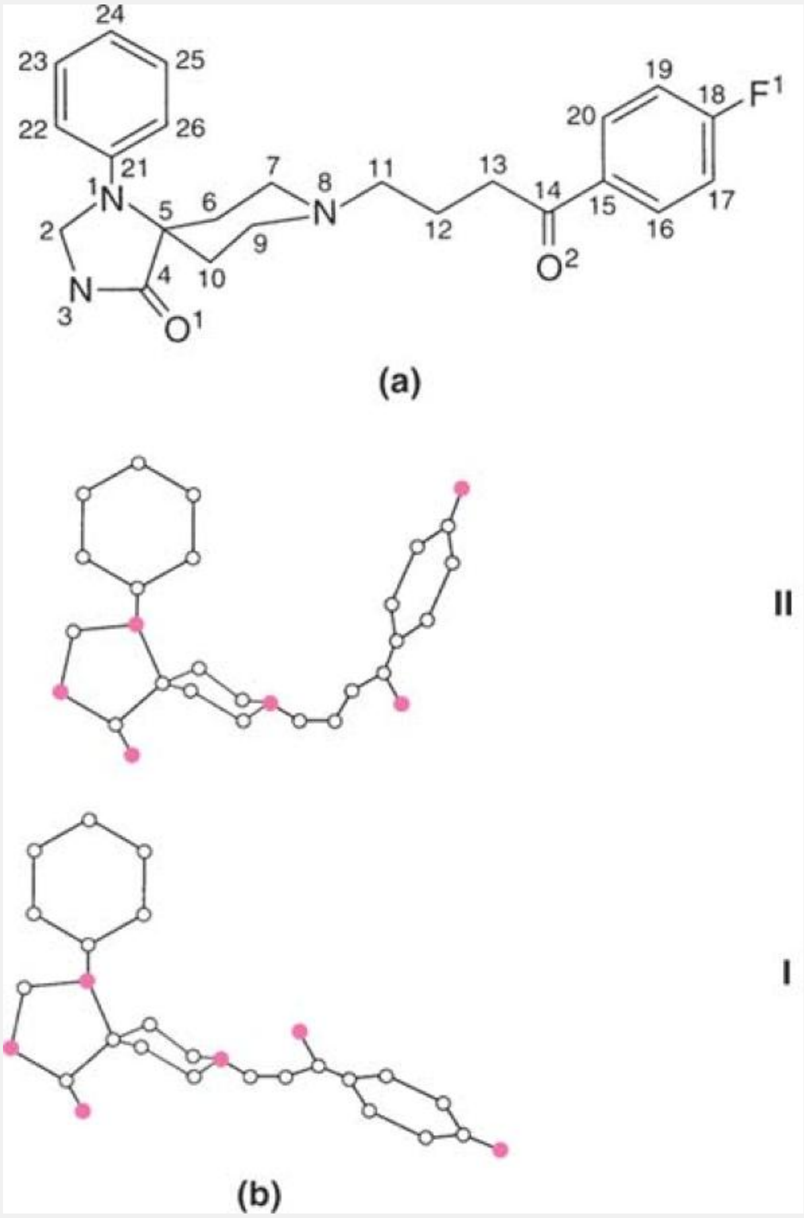


Fig. 2-7. (*a*) Structure and numbering of spiperone. (*b*) Molecular conformation of two polymorphs, I and II, of spiperone. (Modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, p. 93; R. Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd Ed., Macmillan, New York, 1977, p. 162.) (From M. Azibi, M. Draguet-Brughmans, R. Bouche, B. Tinant, G. Germain, J. P. Declercq, and M. Van Meerssche, J. Pharm. Sci. **72**, 232, 1983. With permission.)

Although crystal structure determination has become quite routine with the advent of fast, high-resolution diffractometer systems as well as software allowing solution from powder x-ray diffraction data, it can be challenging to determine the crystal structure of highly unstable polymorphs of a drug. Azibi et al.17 studied two polymorphs of spiperone, a potent antipsychotic agent used mainly in the treatment of schizophrenia. The chemical structure of spiperone is shown in Figure 2-7aand the molecular conformations of the two polymorphs, I and II, are shown in Figure 2-7b. The difference between the two polymorphs is in the positioning of the atoms in the side chains, as seen in Figure 2-7b, together with the manner in which each molecule binds to neighboring spiperone molecules in the crystal. The results of the investigation showed that the crystal of polymorph II is made up of dimers (molecules in pairs), whereas polymorph crystal I is constructed of nondimerized molecules of spiperone. In a later study, Azibi et al.18 examined the polymorphism of a number of drugs to ascertain what properties cause a compound to exist in more than one crystalline form. Differences in intermolecular van der Waals forces and hydrogen bonds were found to produce different crystal structures in antipsychotic compounds such as haloperidol (Fig. 2-8) and bromperidol. Variability in hydrogen bonding also contributes to polymorphism in the sulfonamides.19

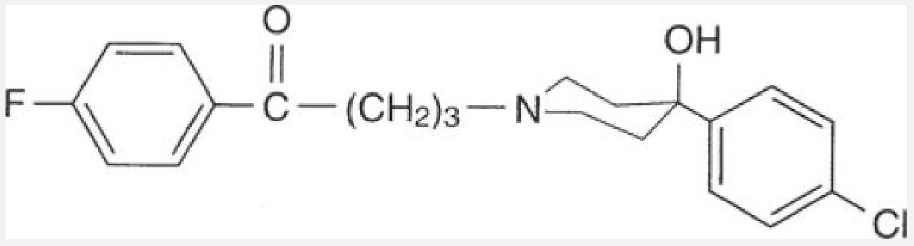


Fig. 2-8. Haloperidol.

Goldberg and Becker20 studied the crystalline forms of tamoxifen citrate, an antiestrogenic and antineoplastic drug used in the treatment of breast cancer and postmenopausal symptoms. The structural formula of tamoxifen is shown in Figure 2-9. Of the two forms found, the packing in the stable polymorph, referred to as form B, is dominated by hydrogen bonding. One carboxyl group of the citric acid moiety donates its proton to the nitrogen atom on an adjacent tamoxifen molecule to bring about the hydrogen-bonding network responsible for the stabilization of form B. The other polymorph, known as form A, is a metastable polymorph of tamoxifen citrate, its molecular structure being less organized than that of the stable B form. An ethanolic suspension of polymorph A spontaneously rearranges into polymorph B.

Lowes et al.21 performed physical, chemical, and x-ray studies on carbamazepine. Carbamazepine is used in the treatment of epilepsy and trigeminal neuralgia (severe pain in the face, lips, and tongue). The *β* polymorph of the drug can be crystallized from solvents of high dielectric constant, such as the aliphatic alcohols. The *α* polymorph is crystallized from solvents of low dielectric constant, such as carbon tetrachloride and cyclohexane. A rather thorough study of the two polymorphic forms of carbamazepine was made using infrared spectroscopy, thermogravimetric analysis (TGA), hot-stage microscopy, dissolution rate, and x-ray powder diffraction. The hydrogen-bonded structure of the *α* polymorph of carbamazepine is shown in Figure 2-10a and its molecular formula in Figure 2-10b.

Estrogens are essential hormones for the development of female sex characteristics. When the potent synthetic estrogen ethynylestradiol is crystallized from the solvents acetonitrile, methanol, and chloroform saturated with water, four different crystalline solvates are formed. Ethynylestradiol had been reported to exist in several polymorphic forms. However, Ishida et al.22 showed from thermal analysis, infrared spectroscopy, and x-ray studies that these forms are crystals containing solvent molecules and thus should be classified as *solvates* rather than as polymorphs. Solvates are sometimes called *pseudopolymorphs*. Of course, solvates may also exhibit polymorphism as long as one compares “like” solvation-state crystal structures.23 Other related estradiol compounds may exist in true polymeric forms.

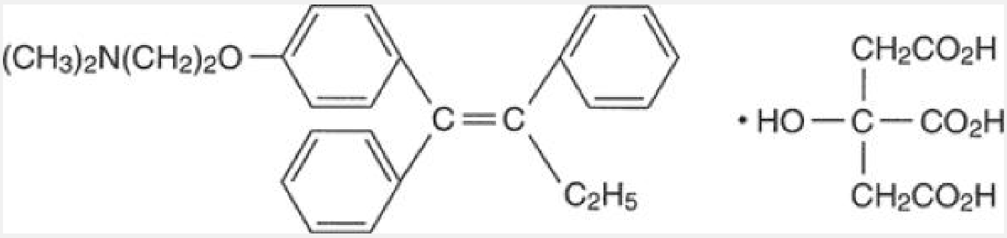


Fig. 2-9. Tamoxifen citrate.

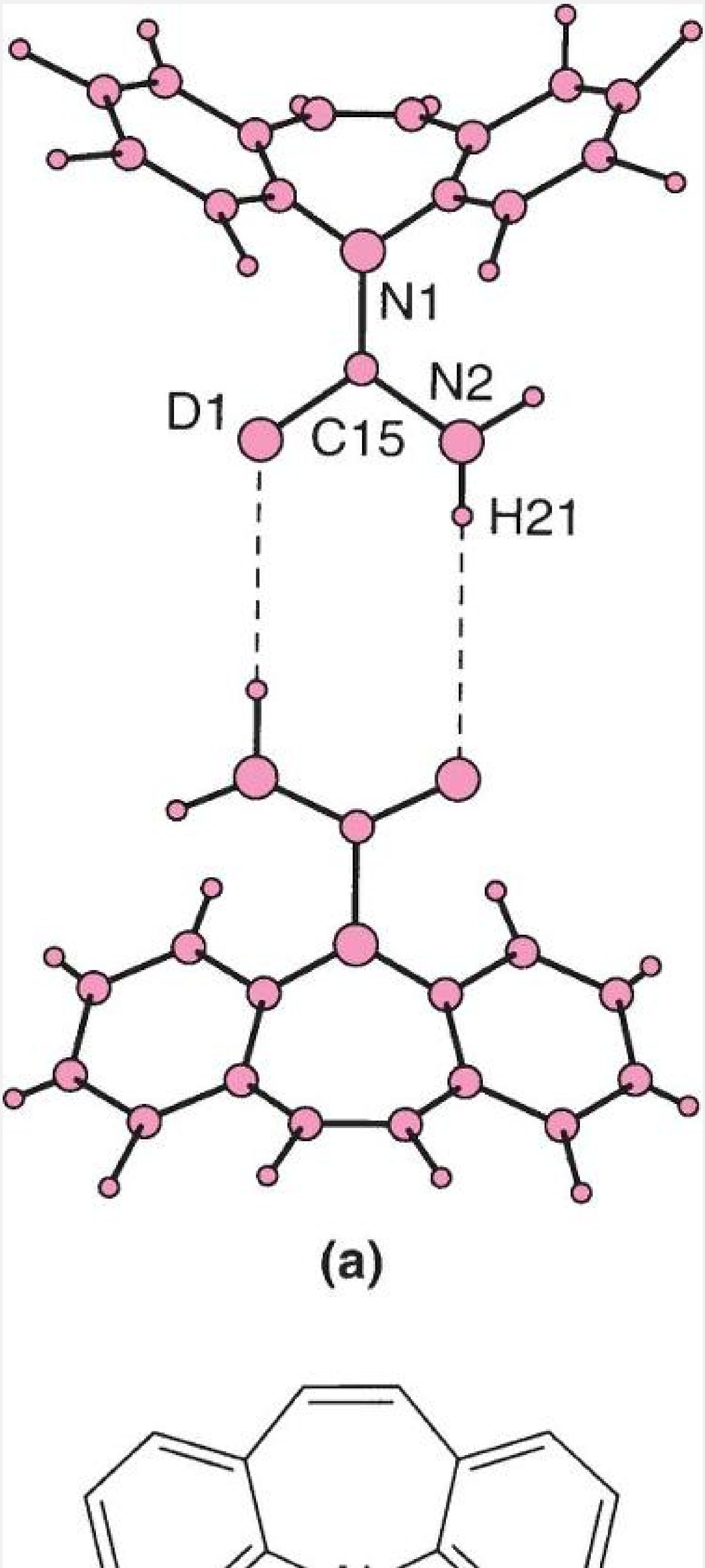

N1
N2
D1
C15
H21
(a)

Fig. 2-10. (*a*) Two molecules of the polymorph α-carbamazepine joined together by hydrogen bonds. (From M. M. J. Lowes, M. R. Caira, A. P. Lotter, and J. G. Van Der Watt, J. Pharm. Sci. **76,** 744, 1987. With permission.) (*b*) Carbamazepine.

Behme et al.24 reviewed the principles of polymorphism with emphasis on the changes that the polymorphic forms may undergo. When the change from one form to another is reversible, it is said to be *enantiotropic*. When the transition takes place in one direction only—for example, from a metastable to a stable form—the change is said to be *monotropic*. Enantiotropism and monotropism are important properties of polymorphs as described by Behme et al.24

The transition temperature in polymorphism is important because it helps characterize the system and determine the more stable form at temperatures of interest. At their transition temperatures, polymorphs have the same free energy (i.e., the forms are in equilibrium with each other), identical solubilities in a particular solvent, and identical vapor pressures. Accordingly, plots of logarithmic solubility of two polymorphic forms against 1/*T* provide the transition temperature at the intersection of the extrapolated curves. Often, the plots are nonlinear and cannot be extrapolated with accuracy. For dilute solutions, in which Henry's law applies, the logarithm of the solubility ratios of two polymorphs can be plotted

against 1/*T*, and the intersection at a ratio equal to unity gives the transition temperature.25 This temperature can also be obtained from the phase diagram of pressure versus temperature and by using differential scanning calorimetry (DSC).26

Solvates

Because many pharmaceutical solids are often synthesized by standard organic chemical methods, purified, and then crystallized out of different solvents, residual solvents can be trapped in the crystalline lattice. This creates a cocrystal, as described previously, termed a *solvate*. The presence of the residual solvent may dramatically affect the crystalline structure of the solid depending on the types of intermolecular interactions that the solvent may have with the crystalline solid. In the following sections we highlight the influence of solvates and how they can be detected using standard solid characterization analyses.

Biles27 and Haleblian and McCrone28 discussed in some detail the significance of polymorphism and solvation in pharmaceutical practice.

Amorphous Solids

Amorphous solids as a first approximation may be considered supercooled liquids in which the molecules are arranged in a somewhat random manner as in the liquid state. Substances such as glass, pitch, and many synthetic plastics are amorphous solids. They differ from crystalline solids in that they tend to flow when subjected to sufficient pressure over a period of time, and they do not have definite melting points. In the Rheology chapter, a solid is characterized as any substance that must be subjected to a definite shearing force before it fractures or begins to flow. This force, below which the body shows elastic properties, is known as the*yield value*.

Amorphous substances, as well as cubic crystals, are usually *isotropic*, that is, they exhibit similar properties in all directions. Crystals other than cubic are*anisotropic*, showing different characteristics (electric conductance, refractive index, crystal growth, rate of solubility) in various directions along the crystal.

It is not always possible to determine by casual observation whether a substance is crystalline or amorphous. Beeswax and paraffin, although they appear to be amorphous, assume crystalline arrangements when heated and then allowed to cool slowly. Petrolatum contains both crystalline and amorphous constituents. Some amorphous materials, such as glass, may crystallize after long standing.

Whether a drug is amorphous or crystalline has been shown to affect its therapeutic activity. Thus, the crystalline form of the antibiotic novobiocin acid is poorly absorbed and has no activity, whereas the amorphous form is readily absorbed and therapeutically active.29 This is due to the differences in the rate of dissolution. Once dissolved, the molecules exhibit no memory of their origin.

X-Ray Diffraction

X-rays are a form of electromagnetic radiation (Chapter 4) having a wavelength on the order of interatomic distances (about 1.54 Å for most laboratory instruments using Cu *Kα* radiation; the C—C bond is about 1.5 Å). X-rays are diffracted by the electrons surrounding the individual atoms in the molecules of the crystals. The regular array of atoms in the crystal (periodicity) causes certain directions to constructively interfere in some directions and destructively interfere in others, just as water waves interfere when you drop two stones at the same time into still water (due to the similarity of the wavelengths to the distance between the atoms or molecules of crystals mentioned). The x-ray diffraction pattern on modern instruments is detected on a sensitive plate arranged behind the crystal and is a “shadow” of the crystal lattice that produced it. Using computational methods, it is possible to determine the conformation of the molecules as well as their relationship to others in the structure. This results in a full description of the structure including the smallest building block, called the unit cell.

