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BINDING FORCES BETWEEN MOLECULES

In order for molecules to exist in 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 the previous discussion of *intra*molecular bonding energies. Cohesion, or the attraction of like molecules, and adhesion, or the attraction of unlike molecules, are manifestations of intermolecular forces. A knowledge of these forces is important for an understanding not only of the properties of gases, liquids, and solids, but also of interfacial phenomena, flocculation in suspensions, stabilization of emulsions, compaction of powders in capsules, and the compression of granules to form tablets.

Repulsive and Attractive Forces. When molecules interact, both repulsive and attractive forces operate. As two molecules are brought close together, the opposite charges in the two molecules are closer together than the like charges and cause the molecules to attract one another. When the molecules are brought so close that the outer charge clouds touch, the molecules repel each other like rigid elastic bodies.

Thus attractive forces are necessary in order that molecules cohere; repulsive forces are necessary in order that the molecules do not interpenetrate and annihilate one another. Moelwyn-Hughes[1] points to the analogy between human behavior and molecular phenomenon. Just as the actions of humans are often influenced by a conflict of loyalties, so molecular behavior is 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 or 4 $\times$ 10^{-8} cm (3 or 4 angstroms), 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 to atoms and to large objects as well.

Under the following headings are discussed the various types of *attractive* intermolecular forces.

Van der Waals Forces. 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) in order to produce *dipole–induced dipole*, or Debye, interactions, and nonpolar molecules can induce polar-

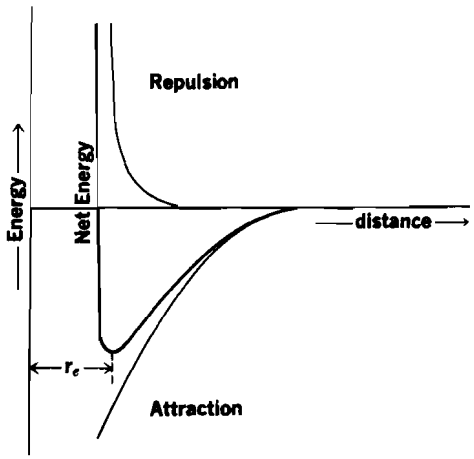


Fig. 2–1. Repulsive and attractive energies and net energy as a function of the distance between molecules. Note that a minimum occurs in the net energy because of the different character of the attraction and repulsion curves.

TABLE 2–1. ***Intermolecular Forces and Valence Bonds***

Bond type		Bond Energy (approx.) (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 Induced dipole–induced dipole interaction, dispersion effect, or London force		1–10
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 Bond		
Electrovalent, ionic, heteropolar		100–200
Covalent, homopolar		50–150

ity 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; that is, 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.

These several classes of interaction, known as van der Waals forces* and listed in Table 2–1, are associated with the condensation of gases, the solubility of some drugs (Chapter 10), the formation of some metal complexes and molecular addition compounds (Chapter 11), and certain biologic processes and drug actions. The energies associated with primary valence bonds are included for comparison.

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 attracting the relatively negative oxygen atom of water and the anion attracting the hydrogen atoms of the dipolar water molecules. Ion–induced dipole forces are presumably involved in the formation of the iodide complex,

$$I_2 + K^+I^- \rightarrow K^+I_3^- \qquad (2-1)$$

Reaction (2–1) accounts for the solubility of iodine in a solution of potassium iodide.

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 a hydrogen atom and its large electrostatic field, it can move in close to the electronegative atom and form an electrostatic type of union known as a *hydrogen bond* or *hydrogen bridge*. Such a bond, discovered by Latimer and Rodebush[2] 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 a loose 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 2–2. 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 also exist between some 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 $(F—H\ .\ .\ .)_n$, where n can have a value as large as 6. Several structures involving hydrogen bonds are shown in Figure 2–2. The dashed

*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 since it accounts for the attraction between nonpolar gas molecules, as expressed by the a/V^2 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 ion-dipole and the hydrogen bond (which have characteristics similar both to ionic and dipolar forces) are designated appropriately where necessary.

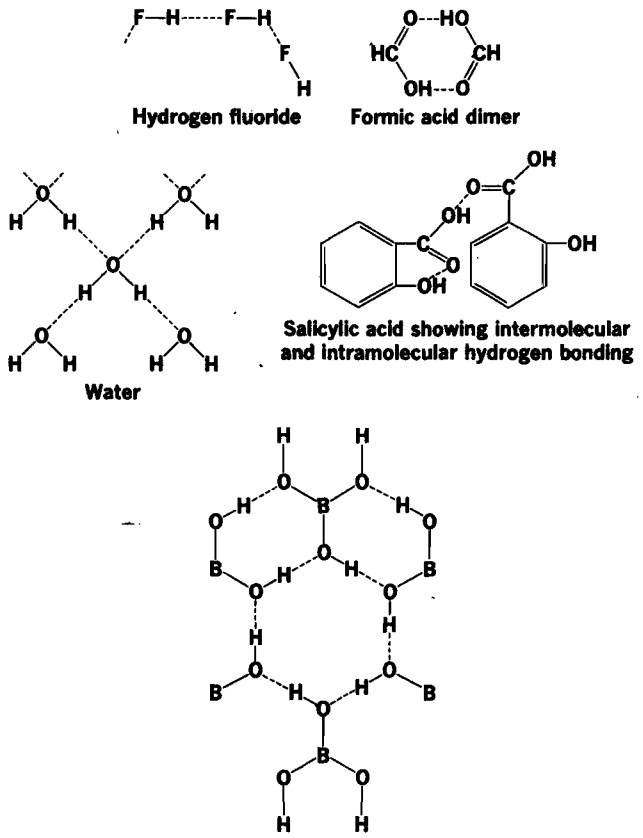


Fig. 2–2. Representative hydrogen-bonded structures.

lines represent the hydrogen bridges. It will be noticed that *intra-* as well as *inter*molecular hydrogen bonds may occur (cf. salicylic acid).

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.

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, and its intermolecular attraction is supplied primarily by the London or dispersion force.

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.

TABLE 2–2. ***Energies Associated with Molecular and Ionic Interactions***

	Interaction in 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

STATES OF MATTER

Gases, liquids, and crystalline solids are the three states of matter. The molecules, atoms, and ions in the solid state are held in close proximity by intermolecular, interatomic, or ionic forces. The particles of the solid can oscillate only about fixed positions. As the temperature of a solid substance is raised, the particles acquire sufficient energy to disrupt the ordered arrangement of the lattice and pass into the liquid form. Finally, when sufficient energy is supplied, the 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. This process is known as *sublimation*, and the reverse process, that is, recondensation to the solid state, may be referred to as *deposition*.

Certain asymmetric 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.

THE GASEOUS STATE

Owing to vigorous and rapid motion, gas molecules travel in random paths, frequently colliding with one another and with the walls of the container in which they are confined. Hence, they exert a *pressure*—a force per unit area—expressed in dynes per 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. The temperature involved in gas equations is given in absolute or Kelvin degrees

(°K). Zero degrees on the centigrade scale is equal to 273.15° K.

The Ideal Gas law. The student may recall from general chemistry that the gas laws were formulated by Boyle, Charles, and Gay-Lussac. Boyle's law relates the volume and pressure of a given mass of gas at constant temperature.

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

or

$$PV = k \tag{2-2}$$

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.

$$V \propto T$$

or

$$V = kT \tag{2-3}$$

These equations can be combined to obtain the relationship

$$\frac{P_1V_1}{T_1} = \frac{P_2V_2}{T_2} \tag{2-4}$$

which should be familiar to the student. 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. 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 of mercury. What is the volume at 0° C and 760 mm Hg? (We assume that the gas behaves ideally.)

$$\frac{740 \times 30.0}{(273 + 20)} = \frac{760 \times V_2}{273}$$

$$V_2 = 27.2 \text{ mL}$$

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

$$PV = RT \tag{2-5}$$

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 gram molecular weight) of gas; for n moles it becomes

$$PV = nRT \tag{2-6}$$

Equation (2-6) is known as the *general ideal gas law*, and since 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 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 equations in electrochemistry, solution theory, colloid chemistry, and other fields, in addition to its appearance in the gas laws. To obtain a numeric 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 (STP) (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

$$1 \text{ atm} \times 22.414 \text{ liters} = 1 \text{ mole} \times R \times 273.16° \text{ K}$$

$$R = 0.08205 \text{ liter atm/mole deg}$$

The molar gas constant may also be given in energy units by expressing the pressure in dyne/cm^2 (1 atm = 1.0133×10^6 dyne/cm^2 as calculated on p. 4 and the volume in the corresponding units of cm^3 (22.414 liters = 22,414 cm^3). Then

$$R = \frac{PV}{T} = \frac{(1.0133 \times 10^6) \times 22{,}414}{273.16°}$$

$$= 8.314 \times 10^7 \text{ erg/mole deg}$$

or, since 1 joule = 10^7 erg

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

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

$$PV = \frac{g}{M}RT \tag{2-7}$$

or

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

Example 2–3. 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.

$$M = \frac{0.30 \times 0.082 \times 373}{1 \times 0.2}$$

$$M = 46.0 \text{ g/mole}$$

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 just given have been formulated from experimental considerations. 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*. Some of the more important statements of the theory are the following:

1. Gases are composed of particles called *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 rather 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 $E = \frac{3}{2}RT$.
4. The molecules exhibit perfect elasticity, that is, there is no net loss of speed after they collide with one another and with 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.