The electron density and, accordingly, the position of the atoms in complex structures, such as penicillin, may be determined from a comprehensive mathematical study of the x-ray diffraction pattern. The electron density map of crystalline potassium benzylpenicillin is shown in Figure 2-11. The elucidation of this structure by x-ray crystallography paved the way for the later synthesis of penicillin by organic chemists. Aspects of x-ray crystallography of pharmaceutical interest are reviewed by Biles30 and Lien and Kennon.31

Where “single” crystals are unavailable or unsuitable for analysis, a powder of the substance may be investigated. The powder x-ray diffraction pattern may be thought of as a fingerprint of the single-crystal structure. Comparing the position and intensity of the lines (the same constructive interference discussed previously) on such a pattern with corresponding lines on the pattern of a known sample allows one to conduct a qualitative and a quantitative analysis. It is important to note that two polymorphs will provide two distinct powder x-ray diffraction patterns. The presence of a solvate will also influence the powder x-ray diffraction pattern because the solvate will have its own unique crystal structure. This may lead to a single polymorphic form appearing as changeable or two distinct polymorphs. One way to determine whether the presence of a change in a powder x-ray diffraction pattern is due to a solvate or is a separate polymorph is to measure the powder x-ray diffraction patterns at various temperatures. Because solvents tend to be driven out of the structure below the melting point, measuring the powder x-ray diffraction patterns at several temperatures may eliminate the solvent and reveal an unsolvated form. Lack of a change in the powder x-ray diffraction patterns at the different temperatures is a strong indication that the form is not really solvated, or minor changes may indicate a structure that maintains its packing motif without the solvent preset (see Fig. 2-12 for spirapril). This can be confirmed by other methods as described later.

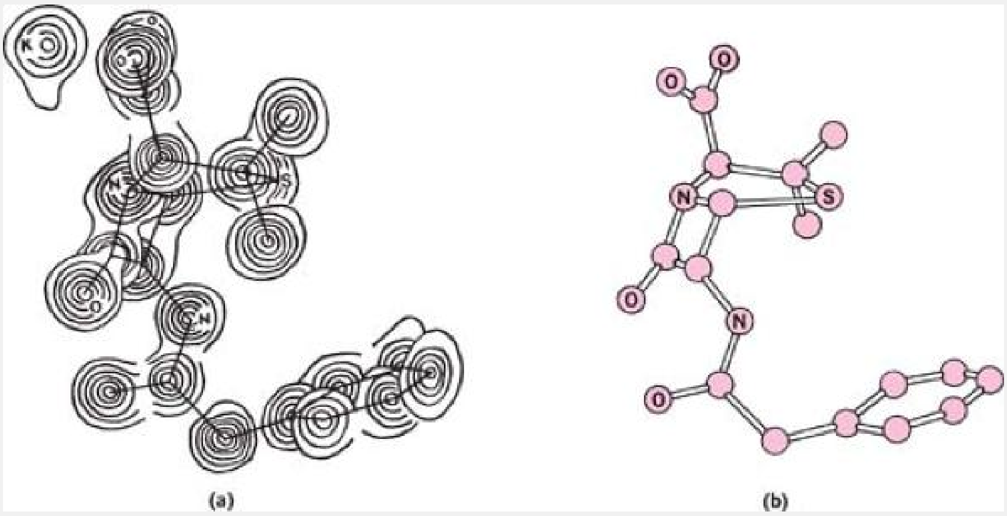


Fig. 2-11. (*a*) Electron density map of potassium benzylpenicillin. (Modified from G. L. Pitt, Acta Crystallogr. **5,** 770, 1952.) (*b*) A model of the structure that can be built from analysis of the electron density projection.

Melting Point and Heat of Fusion

The temperature at which a liquid passes into the solid state is known as the *freezing point*. It is also the *melting point* of a pure crystalline compound. The freezing point or melting point of a pure crystalline solid is strictly defined as the temperature at which the pure liquid and solid exist in equilibrium. In practice, it is taken as the temperature of the equilibrium mixture at an external pressure of 1 atm; this is sometimes known as the *normal freezing* or *melting point*. The student is reminded that different intermolecular forces are involved in holding the crystalline solid together and that the addition of heat to melt the crystal is actually the addition of energy. Recall that in a liquid, molecular motion occurs at a much greater rate than in a solid.

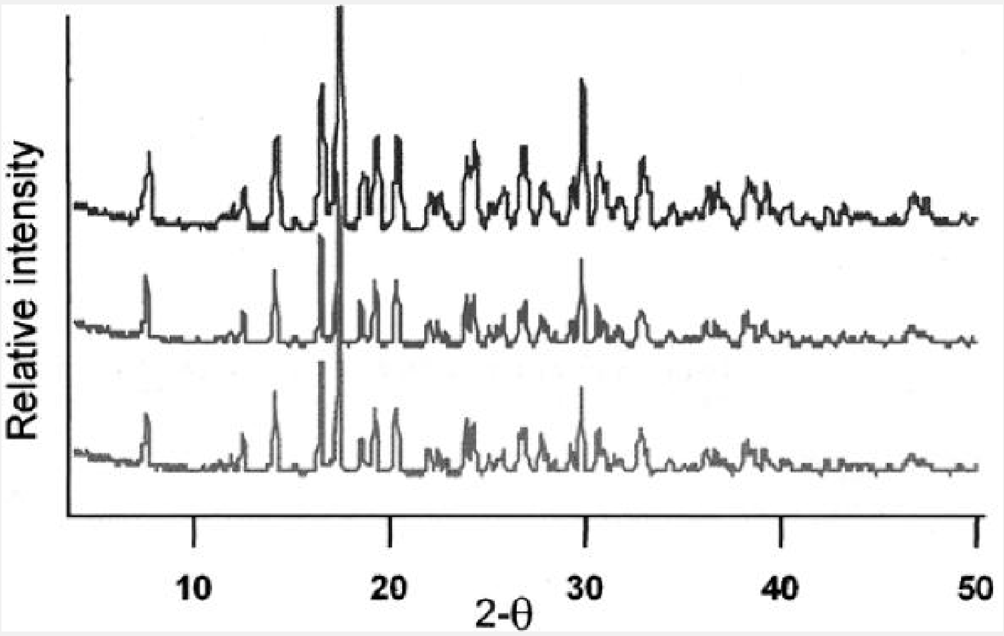


Fig. 2-12. Powder x-ray diffraction patterns for spirapril hydrochloride. The monohydrate (top) and the sample dehydrated at 75°C for 106 and 228 hr (middle and bottom, respectively) demonstrating that the structural motif is essentially unchanged in the "dehydrated hydrate." (From W. Xu, *Investigation of Solid State Stability of Selected Bioactive Compounds*, unpublished dissertation, Purdue University, Purdue, Ind., 1997. With permission.)

The heat (energy) absorbed when 1 g of a solid melts or the heat liberated when it freezes is known as the *latent heat of fusion*, and for water at 0°C it is about 80 cal/g (1436 cal/mole). The heat added during the melting process does not bring about a change in temperature until all of the solid has disappeared because this heat is converted into the potential energy of the molecules that have escaped from the solid into the liquid state. The normal melting points of some compounds are collected in Table 2-5 together with the molar heats of fusion.

Changes of the freezing or melting point with pressure can be obtained by using a form of the Clapeyron equation, written as

$$\frac{\Delta T}{\Delta P} = T\frac{V_l - V_s}{\Delta H_f} \qquad (2\text{–}18)$$

Table 2-5 Normal Melting Points and Molar Heats of Fusion of some Compounds

Substance	Melting Point (K)	Molar Heat of Fusion, ΔH_f (cal/mole)
H_2O	273.15	1440
H_2S	187.61	568
NH_3	195.3	1424
PH_3	139.4	268
CH_4	90.5	226
C_2H_6	90	683
n-C_3H_8	85.5	842
C_6H_6	278.5	2348
$C_{10}H_8$	353.2	4550

where V_l and V_s are the molar volumes of the liquid and solid, respectively. Molar volume (volume in units of cm^3/mole) is computed by dividing the gram molecular weight by the density of the compound. ΔH_f is the molar heat of fusion, that is, the amount of heat absorbed when 1 mole of the solid changes into 1 mole of liquid, and ΔT is the change of melting point brought about by a pressure change of ΔP.

Water is unusual in that it has a larger molar volume in the solid state than in the liquid state ($V_s > V_l$) at the melting point. Therefore, $\Delta T/\Delta P$ is negative, signifying that the melting point is lowered by an increase in pressure. This phenomenon can be rationalized in terms of *Le Chatelier's principle*, which states that a system at equilibrium readjusts so as to reduce the effect of an external stress. Accordingly, if a pressure is applied to ice at 0°C, it will be transformed into liquid water, that is, into the state of lower volume, and the freezing point will be lowered.

Example 2-8

Demonstration of *Le Chatelier's Principle*

What is the effect of an increase of pressure of 1 atm on the freezing point of water (melting point of ice)?

At 0°C, $T = 273.16$ K, ΔH_f [congruent] 1440 cal/mole, the molar volume of water is 18.018, and the molar volume of ice is 19.651, or $V_l - V_s = -1.633\ cm^3$/mole. To obtain the result in deg/atm using equation (2-18), we first convert ΔH_f in cal/mole into units of ergs/mole by multiplying by the factor 4.184×10^7 ergs/cal:

$$\Delta H_f = 6025 \times 10^7 \text{ ergs/mole} \quad \text{or} \quad 6025 \times 10^6 \text{ dyne cm/mole}$$

Then multiplying equation (2-18) by the conversion factor (1.013×10^6 dynes/cm^2)/atm (which is permissible because the numerator and denominator of this factor are equivalent, so the factor equals 1) gives the result in the desired units:

$$\frac{\Delta T}{\Delta P} = \frac{273.16 \text{ deg} \times (-1.633 \text{cm}^3/\text{mole})}{6025 \times 10^7 \text{ dynes cm/mole}} \times (1.013 \times 10^6 \text{ dynes/cm}^2)/\text{atm}$$

$$\frac{\Delta T}{\Delta P} = -0.0075 \text{ deg/atm}$$

Hence, an increase of pressure of 1 atm lowers the freezing point of water by about 0.0075 deg, or an increase in pressure of about 133 atm would be required to lower the freezing point of water by 1 deg. (When the ice–water equilibrium mixture is saturated with air under a total pressure of 1 atm, the temperature is lowered by an additional 0.0023 deg.) Pressure has only a slight effect on the equilibrium temperature of *condensed systems* (i.e., of liquids and solids). The large molar volume or low density of ice (0.9168 g/cm^3 as compared with 0.9988 g/cm^3 for water at 0°C) accounts for the fact that the ice floats on liquid water. The lowering of the melting point with increasing pressure is taken advantage of in ice-skating. The pressure of the skate lowers the melting point and thus causes the ice to melt below the skate. This thin layer of liquid provides lubricating action and allows the skate to glide over the hard surface. Of course, the friction of the skate also contributes greatly to the melting and lubricating action.

Example 2-9

Pressure Effects on Freezing Points

According to Example 2-8, an increase of pressure of 1 atm reduces the freezing (melting) point of ice by 0.0075 deg. To what temperature is the melting point reduced when a 90-lb boy skates across the ice? The area of the skate blades in contact with the ice is 0.085 cm^2.

In addition to the atmospheric pressure, which may be disregarded, the pressure of the skates on the ice is the mass (90 lb = 40.8 kg) multiplied by the acceleration constant of gravity (981 cm/sec^2) and divided by the area of the skate blades (0.085 cm^2):

$$\text{Pressure} = \frac{40{,}800\ \text{g} \times (981\ \text{cm/sec}^2)}{0.085\text{cm}^2} = 4.71 \times 10^8 \text{dynes/cm}^2$$

Changing to atmospheres (1 atm = 1.01325×10^6 dynes/cm^2) yields a pressure of 464.7 atm. The change in volume ΔV from water to ice is 0.018 - 0.01963 liter/mole, or -0.00163 liter/mole for the transition from ice to liquid water.

Use equation (2-18) in the form of a derivative:

$$\frac{dT}{dp} = T\frac{\Delta V}{\Delta H_f}$$

For a pressure change of 1 atm to 464.7 atm when the skates of the 90-lb boy touch the ice, the melting temperature will drop from 273.15 K (0°C) to*T*, the final melting temperature of the ice under the skate blades, which converts the ice to liquid water and facilitates the lubrication. For such a problem, we must put the equation in the form of an integral; that is, integrating between 273.15 K and *T* caused by a pressure change under the skate blades from 1 atm to (464.7 + 1) atm:

$$\int_{273.15\ \text{K}}^{T} \frac{1}{T}dT = \frac{\Delta V}{\Delta H_f}\int_{1\ \text{atm}}^{465.7\ \text{atm}} dP$$

$$\ln T - \ln(273.15) = \frac{-0.00163\ \text{liter/mole}}{1440\ \text{cal/mole}}\,\frac{24.2\ \text{cal}}{1\ \text{liter atm}}(P_2 - P_1)$$

In this integrated equation, 1440 cal/mole is the heat of fusion ΔH_f of water in the region of 0°C, and 24.2 cal/liter atm is a conversion factor (see the front leaf of the book) for converting cal to liter atm. We now have

$$\ln T = (-274 \times 10^{-5}/\text{atm})(465.7 - 1\ \text{atm}) + \ln(273.15)$$
$$T = 269.69\ \text{K}$$

The melting temperature has been reduced from 273.15 to 269.69 K, or a reduction in melting point of 3.46 K by the pressure of the skates on the ice.

A simpler way to do the ice-skating problem is to realize that the small change in temperature, -3.46 K, occurs over a large pressure change of about 465 atm. Therefore, we need not integrate but rather may obtain the temperature change ΔT per unit atmosphere change, ΔP, and multiply this value by the actual pressure, 464.7 atm. Of course, the heat of fusion of water, 1440 cal/mole, must be multiplied by the conversion factor, 1 liter atm/24.2 cal, to yield 59.504 liter atm. We have

$$\frac{\Delta T}{\Delta P} = \frac{T\Delta V}{\Delta H_f} = \frac{(273.15\ \text{K})(0.0180 - 0.0196)\ \text{liter/mole}}{59.504\ \text{liter atm/mole}}$$
$$\frac{\Delta T}{\Delta P} = -0.00734\ \text{K/atm}$$

For a pressure change of 464.7 atm, the decrease in temperature is

$$\Delta T = -0.00734\ \text{K/atm} \times 464.7\ \text{atm} = -3.41\ \text{K}$$

as compared with the more accurate value, -3.46 K.

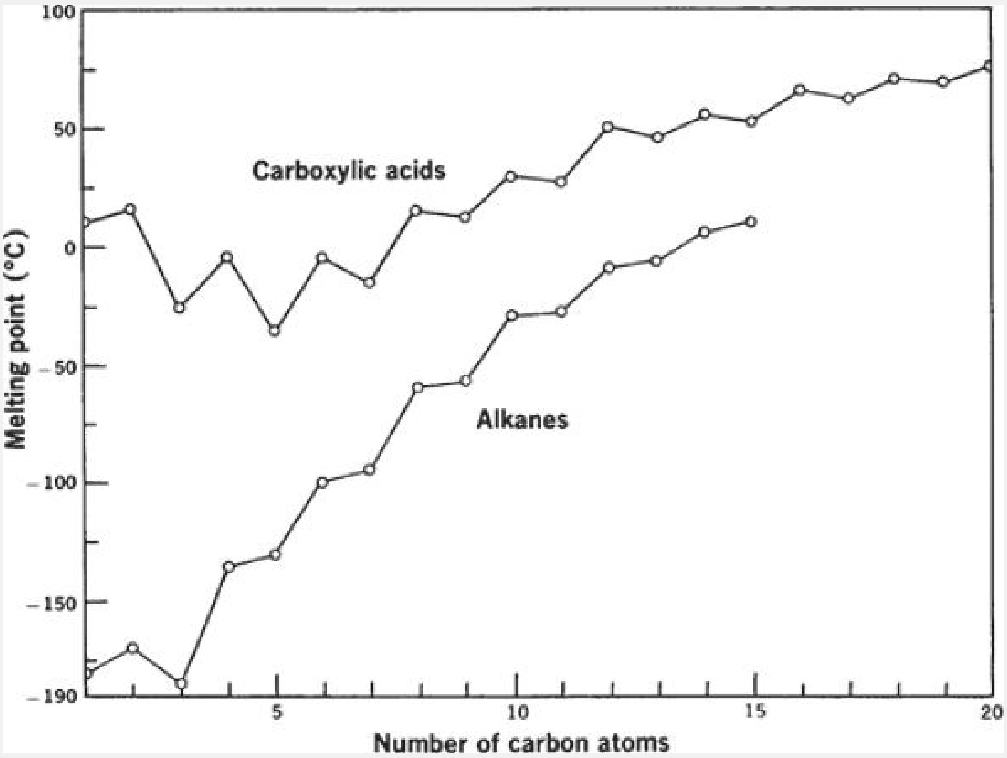


Fig. 2-13. The melting points of alkanes and carboxylic acids as a function of carbon chain length. (Modified from C. R. Noller,*Chemistry of Organic Compounds*, 2nd Ed., Saunders, Philadelphia, 1957, pp. 40, 149.)

Melting Point and Intermolecular Forces

The heat of fusion may be considered as the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting (increased molecular motion) to occur. A crystal that is bound together by weak forces generally has a low heat of fusion and a low melting point, whereas one bound together by strong forces has a high heat of fusion and a high melting point.

Because polymorphic forms represent different molecular arrangements leading to different crystalline forms of the same compound, it is obvious that different intermolecular forces will account for these different forms. Then consider polymorph A, which is held together by higher attractive forces than is polymorph B. It is obvious that more heat will be required to break down the attractive forces in polymorph A, and thus its melting temperature will be higher than that of polymorph B.

Paraffins crystallize as thin leaflets composed of zigzag chains packed in a parallel arrangement. The melting points of normal saturated hydrocarbons increase with molecular weight because the van der Waals forces between the molecules of the crystal become greater with an increasing number of carbon atoms. The melting points of the alkanes with an even number of carbon atoms are higher than those of the hydrocarbons with an odd number of carbon atoms, as shown in Figure 2-13. This phenomenon presumably is because alkanes with an odd number of carbon atoms are packed in the crystal less efficiently.

Table 2-6 Melting Points and Solubilities of some Xanthines*

Compound	Melting Point (°C Uncorrected)	Solubility in Water at 30°C (mole/liter × 10^2)
Theophylline (R = H)	270–274	4.5
Caffeine (R = CH_3)	238	13.3
7-Ethyitheophylline (R = CH_2CH_3)	156–157	17.6
7-Propyltheophylline (R = $CH_2CH_2CH_3$	99–100	104.0

*From D. Guttman and T. Higuchi, J. Am. Pharm. Assoc. Sci. Ed. **46,** 4, 1957.

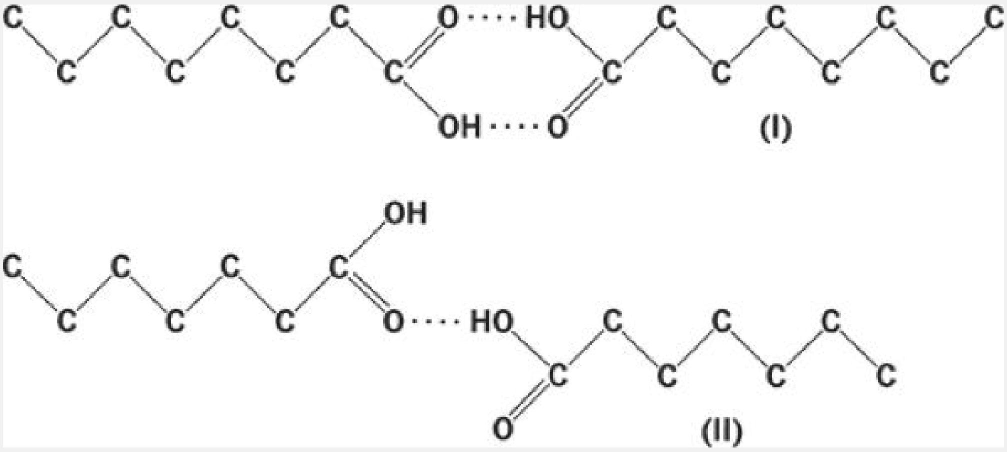


Fig. 2-14. Configuration of fatty acid molecules in the crystalline state. (Modified from A. E. Bailey, *Melting and Solidification of Fats*, Interscience, New York, 1950, p. 120.)

The melting points of normal carboxylic acids also show this alternation, as seen in Figure 2-13. This can be explained as follows. Fatty acids crystallize in molecular chains, one segment of which is shown in Figure 2-14. The even-numbered carbon acids are arranged in the crystal as seen in the more symmetric structure I, whereas the odd-numbered acids are arranged according to structure II. The carboxyl groups are joined at two points in the even-carbon compound; hence, the crystal lattice is more stable and the melting point is higher.

The melting points and solubilities of the xanthines of pharmaceutical interest, determined by Guttman and Higuchi,32 further exemplify the relationship between melting point and molecular structure. Solubilities, like melting points, are strongly influenced by intermolecular forces. This is readily observed in Table 2-6, where the methylation of theophylline to form caffeine and the lengthening of the side chain from methyl (caffeine) to propyl in the 7 position result in a decrease of the melting point and an increase in solubility. These effects presumably are due to a progressive weakening of intermolecular forces.

The Liquid Crystalline State

Three states of matter have been discussed thus far in this chapter: gas, liquid, and solid. A fourth state of matter is the

liquid crystalline state or *mesophase*. The term *liquid crystal* is an apparent contradiction, but it is useful in a descriptive sense because materials in this state are in many ways intermediate between the liquid and solid states.

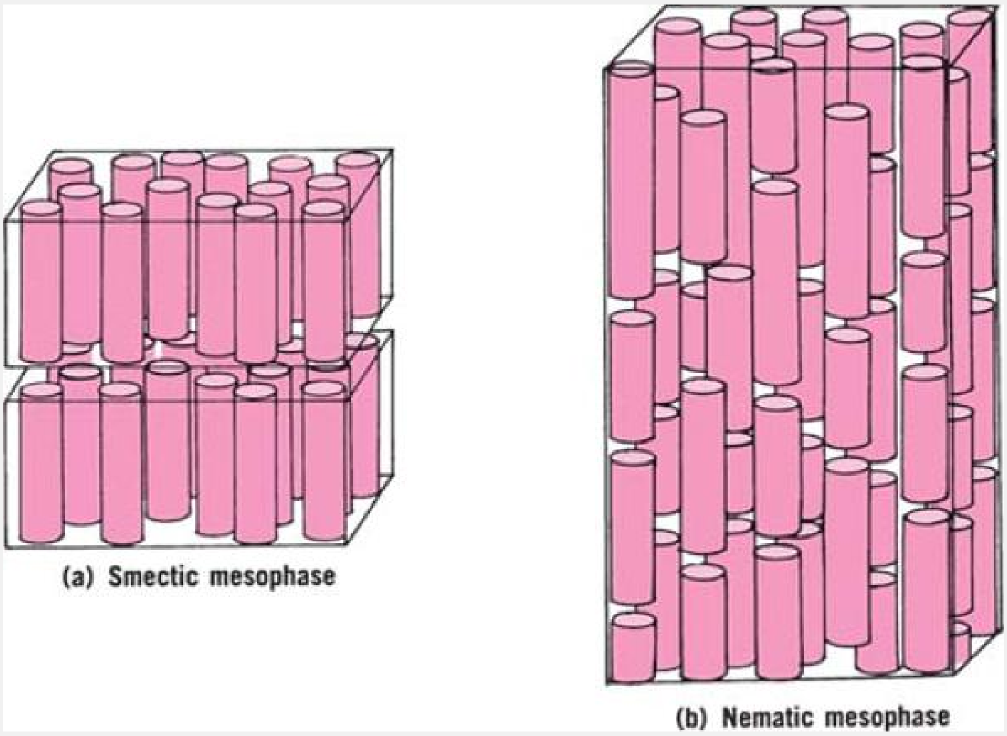


Fig. 2-15. Liquid crystalline state. (*a*) Smectic structure; (*b*) nematic structure.

Structure of Liquid Crystals

As seen earlier, molecules in the liquid state are mobile in three directions and can also rotate about three axes perpendicular to one another. In the solid state, on the other hand, the molecules are immobile, and rotations are not as readily possible.

It is not unreasonable to suppose, therefore, that intermediate states of mobility and rotation should exist, as in fact they do. It is these intermediate states that constitute the liquid crystalline phase, or mesophase, as the liquid crystalline phase is called.

The two main types of liquid crystals are termed *smectic* (soaplike or greaselike) and *nematic* (threadlike). In the smectic state, molecules are mobile in two directions and can rotate about one axis (Fig. 2-15a). In the nematic state, the molecules again rotate only about one axis but are mobile in three dimensions (Fig. 2-15b). A third type of crystal (*cholesteric*) exists but can be considered as a special case of the nematic type. In atherosclerosis, it is the incorporation of cholesterol and lipids in human subendothelial macrophages that leads to an insoluble liquid crystalline biologic membrane33 that ultimately results in plaque formation.

The smectic mesophase is probably of most pharmaceutical significance because it is this phase that usually forms in ternary (or more complex) mixtures containing a surfactant, water, and a weakly amphiphilic or nonpolar additive.

In general, molecules that form mesophases (*a*) are organic, (*b*) are elongated and rectilinear in shape, (*c*) are rigid, and (*d*) possess strong dipoles and easily polarizable groups. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action of certain solvents on solids (lyotropic liquid crystals). The first recorded observation of a thermotropic liquid crystal was made by Reinitzer in 1888 when he heated cholesteryl benzoate. At 145°C, the solid formed a turbid liquid (the thermotropic liquid crystal), which only became clear, to give the conventional liquid state, at 179°C.

Properties and Significance of Liquid Crystals

Because of their intermediate nature, liquid crystals have some of the properties of liquids and some of the properties of solids. For example, liquid crystals are mobile and thus can be considered to have the flow properties of liquids. At the same time they possess the property of being birefringent, a property associated with crystals. In birefringence, the light passing through a material is divided into two components with different velocities and hence different refractive indices.

Some liquid crystals show consistent color changes with temperature, and this characteristic has resulted in their being used to detect areas of elevated temperature under the skin that may be due to a disease process. Nematic liquid crystals may be sensitive to electric fields, a property used to advantage in developing display systems. The smectic mesophase has application in the solubilization of water-insoluble materials. It also appears that liquid crystalline phases of this type are frequently present in emulsions and may be responsible for enhanced physical stability owing to their highly viscous nature.

The liquid crystalline state is widespread in nature, with lipoidal forms found in nerves, brain tissue, and blood vessels. Atherosclerosis may be related to the laying down of

lipid in the liquid crystalline state on the walls of blood vessels. The three components of bile (cholesterol, a bile acid salt, and water), in the correct proportions, can form a smectic mesophase, and this may be involved in the formation of gallstones. Bogardus34 applied the principle of liquid crystal formation to the solubilization and dissolution of cholesterol, the major constituent of gallstones. Cholesterol is converted to a liquid crystalline phase in the presence of sodium oleate and water, and the cholesterol rapidly dissolves from the surface of the gallstones.

Nonaqueous liquid crystals may be formed from triethanolamine and oleic acid with a series of polyethylene glycols or various organic acids such as isopropyl myristate, squalane, squalene, and naphthenic oil as the solvents to replace the water of aqueous mesomorphs. Triangular plots or tertiary phase diagrams were used by Friberg et al.35a,b to show the regions of the liquid crystalline phase when either polar (polyethylene glycols) or nonpolar (squalene, etc.) compounds were present as the solvent.

Ibrahim36 studied the release of salicylic acid as a model drug from lyotropic liquid crystalline systems across lipoidal barriers and into an aqueous buffered solution.

Finally, liquid crystals have structures that are believed to be similar to those in cell membranes. As such, liquid crystals may function as useful biophysical models for the structure and functionality of cell membranes.

Friberg wrote a monograph on liquid crystals.[35b] For a more detailed discussion of the liquid crystalline state, refer to the review by Brown,37 which serves as a convenient entry into the literature.

The Supercritical Fluid State

Supercritical fluids were first described more than 100 years ago and can be formed by many different normal gases such as carbon dioxide. Supercritical fluids have properties that are intermediate between those of liquids and gases, having better ability to permeate solid substances (gaslike) and having high densities that can be regulated by pressure (liquidlike). A *supercritical fluid* is a mesophase formed from the gaseous state where the gas is held under a combination of temperatures and pressures that exceed the *critical point* of a substance (Fig. 2-16). Briefly, a gas that is brought above its *critical temperature* T_c will still behave as a gas irrespective of the applied pressure; the *critical pressure* (P_c) is the minimum pressure required to liquefy a gas at a given temperature. As the pressure is raised higher, the density of the gas can increase without a significant increase in the viscosity while the ability of the supercritical fluid to dissolve compounds also increases. A gas that may have little to no ability to dissolve a compound under ambient conditions can completely dissolve the compound under high pressure in the supercritical range. Figure 2-17 illustrates this phenomenon with CO_2, where CO_2 held at the same temperature can dissolve different chemical classes from a natural product source when the pressure is increased.38 It is also important to note that more than one gas or even the addition of a solvent (termed a cosolvent) such as water and/or ethanol can be made to increase the ability of the supercritical fluid to dissolve compounds.

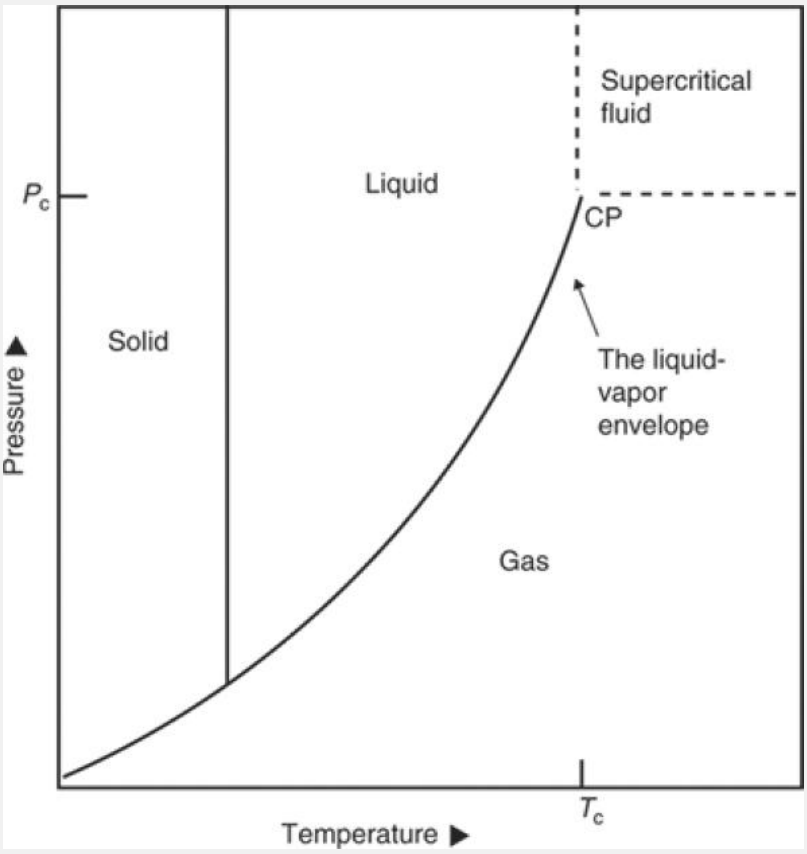


Fig. 2-16. Phase diagram showing the supercritical region of a compressed gas. Key: CP = critical point. (Modified from Milton Roy, Co., *Supercritical Fluid Extraction: Principles and Applications* [Bulletin 37.020], Milton Roy Co., Ivydale, Pa.)

Supercritical fluid applications in the pharmaceutical sciences were excellently reviewed by Kaiser et al.39 There are several common uses for supercritical fluids including extraction,40,41 crystallization,42 and the preparation of formulations (they are increasingly being used to prepare polymer mixtures43,44,45 and for the formation of micro- and nanoparticles46). Supercritical fluids offer several advantages over traditional methodologies: the potential for low-temperature extractions and purification of compounds (consider heat added for distillation procedures), solvent volatility under ambient conditions, selectivity of the extracted compounds (Fig. 2-17), and lower energy requirement and lower viscosity than solvents.38 Most important is the reduced toxicity of the gases and the reduced need for hazardous solvents that require expensive disposal. For example, supercritical CO_2 can be simply disposed of by opening a valve and releasing the CO_2 into the atmosphere.

One of the best examples of the use of supercritical fluids is in the decaffeination of coffee.[39,47] Traditionally, solvents like methylene chloride have been used in the decaffeination process. This leads to great expense in the purchase and disposal of the residual solvents and increases the chance for toxicity. Supercritical CO_2has now been utilized for the decaffeination of coffee and tea. Interestingly, initial supercritical CO_2 resulted in the removal of the caffeine and important flavor-adding compounds from coffee. The loss of the flavor-adding compounds resulted in a poor taste and an unacceptable product. Additional studies demonstrated that adding water to the supercritical CO_2 significantly reduced the loss of the flavor. However, in this process a sample run using coffee beans is performed through the system to saturate the water with the flavor-enhancing compounds. The supercritical CO_2 is passed over an extraction column upon release of the pressure and the residual caffeine it carries is collected on the column. The sample run of beans is removed and disposed of, and then the first batch of marketable coffee beans is passed through the system as the water is recirculated. Several batches of decaffeinated coffee are prepared in this manner before the water is discarded. The process leads to approximately 97% of caffeine being removed from the beans. This is an excellent example of how cosolvents may be added to improve the quality of the supercritical CO_2-processed material.

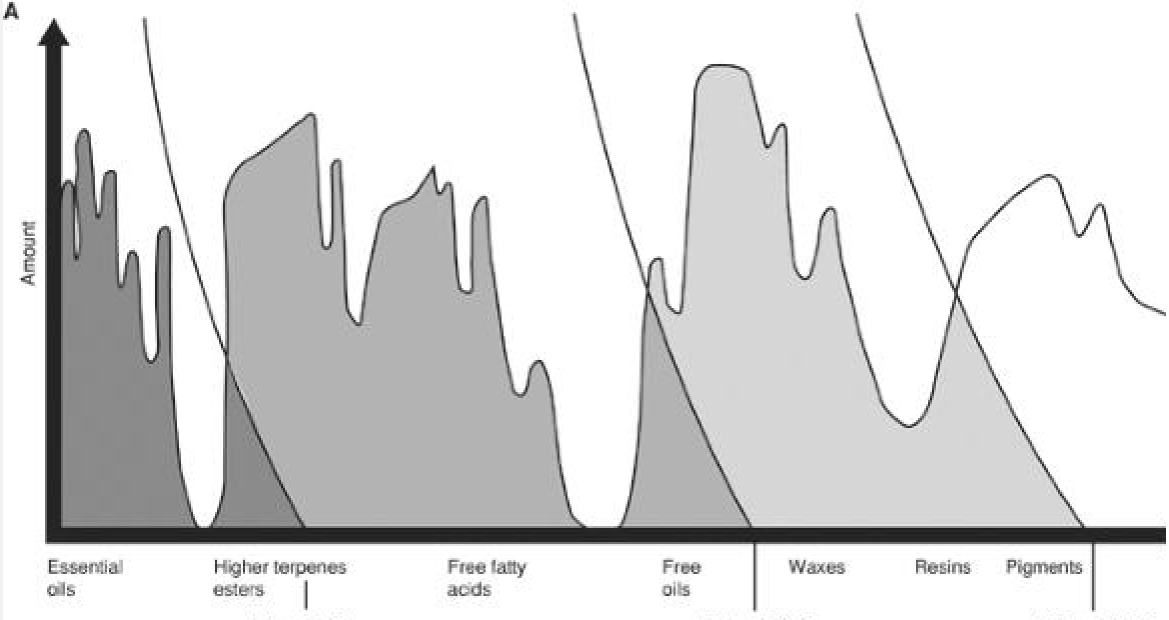


Fig. 2-17. The effect of pressure on the ability of supercritical fluids to selectively extract different compounds. (Modified from Milton Roy Co., *Supercritical Fluid Extraction: Principles and Applications* [Bulletin 37.020], Milton Roy Co., Ivyland, Pa.)

Thermal Analysis

As noted earlier in this chapter, a number of physical and chemical effects can be produced by temperature changes, and methods for characterizing these alterations upon heating or cooling a sample of the material are referred to as *thermal analysis*. The most common types of thermal analysis are DSC, differential thermal analysis (DTA), TGA, and thermomechanical analysis (TMA). These methods have proved to be valuable in pharmaceutical research and quality control for the characterization and identification of compounds, the determination of purity, polymorphism[20,21] solvent, and moisture content, amorphous content, stability, and compatibility with excipients.

In general, thermal methods involve heating a sample under controlled conditions and observing the physical and chemical changes that occur. These methods measure a number of different properties, such as melting point, heat capacity, heats of reaction, kinetics of decomposition, and changes in the flow (rheologic) properties of biochemical, pharmaceutical, and agricultural materials and food. The methods are briefly described with examples of applications. Differential scanning calorimetry is the most commonly used method and is generally a more useful technique because its measurements can be related more directly to thermodynamic properties. It appears that any analysis that can be carried out with DTA can be performed with DSC, the latter being the more versatile technique.

Differential Scanning Calorimetry

In DSC, heat flows and temperatures are measured that relate to thermal transitions in materials. Typically, a sample and a reference material are placed in separate pans and the temperature of each pan is increased or decreased at a predetermined rate. When the sample, for example, benzoic acid, reaches its melting point, in this case 122.4°C, it remains at this temperature until all the material has passed into the liquid state because of the endothermic process of melting. A temperature difference therefore exists between benzoic acid and a reference, indium (melting point [mp] = 156.6°C), as the temperature of the two materials is raised gradually through the range 122°C to 123°C. A second temperature circuit is used in DSC to provide a heat input to overcome this temperature difference. In this way the temperature of the sample, benzoic acid, is maintained at the same value as that of the reference, indium. The difference is heat input to the sample, and the reference per unit time is fed to a computer and plotted as *dH/dt* versus the average temperature to which the sample and reference are being raised. The data collected in a DSC run for a compound such as benzoic acid are shown in the thermogram in Figure 2-18. There are a wide variety of features in DSCs such as autosamplers, mass flow controllers, and built-in computers. An example of a modern DSC, the Q200, is shown in Figure 2-19. The differential heat input is recorded with a sensitivity of ± 0.2 μW, and the temperature range over which the instrument operates is -180°C to 725°C.

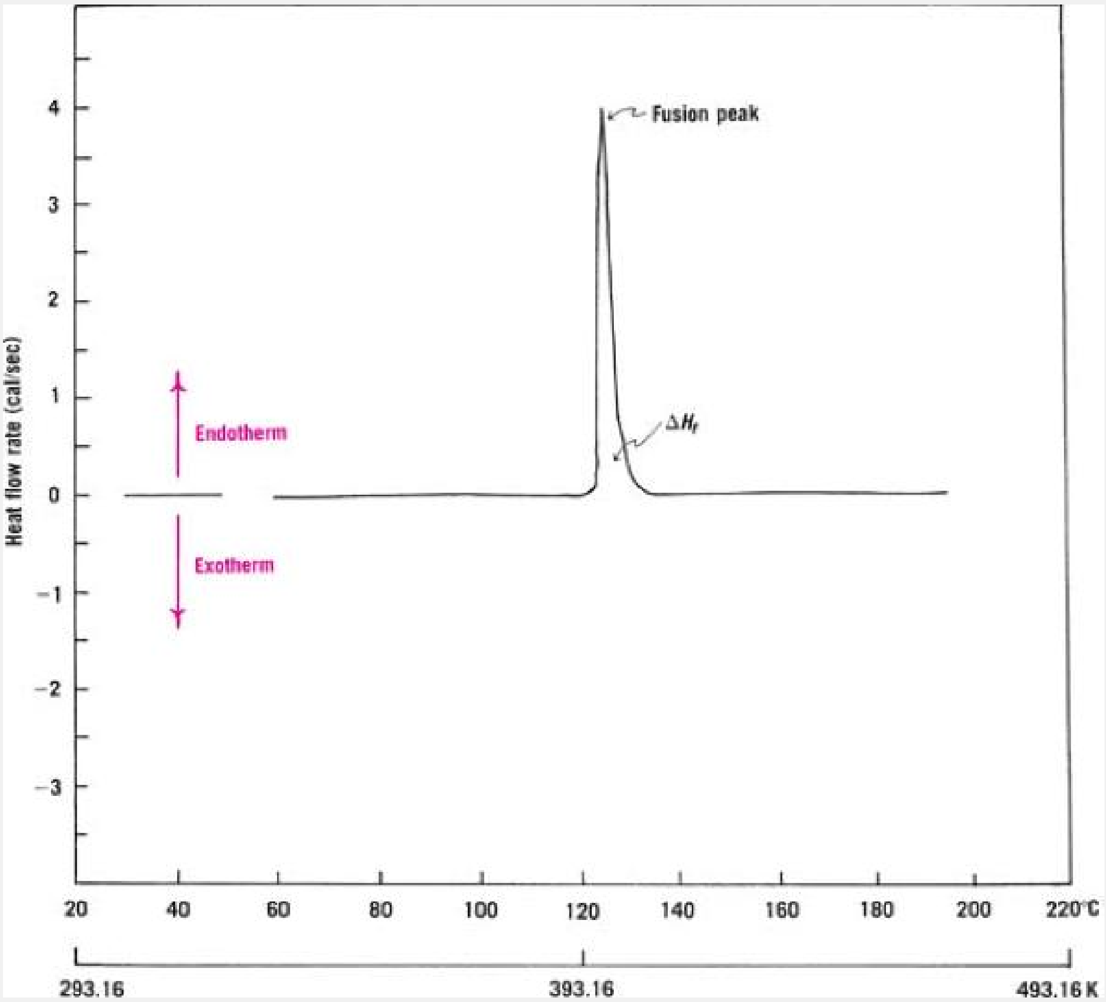


Fig. 2-18. Thermogram of a drug compound. Endothermic transitions (heat absorption) are shown in the upward direction and exothermic transitions (heat loss) are plotted downward. Melting is an endothermic process, whereas crystallization or freezing is an exothermic process. The area of the melting peak is proportional to the heat of fusion, ΔH_f.

Differential scanning calorimetry is a measurement of heat flow into and out of the system. In general, an endothermic (the material is absorbing heat) reaction on a DSC arises from desolvations, melting, glass transitions, and, more rarely, decompositions. An exothermic reaction measured by DSC is usually indicative of a decomposition (energy is released from the bond breaking) process and molecular reorganizations such as crystallization. Differential scanning calorimetry has found increasing use in standardization of the lyophilization process.48 Crystal changes and eutectic formation in the frozen state as well as amorphous character can be detected by DSC (and by DTA) when the instruments are operated below room temperature.

Although DSC is used most widely in pharmacy to establish identity and purity, it is almost as commonly used to obtain heat capacities and heats of fusion and capacities. It

is also useful for constructing phase diagrams to study the polymorphs discussed in this chapter and for carrying out studies on the kinetics of decomposition of solids.

Fig. 2-19. Perkin Elmer differential scanning calorimeter 7 (DSC 7).

Differential scanning calorimetry and other thermal analytic methods have a number of applications in biomedical research and food technology. Guillory and associates[49,50] explored the applications of thermal analysis, DSC, and DTA in particular, in conjunction with infrared spectroscopy and x-ray diffraction. Using these techniques, they characterized various solid forms of drugs, such as sulfonamides, and correlated a number of physical properties of crystalline materials with interactions between solids, dissolution rates, and stabilities in the crystalline and amorphous states.

For additional references to the use of DSC in research and technology, contact the manufacturers of differential thermal equipment for complete bibliographies.

Differential Thermal Analysis

In DTA, both the sample and the reference material are heated by a common heat source (Fig. 2-20) rather than the individual heaters used in DSC (Fig. 2-21). Thermocouples are placed in contact with the sample and the reference material in DTA to monitor the difference in temperature between the sample and the reference material as they are heated at a constant rate. The temperature difference between the sample and the reference material is plotted against time, and the endotherm as melting occurs (or exotherm as obtained during some decomposition reactions) is represented by a peak in the thermogram.

Although DTA is a useful tool, a number of factors may affect the results. The temperature difference, ΔT, depends, among other factors, on the resistance to heat flow, R. In turn, R depends on temperature, nature of the sample, and packing of the material in the pans. Therefore, it is not possible to directly calculate energies of melting, sublimation, and decomposition, and DTA is used as a qualitative or semiquantitative method for calorimetric measurements. The DSC, although more expensive, is needed for accurate and precise results.

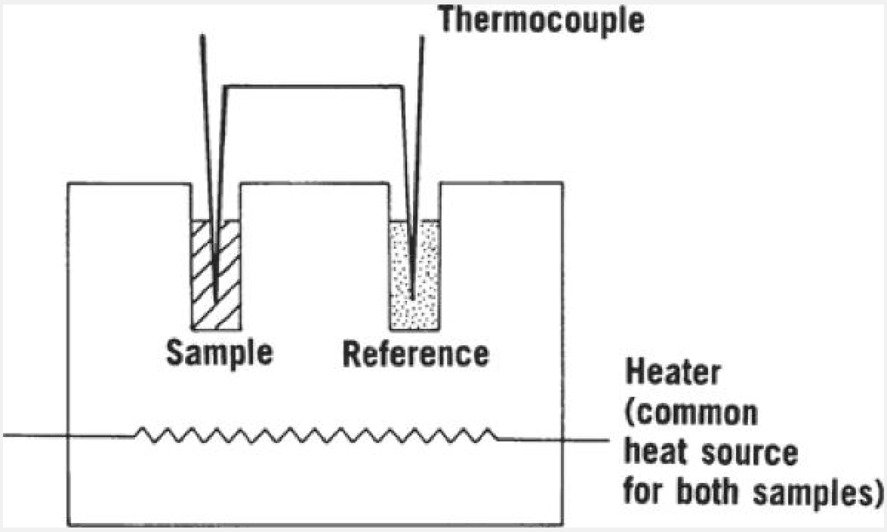


Fig. 2-20. Common heat source of differential thermal analyzer with thermocouples in contact with the sample and the reference material.

A related technique is dielectric analysis, also discussed in Chapter 4. The concept is that molecules move in response to an applied electric field according to their size, dipole moments, and environment (which changes with temperature). In this technique, the sample serves as the dielectric medium in a capacitor, and as the ac electric field oscillates, the motion of permanent dipoles is sensed as a phase shift relative to the timescale of the frequencies used. Each sample will have a characteristic response or permittivity at a given temperature and frequency. As the sample is heated or cooled, the response will vary because the mobility of the molecular dipoles will change. On going through a first-order transition such as melting, the mobility will exhibit a drastic frequency-independent change giving rise to a family of curves with different intensities but a common maximum occurring at the transition temperature. For glass transitions (pseudosecond order) where the transition occurs over a broad temperature range, there will be a distinct variation in both intensity and temperature, allowing extremely sensitive detection of such

events. Dielectric analysis detects the microscopic “viscosity” of the system and can yield information on activation energies of changes as well as the homogeneity of samples. The technique does, however, require significantly more data analysis than the other thermal methods discussed.

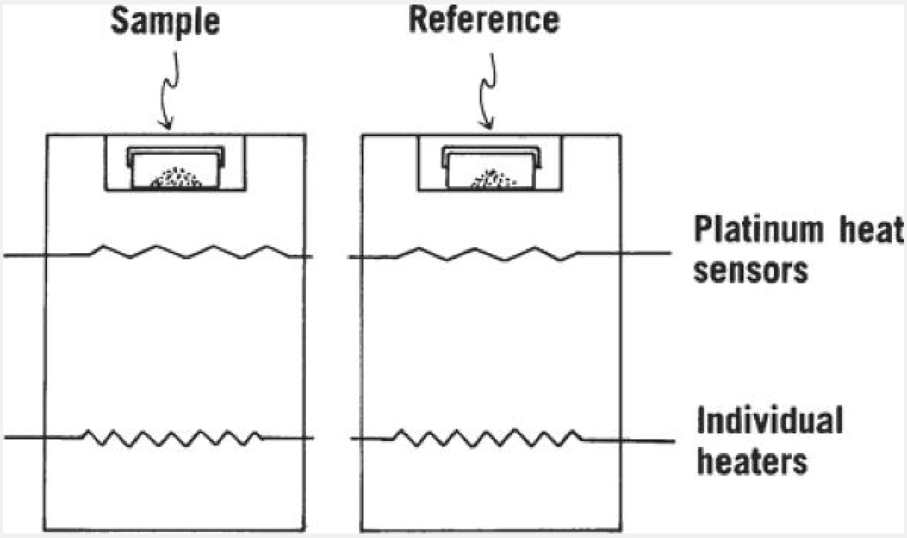


Fig. 2-21. Separate heat sources and platinum heat sensors used in differential scanning calorimetry.

Key Concept

Practical Application of Thermal Analysis

Using TGA combined with DSC or DTA, we can classify endothermic and exothermic reactions. For example, if a DSC thermogram contains an endothermic reaction at 120°C, another endotherm at 190°C, and an exotherm at 260°C, the scientist must determine the cause of each of these heat exchange processes. With the utilization of a TGA instrument, the change in the weight of a sample is measured as a function of temperature. If the same material is subjected to TGA analysis, the transitions can be classified according to weight changes. Therefore, if a 4% weight loss is observed at 120°C, no weight change is observed at 190°C, and the weight is lost at 260°C, certain assumptions can be made. The 4% weight loss was associated with an endothermic change, which can correspond to a desolvation, making it a likely choice for the endothermic response. The lack of a weight change at 190°C would most likely suggest a melt due to the endotherm observed on the DSC. The final loss of all of the remaining mass at 260°C is most likely due to decomposition; the exotherm on the DSC would support that conclusion. In addition, Karl Fisher analysis, described in the next subsection, could be used to determine whether the solid is a water solvate to determine whether the 4% loss in mass at 120°C is due to water.

Thermogravimetric and Thermomechanical Analyses

Changes in weight with temperature (thermogravimetric analysis, TGA) and changes in mechanical properties with temperature (thermomechanical analysis, TMA) are used in pharmaceutical engineering research and in industrial quality control. In TGA, a vacuum recording balance with a sensitivity of 0.1 μg is used to record the sample weight under pressures of 10^{-4} mm to 1 atm.

Thermogravimetric analysis instruments have now begun to be coupled with infrared or mass spectrometers to measure the chemical nature of the evolved gases being lost from the sample. The next subsection describes Karl Fisher analysis, which can also help in determining whether the desolvation may be attributed to water or residual solvents from chemical processing. The changes with temperature in hydrated salts such as calcium oxalate, $CaC_2O_4 \cdot H_2O$, are evaluated using TGA, as discussed by Simons and Newkirk.51

The characterization by TGA of bone tissue associated with dental structures was reported by Civjan et al.52 Thermogravimetric analysis also can be used to study drug stability and the kinetics of decomposition.

Thermomechanical analysis measures the expansion and extension of materials or changes in viscoelastic properties and heat distortions, such as shrinking, as a function of temperature. By use of a probe assembly in contact with the test material, any motion due to expansion, melting, or other physical change delivers an electric signal to a recorder. The furnace, in which are placed a sample and a probe, controls the temperature, which can be programmed over a range from -150°C to 700°C. The apparatus serves essentially as a penetrometer, dilatometer, or tensile tester over a wide range of programmed temperatures. Humphries et al.53used TMA in studies on the mechanical and viscoelastic properties of hair and the stratum corneum of the skin. Thermomechanical analysis is also widely used to look at polymer films and coatings used in pharmaceutical processes.

Karl Fisher Method

The Karl Fisher method is typically performed as a potentiometric titration method commonly used to determine the amount of water associated with a solid material. The method follows the reaction of iodine (generated electrolytically at the anode in the reagent bath) and sulfur with water. One mole of iodine reacts with 1 mole of water, so the amount of water is directly proportional to the electricity produced. As mentioned, a DSC measurement may indicate an endothermic reaction at 120°C. This endothermic reaction may constitute an actual melt of the crystalline material or may be due to either desolvation or a polymorphic conversion. If one measured the same material using TGA and found a weight loss of about 4% at the same temperature as the endotherm, one could determine that the endotherm arose from a desolvation process.

Utilizing Karl Fisher analysis, one can add the solid material to the titration unit and determine the amount of water by mixing of reagents and the potentiometric electrodes. The Karl Fisher method is an aid in that it can determine whether the desolvation is all water (showing a 4% water content) or arises from the loss of a separate solvent trapped in the crystalline lattice. This method is routinely used for pharmaceutical applications, including the study of humidity effects in solids undergoing water sorption from the air and in quality control efforts to demonstrate the amount of water associated in different lots of manufactured solid products.

Vapor Sorption/Desorption Analysis

This technique is similar to that of TGA in that it measures weight changes in solids as they are exposed to different solvent vapors and humidity and/or temperature conditions, although it is typically operated isothermally. Greenspan54

published a definitive list of saturated salt solutions that can be used to control the relative humidity and are widely used to study many physicochemical properties of drugs. For example, if a selected saturated salt solution providing a high relative humidity is placed in a sealed container, the hygroscopicity of a drug can be assessed by determining the weight change in the solid under that humidity. A positive change in the weight would indicate that the solid material is absorbing (collectively called sorption) the solvent, in this case water, from the atmosphere inside the container. The ability of a solid to continuously absorb water until it goes into solution is called deliquescence. A weight loss could also be measured under low relative humidities controlled with different salts, which is termed desorption. Water vapor sorption/desorption can be used to study changes in the solvate state of a crystalline material.55,56 Variations of commercial instruments also allow the determination of the sorption/desorption of other solvents. The degree of solvation of a crystalline form could have an adverse effect on its chemical stability57and/or its manufacturability.

Generally, the less sensitive a solid material or formulation is to changes in the relative humidity, the more stable will be the pharmaceutical shelf life and product performance. The pharmaceutical industry supplies products throughout the world, with considerable variation in climate. Therefore, the measurement of moisture sorption/desorption rates and extents is very important for the prediction of the stability of drugs.

Phase Equilibria and the Phase Rule

The three primary phases (solid, liquid, and gaseous) of matter are often defined individually under different conditions, but in most systems we usually encounter phases in coexistence. For example, a glass of ice water on a hot summer day comprises three coexisting phases: ice (solid), water (liquid), and vapor (gaseous). The amount of ice in the drink depends heavily on several variables including the amount of ice placed in the glass, the temperature of the water in which it was placed, and the temperature of the surrounding air. The longer the drink is exposed to the warm air, the more the amount of ice in the drink will decrease, and the more water the melting ice will produce. However, evaporation of the water into vapor that is released into the large volume of air will also decrease the liquid volume. For this system, there is no establishment of equilibrium because the volume for vapor is infinite in contrast to the ice and liquid volumes.

If the ice water is sealed in a bottle, evaporation effects are limited to the available headspace, the ice melts to liquid, and evaporation becomes time and temperature dependent. For example, if the container is placed in a freezer, only one phase, ice, may be present after long-term storage. Heating of the container, provided the volume stays fixed, could potentially cause the formation of only a vapor phase. Opening and closing of the container would change the vapor phase composition and thus affect equilibrium. This one-component example can be extended to the two-component system of a drug suspension where solid drug is suspended and dissolved in solution and evaporation may take place in the headspace of the container. The suspended system will sit at equilibrium until the container is opened for administration of the drug, and then equilibrium would have to be reestablished for the new system. A new equilibrium or nonequilibrium state is established because dispensing of the suspension will decrease the volume of the liquid and solid in the container. Therefore, a new system is created after each opening, dispensing of the dose, and then resealing. This will be discussed in more detail later.

Before we get into detail about the individual phases, it is important to understand how the phases coexist, the rules that govern their coexistence, and the number of variables required to define the state(s) of matter present under defined conditions.

The Phase Rule

In each of the examples just given, each phase can be defined by a series of independent variables (e.g., temperature) and their coexistence can only occur over a limited range. For example, ice does not last as long in boiling water as it does in cold water. Therefore, to understand and define the state of each phase, knowledge of several variables is required. J. Willard Gibbs formulated the *phase rule*, which is a relationship for determining the least number of intensive variables (independent variables that do not depend on the volume or size of the phase, e.g., temperature, pressure, density, and concentration) that can be changed without changing the equilibrium state of the system, or, alternately, the least number required to define the state of the system. This critical number is called **F**, the number of degrees of freedom of the system, and the rule is expressed as follows:

$$\mathbf{F} = C - P + 2 \qquad (2\text{–}19)$$

where C is the number of components and P is the number of phases present.

Looking at these terms in more detail, we can define a *phase* as a homogeneous, physically distinct portion of a system that is separated from other portions of the system by bounding surfaces. Thus, a system containing water and its vapor is a two-phase system. An equilibrium mixture of ice, liquid water, and water vapor is a three-phase system.

The *number of components* is the smallest number of constituents by which the composition of each phase in the system at equilibrium can be expressed in the form of a chemical formula or equation. The number of components in the equilibrium mixture of ice, liquid water, and water vapor is one because the composition of all three phases is described by the chemical formula H_2O. In the three-phase system $CaCO_3 = CaO + CO_2$, the composition of each phase can be expressed by a combination of any two of the chemical species present. For example, if we choose to use $CaCO_3$ and CO_2, we can write CaO as ($CaCO_3$ - CO_2). Accordingly, the number of components in this system is two.

Table 2-7 Application of the Phase Rule to Single-Component Systems*

System	Number of Phases	Degrees of Freedom	Comments
Gas, liquid, or solid	1	$\mathbf{F} = C - P + 2 = \mathbf{1} - 1 + 2 = 2$	System is *bivariant* (**F** = 2) and lies anywhere within the area marked vapor, liquid, or solid in Figure 2-22. We must fix two variables, e.g., P_2 and t_2, to define system D.
Gas–liquid, liquid–solid, or gas–solid	2	$\mathbf{F} = C - P + 2 = \mathbf{1} - 2 + 2 = 1$	System is *univariant* (**F** = 1) and lies anywhere along a *line* between two-phase regions, i.e., AO, BO, or CO in Figure 2-22. We must fix one variable, e.g., either P_1 or t_2, to define system E.
Gas–liquid–solid	3	$\mathbf{F} = C - P + 2 = \mathbf{1} - 3 + 2 = 0$	System is *invariant* (**F** = 0) and can lie only at the *point* of intersection of the lines bounding the three-phase regions, i.e., point O in Figure 2-22.

*Key: C = number of components; P = number of phases.

The *number of degrees of freedom* is the *least* number of intensive variables that must be fixed/known to describe the system completely. Herein lies the utility of the phase rule. Although a large number of intensive properties are associated with any system, it is not necessary to report all of these to define the system. For example, let us consider a given mass of a gas, say, water vapor, confined to a particular volume. Using the phase rule only two independent variables are required to define the system, **F** = 1 - 1 + 2 = 2. Because we need to know two of the variables to define the gaseous system completely, we say that the system has two degrees of freedom. Therefore, even though this volume is known, it would be impossible for one to duplicate this system exactly (except by pure chance) unless the temperature, pressure, or another variable is known that may be varied *independent* of the volume of the gas. Similarly, if the temperature of the gas is defined, it is necessary to know the volume, pressure, or some other variable to define the system completely.

Next, consider a system comprising a liquid, say water, in equilibrium with its vapor. By stating the temperature, we define the system completely because the pressure under which liquid and vapor can coexist is also defined. If we decide to work instead at a particular pressure, then the temperature of the system is automatically defined. Again, this agrees with the phase rule because equation **(**2-18**)** now gives **F** = 1 - 2 + 2 = 1.

As a third example, suppose we cool liquid water and its vapor until a third phase (ice) separates out. Under these conditions, the state of the three-phase ice–water–vapor system is completely defined, and the rule gives **F** = 1 - 3 + 2 = 0; in other words, there are no degrees of freedom. If we attempt to vary the particular conditions of temperature or pressure necessary to maintain this system, we will lose a phase. Thus, if we wish to prepare the three-phase system of ice–water–vapor, we have no choice as to the temperature or pressure at which we will work; the combination is fixed and unique. This is known as the critical point, and later we discuss it in more detail.

The relation between the number of phases and the degrees of freedom in one-component systems is summarized in Table 2-7. The student should confirm these data by reference to Figure 2-22, which shows the phase equilibria of water at moderate pressures.

It is important to appreciate that as the number of components increases, so do the required degrees of freedom needed to define the system. Therefore, as the system becomes more complex, it becomes necessary to fix more variables to define the system. The greater the number of phases in equilibrium, however, the fewer are the degrees of freedom. Thus:

- Liquid water + vapor
- Liquid ethyl alcohol + vapor
- Liquid water + liquid ethyl alcohol + vapor mixture

(*Note*: Ethyl alcohol and water are completely miscible both as vapors and liquids.)

- Liquid water + liquid benzyl alcohol + vapor mixture

(*Note*: Benzyl alcohol and water form two separate liquid phases and one vapor phase. Gases are miscible in all proportions; water and benzyl alcohol are only partially miscible. It is therefore necessary to define the two variables in the completely miscible [one-phase] ethyl alcohol–water system but only one variable in the partially miscible [two-phase] benzyl–water system.)

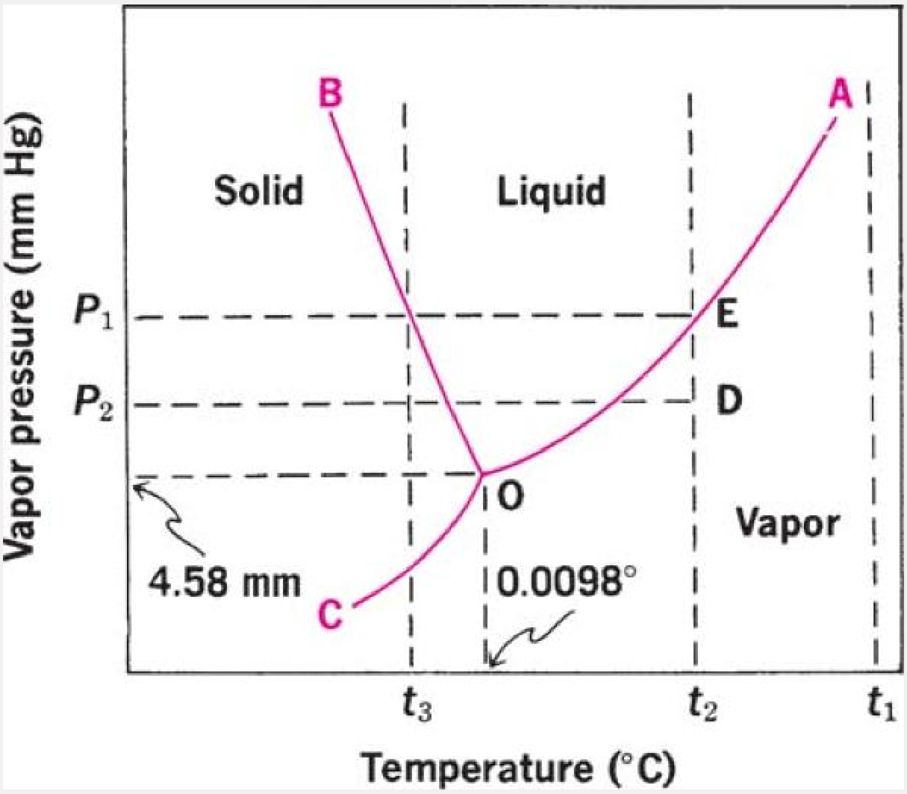


Fig. 2-22. Phase diagram for water at moderate pressures.

Systems Containing One Component

We have already considered a system containing one component, namely, that for water, which is illustrated in Figure 2-22 (not drawn to scale). The curve OA in the*P–T* (pressure–temperature) diagram in Figure 2-22 is known as the *vapor pressure curve*. Its upper limit is at the critical temperature, 374°C for water, and its lower end terminates at 0.0098°C, called the *triple point*. Along the vapor pressure curve, vapor and liquid coexist in equilibrium. This curve is analogous to the curve for water seen in Figure 2-5. Curve OC is the sublimation curve, and here vapor and solid exist together in equilibrium. Curve OB is the melting point curve, at which liquid and solid are in equilibrium. The negative slope of OB shows that the freezing point of water decreases with increasing external pressure, as we already found in Example 2-8.

The result of changes in pressure (at fixed temperature) or changes in temperature (at fixed pressure) becomes evident by referring to the phase diagram. If the temperature is held constant at t_1, where water is in the gaseous state above the critical temperature, no matter how much the pressure is raised (vertically along the dashed line), the system remains as a gas. At a temperature t_2 below the critical temperature, water vapor is converted into liquid water by an increase of pressure because the compression brings the molecules within the range of the attractive intermolecular forces. It is interesting to observe that at a temperature below the triple point, say t_3, an increase of pressure on water in the vapor state converts the vapor first to ice and then at higher pressure into liquid water. This sequence, vapor → ice → liquid, is due to the fact that ice occupies a larger volume than liquid water below the triple point. At the triple point, all three phases are in equilibrium, that is, the only equilibrium is at this pressure at this temperature of 0.0098°C (or with respect to the phase rule, **F** = 0).

As was seen in Table 2-7, in any one of the three regions in which pure solid, liquid, or vapor exists and *P* = 1, the phase rule gives

$$\mathbf{F} = 1 - 1 + 2 = 2$$

Therefore, we must fix two conditions, namely temperature and pressure, to specify or describe the system completely. This statement means that if we were to record the results of a scientific experiment involving a given quantity of water, it would not be sufficient to state that the water was kept at, say, 76°C. The pressure would also have to be specified to define the system completely. If the system were open to the atmosphere, the atmospheric pressure obtaining at the time of the experiment would be recorded. Conversely, it would not be sufficient to state that liquid water was present at a certain pressure without also stating the temperature. The phase rule tells us that the experimenter may alter two conditions without causing the appearance or disappearance of the liquid phase. Hence, we say that liquid water exhibits two degrees of freedom.

Along any three of the curves where two phases exist in equilibrium, **F** = 1 (see Table 2-7). Hence, only one condition need be given to define the system. If we state that the system contains both liquid water and water vapor in equilibrium at 100°C, we need not specify the pressure, for the vapor pressure can have no other value than 760 mm Hg at 100°C under these conditions. Similarly, only one variable is required to define the system along line OB or OC. Finally, at the triple point where the three phases—ice, liquid water, and water vapor—are in equilibrium, we saw that **F** = 0.

As already noted, the triple point for air-free water is 0.0098°C, whereas the freezing point (i.e., the point at which liquid water saturated with air is in equilibrium with ice at a total pressure of 1 atm) is 0°C. In increasing the pressure from 4.58 mm to 1 atm, we lower the freezing point by about 0.0075 deg (Example 2-8). The freezing point is then lowered an additional 0.0023 deg by the presence of dissolved air in water at 1 atm. Hence, the normal freezing point of water is 0.0075 deg + 0.0023 deg = 0.0098 deg below the triple point. In summary, the temperature at which a solid melts depends (weakly) on the pressure. If the pressure is that of the liquid and solid in equilibrium with the vapor, the temperature is known as the triple point; however, if the pressure is 1 atm, the temperature is the normal freezing point.

Condensed Systems

We have seen from the phase rule that in a single-component system the maximum number of degrees of freedom is two. This situation arises when only one phase is present, that is, **F** = 1 - 1 + 2 = 2. As will become apparent in the next section, a maximum of three degrees of freedom is possible in a two-component system, for example, temperature, pressure, and concentration. To represent the effect of all these variables upon the phase equilibria of such a system, it would be necessary to use a three-dimensional model rather than the planar figure used in the case of water. Because in practice we are primarily concerned with liquid and/or solid phases in the particular system under examination, we frequently choose to disregard the vapor phase and work under normal conditions of 1 atm pressure. In this manner, we reduce the number of degrees of freedom by one. In a two-component system, therefore, only two variables (temperature and concentration) remain, and we are able to portray the interaction of these variables by the use of planar figures on rectangular-coordinate graph paper. Systems in which the vapor phase is ignored and only solid and/or liquid phases are considered are termed *condensed systems*. We shall see in the later discussion of three-component systems that it is again more convenient to work with condensed systems.

It is important to realize that in aerosol and gaseous systems, vapor cannot be ignored. Condensed systems are most appropriate for solid and liquid dosage forms. As will be discussed in this and later chapters, solids can also have liquid phase(s) associated with them, and the converse is true. Therefore, even in an apparently dry tablet form, small amounts of “solution” can be present. For example, it will be

shown in the chapter on stability that solvolysis is a primary mechanism of solid drug degradation.

Two-Component Systems Containing Liquid Phases

We know from experience that ethyl alcohol and water are miscible in all proportions, whereas water and mercury are, for all practical purposes, completely immiscible regardless of the relative amounts of each present. Between these two extremes lies a whole range of systems that exhibit partial miscibility (or immiscibility). One such system is phenol and water, and a portion of the condensed phase diagram is plotted in Figure 2-23. The curve *gbhci* shows the limits of temperature and concentration within which two liquid phases exist in equilibrium. The region outside this curve contains systems having but one liquid phase. Starting at the point *a*, equivalent to a system containing 100% water (i.e., pure water) at 50°C, adding known increments of phenol to a fixed weight of water, the whole being maintained at 50°C, will result in the formation of a single liquid phase until the point *b* is reached, at which point a minute amount of a second phase appears. The concentration of phenol and water at which this occurs is 11% by weight of phenol in water. Analysis of the second phase, which separates out on the bottom, shows it to contain 63% by weight of phenol in water. This phenol-rich phase is denoted by the point *c* on the phase diagram. As we prepare mixtures containing increasing quantities of phenol, that is, as we proceed across the diagram from point *b* to point *c*, we form systems in which the amount of the phenol-rich phase (B) continually increases, as denoted by the test tubes drawn in Figure 2-23. At the same time, the amount of the water-rich phase (A) decreases. Once the total concentration of phenol exceeds 63% at 50°C, a single phenol-rich liquid phase is formed.

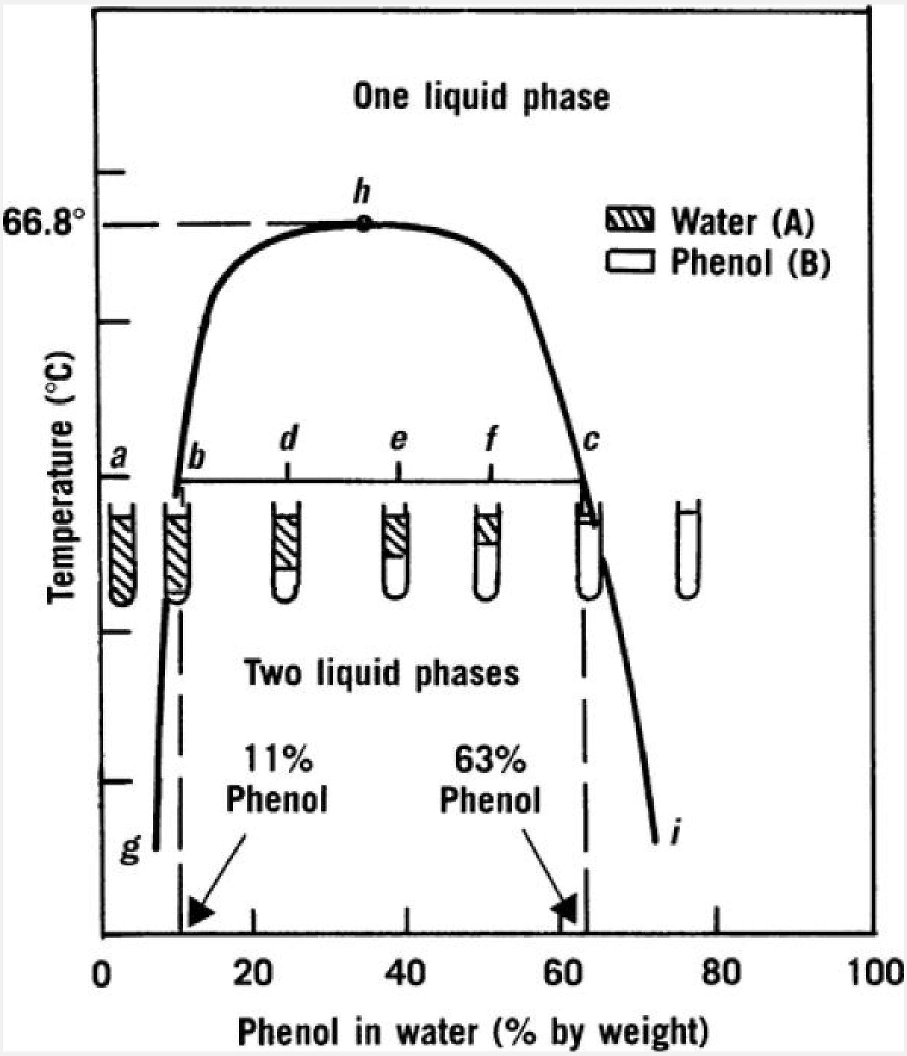


Fig. 2-23. Temperature–composition diagram for the system consisting of water and phenol. (From A. N. Campbell and A. J. R. Campbell, J. Am. Chem. Sec. **59**, 2481, 1937.)

The maximum temperature at which the two-phase region exists is termed the *critical solution*, or *upper consolute*, *temperature*. In the case of the phenol–water system, this is 66.8°C (point *h* in Fig. 2-23). All combinations of phenol and water above this temperature are completely miscible and yield one-phase liquid systems.

The line *bc* drawn across the region containing two phases is termed a *tie line*; it is always parallel to the base line in two-component systems. An important feature of phase diagrams is that all systems prepared on a tie line, at equilibrium, will separate into phases of constant composition. These phases are termed *conjugate phases*. For example, any system represented by a point on the line *bc* at 50°C separates to give a pair of conjugate phases whose compositions are *b* and *c*. The*relative amounts* of the two layers or phases vary, however, as seen in Figure 2-23. Thus, if we prepare a system containing 24% by weight of phenol and 76% by weight of water (point *d*), at equilibrium we have two liquid phases present in the tube. The upper one, A, has a composition of 11% phenol in water (point *b* on the diagram), whereas the lower layer, B, contains 63% phenol (point *c* on the diagram). Phase B will lie below phase A because it is rich in phenol, and phenol has a higher density than water. In terms of the relative weights of the two phases, there will be more of the water-rich phase A than the phenol-rich phase B at point *d*. Thus:

$$\frac{\text{Weight of phase A}}{\text{Weight of phase B}} = \frac{\text{Length } dc}{\text{Length } bd}$$

The right-hand term might appear at first glance to be the reciprocal of the proportion one should write. The weight of phase A is greater than that of phase B, however, because point *d* is closer to point *b* than it is to point *c*. The lengths *dc* and *bd* can be measured with a ruler in centimeters or inches from the phase diagram, but it is frequently more convenient to use the units of percent weight of phenol as found on the abscissa of Figure 2-23. For example, because point *b* = 11%, point *c* = 63%, and point *d* = 24%, the ratio *dc/bd* = (63 - 24)/(24 - 11) = 39/13 = 3/1. In other words, for every 10 g of a liquid system in equilibrium represented by point *d*, one finds 7.5 g of phase A and 2.5 g of phase B. If, on the other hand, we prepare a system containing 50% by weight of phenol (point *f*, Fig. 2-23), the ratio of phase A to phase B is *fc*/*bf* = (63 - 50)/(50 - 11) = 13/39 = 1/3. Accordingly, for every 10 g of system *f* prepared, we obtain an equilibrium mixture of 2.5 g of phase A and 7.5 g of phase B. It should be apparent that a system containing 37% by weight of phenol will, under equilibrium conditions at 50°C, give equal weights of phase A and phase B.

Working on a tie line in a phase diagram enables us to calculate the *composition* of each phase in addition to the weight of the phases. Thus, it becomes a simple matter to calculate the distribution of phenol (or water) throughout the system as a whole. As an example, let us suppose that we mixed 24 g of phenol with 76 g of water, warmed the mixture to 50°C,

and allowed it to reach equilibrium at this temperature. On separation of the two phases, we would find 75 g of phase A (containing 11% by weight of phenol) and 25 g of phase B (containing 63% by weight of phenol). Phase A therefore contains a total of (11 × 75)/100 = 8.25 g of phenol, whereas phase B contains a total of (63 × 25)/100 = 15.75 g of phenol. This gives a sum total of 24 g of phenol in the whole system. This equals the amount of phenol originally added and therefore confirms our assumptions and calculations. It is left to the reader to confirm that phase A contains 66.75 g of water and phase B 9.25 g of water. The phases are shown at *b*and *c* in Figure 2-23.

Applying the phase rule to Figure 2-23 shows that with a two-component condensed system having one liquid phase, **F** = 3. Because the pressure is fixed, **F** is reduced to 2, and it is necessary to fix both temperature and concentration to define the system. When two liquid phases are present, **F** = 2; again, pressure is fixed. We need only define temperature to completely define the system because **F** is reduced to 1.* From Figure 2-23, it is seen that if the temperature is given, the compositions of the two phases are fixed by the points at the ends of the tie lines, for example, points *b* and *c* at 50°C. The compositions (relative amounts of phenol and water) of the two liquid layers are then calculated by the method already discussed.

The phase diagram is used in practice to formulate systems containing more than one component where it may be advantageous to achieve a single liquid-phase product. For example, the handling of solid phenol, a necrotic agent, is facilitated in the pharmacy if a solution of phenol and water is used. A number of solutions containing different concentrations of phenol are official in several pharmacopeias. Unless the freezing point of the phenol–water mixture is sufficiently low, however, some solidification may occur at a low ambient temperature. This will lead to inaccuracies in dispensing as well as a loss of convenience. Mulley58 determined the relevant portion of the phenol–water phase diagram and suggested that the most convenient formulation of a single liquid phase solution was 80% w/v, equivalent to about 76% w/w. This mixture has a freezing point of about 3.5°C compared with liquefied phenol, USP, which contains approximately 90% w/w of phenol and freezes at about 17°C. It is not possible, therefore, to use the official preparation much below 20°C, or room temperature; the formulation proposed by Mulley from a consideration of the phenol–water phase diagram therefore is to be preferred. A number of other binary liquid systems of the same type as phenol and water have been studied, although few have practical application in pharmacy. Some of these are water–aniline, carbon disulfide–methyl alcohol, isopentane–phenol, methyl alcohol–cyclohexane, and isobutyl alcohol–water.

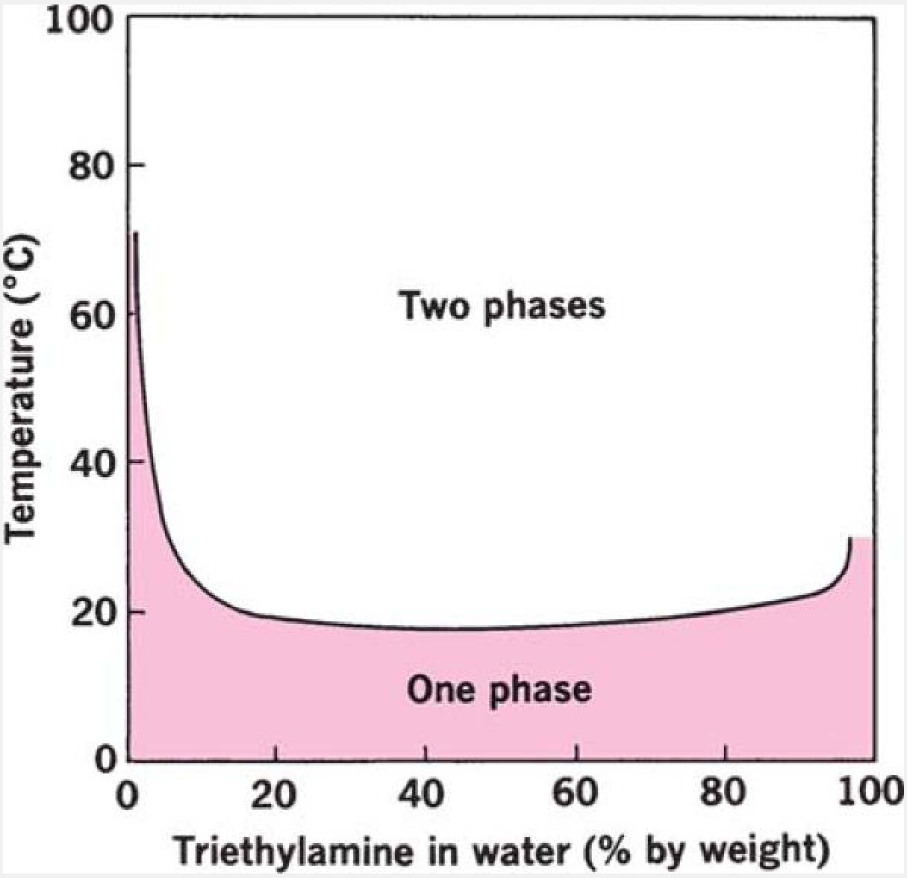


Fig. 2-24. Phase diagram for the system triethylamine–water showing lower consolute temperature.

Figure 2-24 illustrates a liquid mixture that shows no upper consolute temperature, but instead has a *lower* consolute temperature below which the components are miscible in all proportions. The example shown is the triethylamine–water system. Figure 2-25 shows the phase diagram for the nicotine–water system, which has both a lower and an upper consolute temperature. Lower consolute temperatures arise presumably because of an interaction between the components that brings about complete miscibility only at lower temperatures.

Two-Component Systems Containing Solid and Liquid Phases: Eutectic Mixtures

We restrict our discussion, in the main, to those solid–liquid mixtures in which the two components are completely miscible in the liquid state and completely immiscible as solids, that is, the solid phases that form consist of pure crystalline

components. Examples of such systems are salol–thymol, salol–camphor, and acetaminophen–propyphenazone.

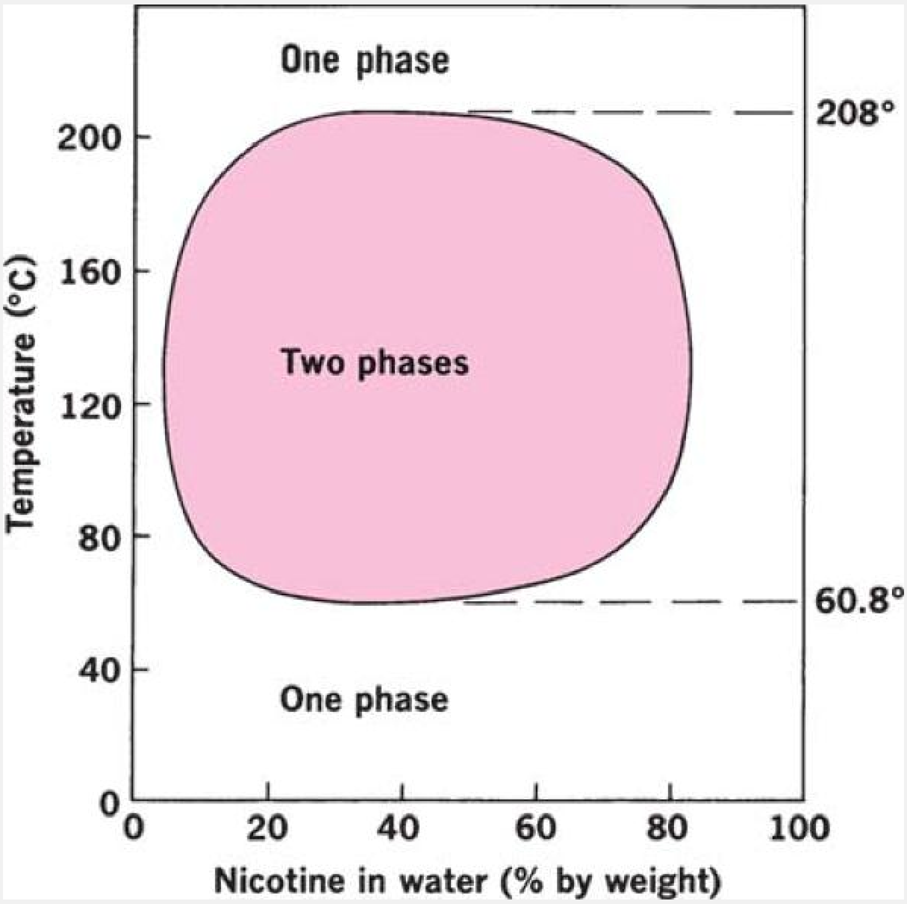


Fig. 2-25. Nicotine–water system showing upper and lower consolute temperatures.

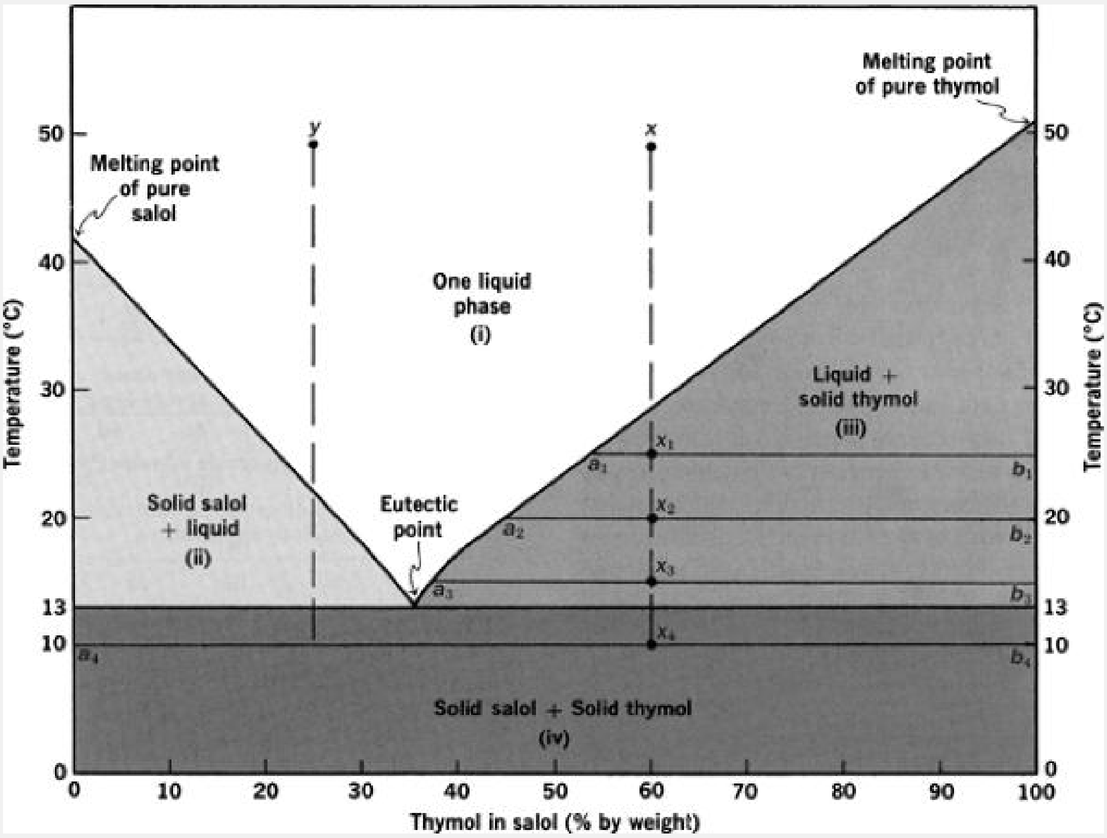


Fig. 2-26. Phase diagram for the thymol–salol system showing the eutectic point. (Data from A. Siedell, *Solubilities of Organic Compounds*, 3rd Ed., Vol. 2, Van Nostrand, New York, 1941, p. 723.)

The phase diagram for the salol–thymol system is shown in Figure 2-26. Notice that there are four regions: (i) a single liquid phase, (ii) a region containing solid salol and a conjugate liquid phase, (iii) a region in which solid thymol is in equilibrium with a conjugate liquid phase, and (iv) a region in which both components are present as pure solid phases. Those regions containing two phases (ii, iii, and iv) are comparable to the two-phase region of the phenol–water system shown inFigure 2-23. Thus it is possible to calculate both the composition and relative amount of each phase from knowledge of the tie lines and the phase boundaries.

Suppose we prepare a system containing 60% by weight of thymol in salol and raise the temperature of the mixture to 50°C. Such a system is represented by point *x*in Figure 2-26. On cooling the system, we observe the following sequence of phase changes. The system remains as a single liquid until the temperature falls to 29°C, at which point a minute amount of solid thymol separates out to form a two-phase solid–liquid system. At 25°C (room temperature), system *x* (denoted in Fig. 2-26 as x_1) is composed of a liquid phase, a_1 (composition 53% thymol in salol), and pure solid thymol, $b_{1.}$ The weight ratio of a_1 to b_1 is (100 - 60)/(60 - 53) = 40/7, that is, a_1:b_1 = 5.71:1. When the temperature is reduced to 20°C (point x_2), the composition of the liquid phase is a_2 (45% by weight of thymol in salol), whereas the solid phase is still pure thymol, b_2. The phase ratio is a_2:b_2 = (100 - 60)/(60 - 45) = 40/15 = 2.67:1. At 15°C (point x_3), the composition of the liquid phase is now 37% thymol in salol (a_3) and the weight ratio of liquid phase to pure solid thymol (a_3:b_3) is (100 - 60)/(60 - 37) - 40/23 = 1.74:1. Below 13°C, the liquid phase disappears altogether and the system contains two solid phases of pure salol and pure thymol. Thus, at 10°C (point x_4), the system contains an equilibrium mixture of pure solid salol (a_4) and pure solid thymol (b_4) in a weight ratio of (100 - 60)/(60 - 0) = 40/60 = 0.67:1. As system *x* is progressively cooled, the results indicate that more and more of the thymol separates as solid. A similar sequence of phase changes is observed if system *y* is cooled in a like manner. In this case, however, the solid phase that separates at 22°C is pure salol.

The lowest temperature at which a liquid phase can exist in the salol–thymol system is 13°C, and this occurs in a mixture containing 34% thymol in salol. This point on the phase diagram is known as the *eutectic point*. At the eutectic point, three phases (liquid, solid salol, and solid thymol) coexist. The eutectic point therefore denotes an invariant system because, in a condensed system, **F** = 2 - 3 + 1 = 0. The eutectic point is the point at which the liquid and solid phases have the same composition (*the eutectic composition*). The solid phase is an intimate mixture of fine crystals of the two compounds. The intimacy of the mixture gives rise to the phenomenon of "contact melting," which results in the lowest melting temperature over a composition range. Alternately explained, a eutectic composition is the composition of two or more compounds that exhibits a melting temperature lower than that of any other mixture of the compounds. Mixtures of salol and camphor show similar behavior. In this combination, the eutectic point occurs in a system containing 56% by weight of salol in camphor at a temperature of 6°C. Many other substances form eutectic mixtures (e.g., camphor, chloral hydrate, menthol, and betanaphthol). The primary criterion for eutectic formation is the mutual solubility of the components in the liquid or melt phase.

In the thermal analysis section in this chapter, we showed that calorimetry can be used to study phase transitions. Eutectic points are often determined by studying freezing point (melting point if one is adding heat) depression. Note that the freezing point in a one-component system is influenced simply by the temperature. In systems of two or more components, interactions between the components can occur, and depending on the concentrations of the components, the absolute freezing point may change. A eutectic point is the component ratio that exhibits the lowest observed melting point. This relationship is often used to provide information about how solutes interact in solution, with the eutectic point providing the favored composition for the solutes in solution, as illustrated in salol–thymol example. Lidocaine and prilocaine, two local anesthetic agents, form a 1:1 mixture having a eutectic temperature of 18°C. The mixture is therefore liquid at room temperature and forms a mixed local anesthetic that may be used for topical application. The liquid eutectic can be emulsified in water, opening the possibility for topical bioabsorption of the two local anesthetics.[59,60]

Solid Dispersions

Eutectic systems are examples of solid dispersions. The solid phases constituting the eutectic each contain only one component and the system may be regarded as an intimate crystalline *mixture* of one component in the other. A second major group of solid dispersions are the *solid solutions*, in which each solid phase contains both components, that is, a solid solute is *dissolved* in a solid solvent to give a mixed crystal. Solid solutions are typically not stoichiometric, and the minor component or "guest" inserts itself into the structure of the "host" crystal taking advantage of molecular similarities and/or open spaces in the host lattice. Solid solutions may exhibit higher, lower, or unchanged melting behavior depending upon the degree of interaction of the guest in the crystal structure. A third common dispersion is the molecular dispersion of one component in another where the overall solid is amorphous. Such mixed amorphous or glass solutions exhibit an intermediate glass transition temperature between those of the pure amorphous solids. The dispersion of solid particles in semisolids is also a common dispersion strategy in which crystalline or amorphous solids are dispersed to aid delivery, as in some topical products (e.g., [tioconazole vaginal] Monistat-1).

There is widespread interest in solid dispersions because they may offer a means of facilitating the dissolution and frequently, therefore, the bioavailability of poorly soluble drugs when combined with freely soluble "carriers" such as urea or polyethylene glycol. This increase in dissolution rate is achieved by a combination of effects, the most significant of which is reduction of particle size to an extent that cannot be readily achieved by conventional comminution approaches. Other contributing factors include increased wettability of the material, reduced aggregation and agglomeration, and a likely increase in solubility of the drug owing to the presence of the water-soluble carrier. Consult the reviews by Chiou and Riegelman61 and Goldberg62 for further details.

Phase Equilibria in Three-Component Systems

In systems containing three components but only one phase, **F** = 3 - 1 + 2 = 4 for a noncondensed system. The four degrees of freedom are temperature, pressure, and the concentrations of two of the three components. Only two concentration terms are required because the sum of these subtracted from the total will give the concentration of the third component. If we regard the system as condensed and hold the temperature constant, then **F** = 2, and we can again use a planar diagram to illustrate the phase equilibria. Because we are dealing with a three-component system, it is more convenient to use triangular coordinate graphs, although it is possible to use rectangular coordinates.

The various phase equilibria that exist in three-component systems containing liquid and/or solid phases are frequently complex and beyond the scope of the present text. Certain typical three-component systems are discussed here, however, because they are of pharmaceutical interest. For example, several areas of pharmaceutical processing such as crystallization, salt form selection, and chromatographic analyses rely on the use of ternary systems for optimization.

Rules Relating to Triangular Diagrams

Before discussing phase equilibria in ternary systems, it is essential that the reader becomes familiar with certain “rules” that relate to the use of triangular coordinates. It should have been apparent in discussing two-component systems that all concentrations were expressed on a weight–weight basis. This is because, although it is an easy and direct method of preparing dispersions, such an approach also allows the concentration to be expressed in terms of the mole fraction or the molality. The concentrations in ternary systems are accordingly expressed on a weight basis. The following statements should be studied in conjunction with Figure 2-27:

1. Each of the three corners or apexes of the triangle represent 100% by weight of one component (*A*, *B*, or *C*). As a result, that same apex will represent 0% of the other two components. For example, the top corner point in Figure 2-27 represents 100% of *B*.
2. The three lines joining the corner points represent two-component mixtures of the three possible combinations of *A*, *B*, and *C*. Thus the lines *AB*, *BC*, and *CA*are used for

two-component mixtures of *A* and *B*, *B* and *C*, and *C* and *A*, respectively. By dividing each line into 100 equal units, we can directly relate the location of a point along the line to the percent concentration of one component in a two-component system. For example, point *y*, midway between *A* and *B* on the line *AB*, represents a system containing 50% of *B* (and hence 50% of *A* also). Point *z*, three fourths of the way along *BC*, signifies a system containing 75% of *C* in *B*.

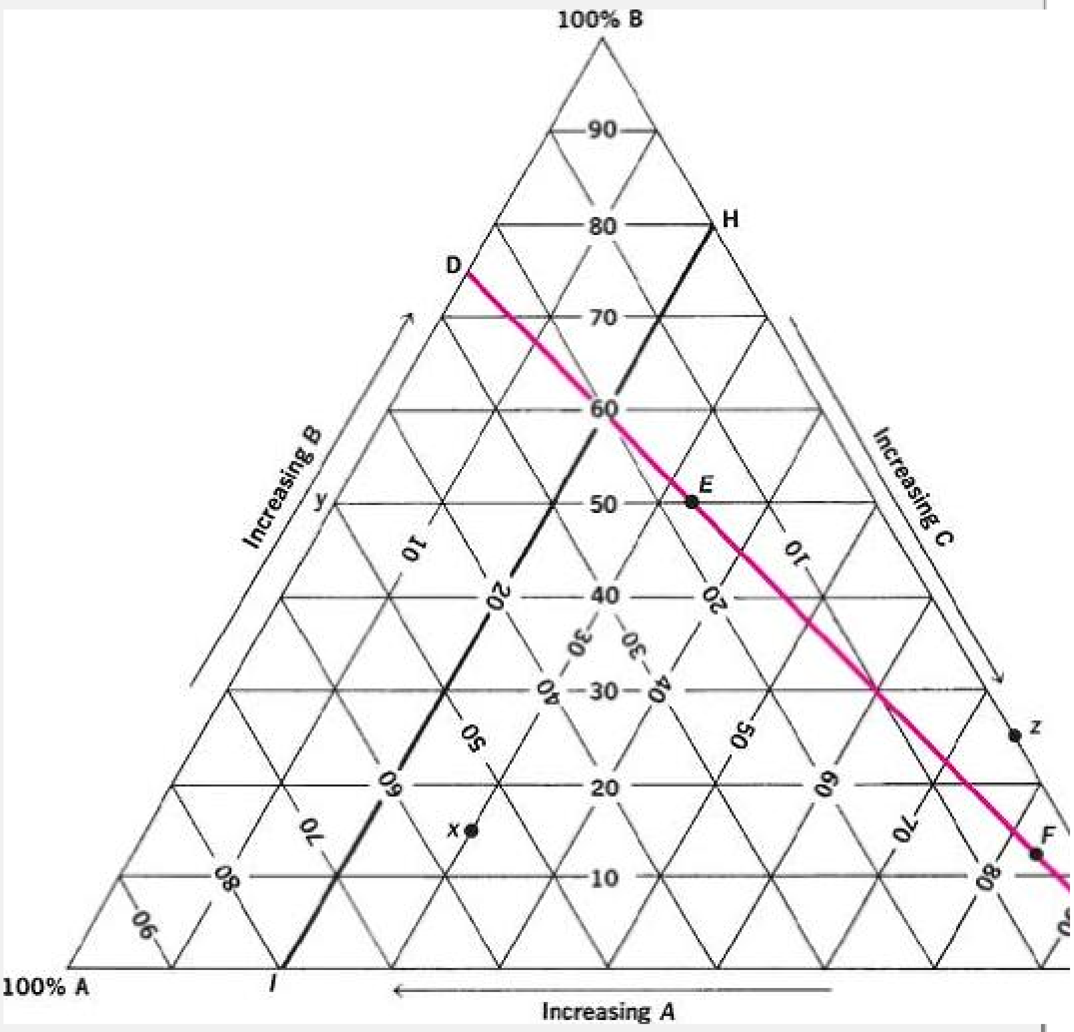


Fig. 2-27. The triangular diagram for three-component systems.

In going along a line bounding the triangle so as to represent the concentration in a two-component system, it does not matter whether we proceed in a clockwise or a counterclockwise direction around the triangle, provided we are consistent. The more usual convention is clockwise and has been adopted here. Hence, as we move along *AB* in the direction of *B*, we are signifying systems of *A* and *B* containing increasing concentrations of *B*, and correspondingly smaller amounts of *A*. Moving along *BC* toward *C* will represent systems of *B* and *C* containing more and more of *C*; the closer we approach *A* on the line *CA*, the greater will be the concentration of *A* in systems of *A* and *C*.

3. The area within the triangle represents all the possible combinations of *A*, *B*, and *C* to give three-component systems. The location of a particular three-component system within the triangle, for example, point *x*, can be undertaken as follows.

   The line *AC* opposite apex *B* represents systems containing *A* and *C*. Component *B* is absent, that is, *B* = 0. The horizontal lines running across the triangle parallel to *AC* denote increasing percentages of *B* from *B* = 0 (on line *AC*) to *B* = 100 (at point *B*). The line parallel to *AC* that cuts point *x* is equivalent to 15%*B*; consequently, the system contains 15% of *B* and 85%

of *A* and *C* together. Applying similar arguments to the other two components in the system, we can say that along the line *AB*, *C* = 0. As we proceed from the line *AB* toward *C* across the diagram, the concentration of *C* increases until at the apex, *C* = 100%. The point *x* lies on the line parallel to *AB* that is equivalent to 30% of *C*. It follows, therefore, that the concentration of *A* is 100 - (*B* + *C*) = 100 - (15 + 30) = 55%. This is readily confirmed by proceeding across the diagram from the line *BC* toward apex *A*; point *x* lies on the line equivalent to 55% of *A*.

4. If a line is drawn through any apex to a point on the opposite side (e.g., line *DC* in Fig. 2-27), then all systems represented by points on such a line have a constant ratio of two components, in this case *A* and *B*. Furthermore, the continual addition of *C* to a mixture of *A* and *B* will produce systems that lie progressively closer to apex *C* (100% of component *C*). This effect is illustrated in Table 2-8, in which increasing weights of *C* are added to a constant-weight mixture of *A* and *B*. Note that in all three systems, the ratio of *A* to *B* is constant and identical to that existing in the original mixture.
5. Any line drawn parallel to one side of the triangle, for example, line *HI* in Figure 2-27, represents ternary system in which the proportion (or percent by weight) of *one* component is constant. In this instance, all systems prepared along *HI* will contain 20% of *C* and varying concentrations of *A* and *B*.

Ternary Systems with One Pair of Partially Miscible Liquids

Water and benzene are miscible only to a slight extent, and so a mixture of the two usually produces a two-phase system. The heavier of the two phases consists of water saturated with

benzene, while the lighter phase is benzene saturated with water. On the other hand, alcohol is completely miscible with both benzene and water. It is to be expected, therefore, that the addition of sufficient alcohol to a two-phase system of benzene and water would produce a single liquid phase in which all three components are miscible. This situation is illustrated in Figure 2-28, which depicts such a ternary system. It might be helpful to consider the alcohol as acting in a manner comparable to that of temperature in the binary phenol–water system considered earlier. Raising the temperature of the phenol–water system led to complete miscibility of the two conjugate phases and the formation of one liquid phase. The addition of alcohol to the benzene–water system achieves the same end but by different means, namely, a solvent effect in place of a temperature effect. There is a strong similarity between the use of heat to break cohesive forces between molecules and the use of solvents to achieve the same result. The effect of alcohol will be better understood when we introduce dielectric constants of solutions and solvent polarity in later chapters. In this case, alcohol serves as an intermediate polar solvent that shifts the electronic equilibrium of the dramatically opposed highly polar water and nonpolar benzene solutions to provide solvation.

Table 2-8 Effect of Adding a third Component (*C*) to a Binary System of *A* (5.0 *G*) and *B* (15.0 *G*)

	Final System				
Weight of Third Component *C* Added (g)	Component	Weight (g)	Weight (%)	Ratio of *A* to *B*	Location of System in Figure 2-27
10.0	*A*	5.0	16.67	3:1	Point *E*
	B	15.0	50.00		
	C	10.0	33.33		
100.0	*A*	5.0	4.17	3:1	Point *F*
	B	15.0	12.50		
	C	100.0	83.33		
1000.0	*A*	5.0	0.49	3:1	Point *G*
	B	15.0	1.47		
	C	1000.0	98.04		

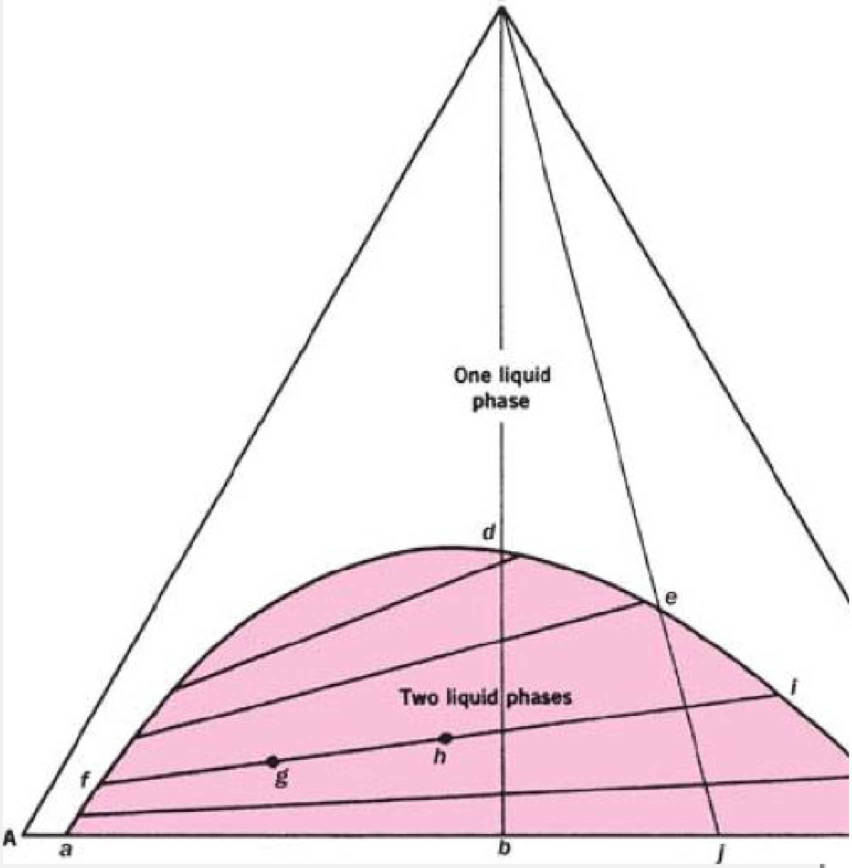


Fig. 2-28. A system of three liquids, one pair of which is partially miscible.

In Figure 2-28, let us suppose that *A*, *B*, and *C* represent water, alcohol, and benzene, respectively. The line *AC* therefore depicts binary mixtures of *A* and *C*, and the points *a* and *c* are the limits of solubility of *C* in *A* and of *A* in *C*, respectively, at the particular temperature being used. The curve *afdeic*, frequently termed a *binodal curve or binodal*, marks the extent of the two-phase region. The remainder of the triangle contains one liquid phase. The tie lines within the binodal are not necessarily parallel to one another or to the base line, *AC*, as was the case in the two-phase region of binary systems. In fact, the directions of the tie lines are related to the shape of the binodal, which in turn depends on the relative solubility of the third component (in this case, alcohol) in the other two components. Only when the added component acts equally on the other two components to bring them into solution will the binodal be perfectly symmetric and the tie lines run parallel to the baseline.

The properties of tie lines discussed earlier still apply, and systems *g* and *h* prepared along the tie line *fi* both give rise to two phases having the compositions denoted by the points *f* and *i*. The relative amounts, by weight, of the two conjugate phases will depend on the position of the original system along the tie line. For example, system *g*, after reaching equilibrium, will separate into two phases, *f* and *i*: The ratio of phase *f* to phase *i*, on a weight basis, is given by the ratio *gi*:*fg*. Mixture *h*, halfway along the tie line, will contain equal weights of the two phases at equilibrium.

The phase equilibria depicted in Figure 2-28 show that the addition of component *B* to a 50 : 50 mixture of components *A* and *C* will produce a phase change from a two-liquid system to a one-liquid system at point *d*. With a 25:75 mixture of *A* and *C*, shown as point *j*, the addition of *B* leads to *a* phase change at point *e*. Naturally, all mixtures lying along *dB* and *eB* will be one-phase systems.

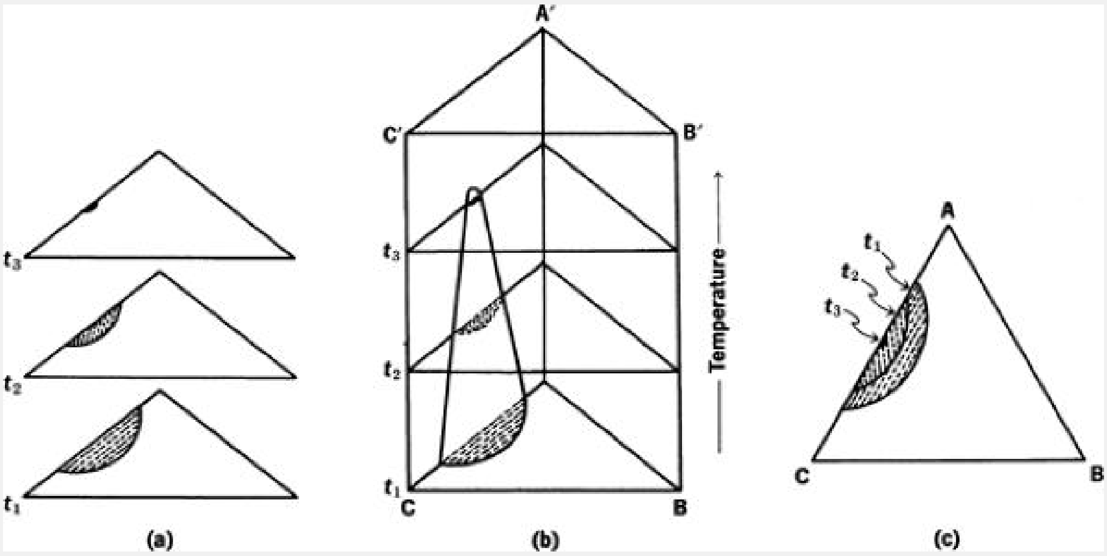


Fig. 2-29. Alterations of the binodal curves with changes in temperature. (*a*) Curves on the triangular diagrams at temperatures t_1, t_2, and t_3. (*b*) The three-dimensional arrangement of the diagrams in the order of increasing temperature. (*c*) The view one would obtain by looking down from the top of (*b*).

As we saw earlier, **F** = 2 in a single-phase region, and so we must define two concentrations to fix the particular system. Along the binodal curve *afdeic*, **F** = 1, and we need only know one concentration term because this will allow the composition of one phase to be fixed on the binodal curve. From the tie line, we can then obtain the composition of the conjugate phase.

Effect of Temperature

Figure 2-29 shows the phase equilibria in a three-component system under isothermal conditions. Changes in temperature will cause the area of immiscibility, bounded by the binodal curve, to change. In general, the area of the binodal decreases as the temperature is raised and miscibility is promoted. Eventually, a point is reached at which complete miscibility is obtained and the binodal vanishes. To study the effect of temperature on the phase equilibria of three-component systems, a three-dimensional figure, the triangular prism, is frequently used (Fig. 2-29b). Alternatively, a family of curves representing the various temperatures may be used, as shown in Figure 2-29c. The three planar sides of the prism are simply three-phase diagrams of binary-component systems. Figure 2-29 illustrates the case of a ternary-component system containing one pair of partially immiscible liquids (A and C). As the temperature is raised, the region of immiscibility decreases. The volume outside the shaded region of the prism consists of a single homogeneous liquid phase.

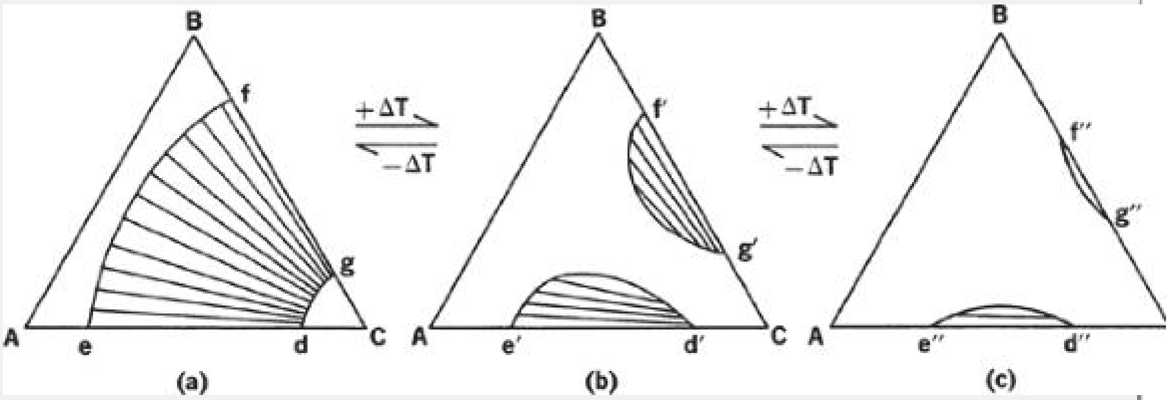


Fig. 2-30. Effect of temperature changes on the binodal curves representing a system of two pairs of partially miscible liquids.

Ternary Systems with Two or Three Pairs of Partially Miscible Liquids

All the previous considerations for ternary systems containing one pair of partially immiscible liquids still apply. With two pairs of partially miscible liquids, there are two binodal curves. The situation is shown in Figure 2-30b, in which A and C as well as B and C show partial miscibility; A and B are completely miscible at the temperature used. Increasing the temperature generally leads to a reduction in the areas of the two binodal curves and their eventual disappearance (Fig. 2-30c). Reduction of the temperature expands the binodal curves, and, at a sufficiently low temperature, they meet and fuse to form a single band of immiscibility as shown in Figure 2-30a. Tie lines still exist in this region, and the usual rules apply. Nor do the number of degrees of freedom change—when$P$ = 1, **F** = 2; when P = 2, **F** = 1.

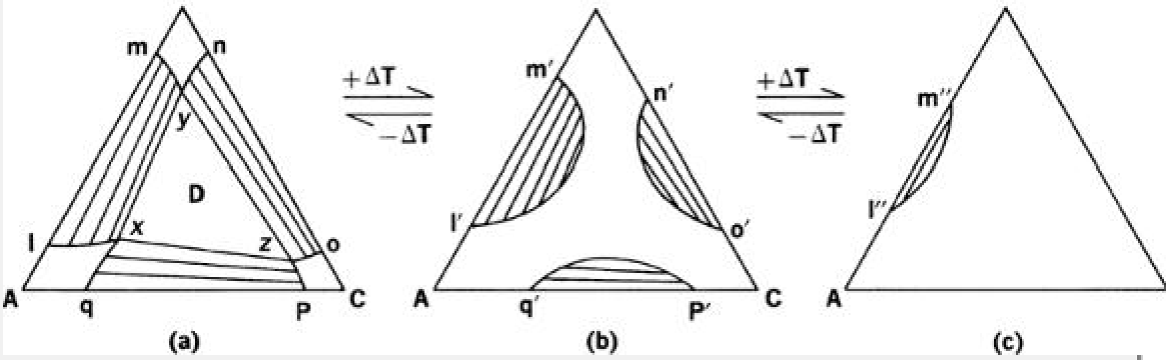


Fig. 2-31. Temperature effects on a system of three pairs of partially miscible liquids.

Systems containing three pairs of partially miscible liquids are of interest. Should the three binodal curves meet (Fig. 2-31a), a central region appears in which *three*conjugate liquid phases exist in equilibrium. In this region, D, which is triangular, **F** = 0 for a condensed system under isothermal conditions. As a result, *all* systems lying within this region consist of three phases whose compositions are always given by the points *x*, *y*, and *z*. The only quantities that vary are the relative amounts of these three conjugate phases. Increasing the temperature alters the shapes and sizes of the regions, as seen in Figures 2-31b and c.

The application and discussion of phase phenomena and their application in certain pharmaceutical systems will be discussed in later chapters.

Chapter Summary

As one of the foundational chapters of this text, many important subject areas have been covered from the examination of the binding forces between molecules to the various states of matter. Many of these subjects in this chapter are aimed at the more experienced pharmacy student or graduate student who is interested in understanding the fundamental physical aspects of the pharmaceutical sciences.

Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

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Recommended Readings

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*The term van der Waals forces is often used loosely. Sometimes all combinations of intermolecular forces among ions, permanent dipoles, and induced dipoles are referred to as van der Waals forces. On the other hand, the London force alone is frequently referred to as the van der Waals force because it accounts for the attraction between nonpolar gas molecules, as expressed by the a/V2 term in the van der Waals gas equation. In this book, the three dipolar forces of Keesom, Debye, and London are called van der Waals forces. The other forces such as the ion-dipole interaction and the hydrogen bond (which have characteristics similar both to ionic and dipolar forces) are designated appropriately where necessary.

*Note that the root mean square velocity $(\overline{c^2})^{1/2}$ is not the same as the average velocity, [C with bar above]. This can be shown by a simple example: Let c have the three values 2, 3, and 4. Then [C with bar above] = (2 + 3 + 4)/3 = 3, whereas $(\overline{c^2})^{1/2}$ is the square root of the mean of the sum of the squares, or $\sqrt{(2^2 + 3^2 + 4^2)/3} = \sqrt{9.67}$, and $\mu = 3.11$.

*A gas is known as a *vapor* below its critical temperature. A less rigorous definition of a *vapor* is a substance that is a liquid or a solid at room temperature and passes into the gaseous state when heated to a sufficiently high temperature. A *gas* is a substance that exists in the gaseous state even at room temperature. Menthol and ethanol are vapors at sufficiently high temperatures; oxygen and carbon dioxide are gases.

*The number of degrees of freedom calculated from the phase rule if the system is not condensed is still the same. Thus, when one liquid phase and its vapor are present, **F** = 2 - 2 + 2 = 2; it is therefore necessary to define two conditions: temperature and concentration. When two liquids and the vapor phase exist, **F** = 2 - 3 + 2 = 1, and only temperature need be defined.

Chapter Legacy

Fifth Edition: published as Chapter 2. Updated by Gregory Knipp, Susan Bogdanowich-Knipp and Kenneth Morris.

Sixth Edition: published as Chapter 2. Updated by Patrick Sinko.