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

$$PV = \tfrac{1}{3}nm\overline{c^2} \qquad (2-9)$$

where P is the pressure and V the volume occupied by any number n of molecules of mass m having an average velocity $\bar{c}$.

Using this fundamental equation, the root mean square velocity $(\overline{c^2})^{1/2}$ (usually written μ) of the molecules is an ideal gas can be obtained.* Solving for $\overline{c^2}$ in equation (2–8) and taking the square root of both sides of the equation leads to the formula

$$\mu = \sqrt{\frac{3PV}{nm}} \qquad (2-10)$$

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

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

Example 2–4. What is the root mean square velocity of oxygen (molecular weight, 32.0) at 25° C (298° K)?

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

Since the term nm/V is equal to density, we may write equation (2–10) as

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

In other words, 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 light gas diffused more rapidly through a porous membrane than did a heavier one.

The van der Waals Equation for Real Gases. The fundamental kinetic equation (2–9) is found to compare with the ideal gas equation, since 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 one of the best known of these. For 1 mole of gas, the van der Waals equation is written as

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

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

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

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*Note that the root mean square velocity $\sqrt{\overline{c^2}}$ is not the same as the average velocity, $\bar{c}$. This can be shown in a simple example where $\bar{c}$ has the three values 2, 3, and 4. $\bar{c} = (2 + 3 + 4)/3 = 3$, whereas $\mu = \sqrt{\overline{c^2}}$ 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 $\mu = 3.11$.

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

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. It will be seen in Chapter 10 that internal pressure is also used to describe the cohesive forces in liquids. 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, 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.

Example 2–5. 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^{-1}. To solve for pressure, the van der Waals equation may be rearranged as follows:

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

(a)

$$P = \frac{0.193 \text{ mole} \times 0.0821 \text{ liter atm/deg mole} \times 295 \text{ deg}}{7.35 \text{ liter}}$$

$$= 0.636 \text{ atm}$$

(b)

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

$$= 0.626 \text{ atm}$$

Example 2–6. 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 critical pressure P_c (see Liquefaction of Gases for definition):

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

The critical temperature and critical pressure of CO_2 are 31.0° C and 72.9 atm, respectively.

Using the ideal gas equation,

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

$$= 12.32 \text{ atm}$$

Using the van der Waals equation,

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

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

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

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

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

$$= \frac{(0.5 \text{ mole} \times 0.0821 \text{ liter atm/deg mole}) \times 300.15 \text{ deg}}{1 \text{ liter} - (0.5 \text{ mole} \times 0.0428 \text{ liter/mole})} - \frac{3.608 \text{ liter}^2 \text{ atm/mole}^2 \times (0.5 \text{ mole})^2}{(1 \text{ liter})^2}$$

$$= 11.69 \text{ atm}$$

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.

The critical temperature of water is 374° C or 647° K, and its critical pressure is 218 atm, while 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, for 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 particles to "stick" together. The high critical values for water result because of the strong dipolar forces between the molecules and particularly the hydrogen bonding that exists. Conversely, helium molecules are attracted only by the weak London force, 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, may 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 that has to be done to bring about expansion therefore must come from the gas itself at the expense of its own heat energy content. 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. As mentioned earlier, gases can be liquefied by increasing pressure, provided we work 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. The propellant used in these products is frequently a mixture of fluorinated hydrocarbons, although other gases, such as nitrogen and carbon dioxide, are increasingly used. 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 presently under investigation (Byron, Dalby et al.[3]).

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, while 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, since 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 the minimum of discomfort to the patient. 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 Pickthall et al.[4] and Sciarra.[5] Byron and Clark[6] have studied drug absorption from inhalation aerosols and provided a rather complete analysis of the problem. The USP XXII, 1990, includes a discussion of metered-dose inhalation products and provides standards and test procedures (see USP XXII, pp. 1556, 1689, and 1857, and a list of aerosol monographs on p. 2001).

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.

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

*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 solid at room temperature and that 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 vapor pressure in millimeters of mercury. The presence of a gas, such as air, above the liquid would decrease the rate of evaporation, but it would not affect the equilibrium pressure of the vapor.

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 2–3. 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):

$$\log \frac{p_2}{p_1} = \frac{\Delta H_v(T_2 - T_1)}{2.303RT_1T_2} \qquad (2\text{–}15)$$

in which 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 ΔH_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 like an ideal gas and that the molar volume of the liquid is negligible with respect to that of the vapor.

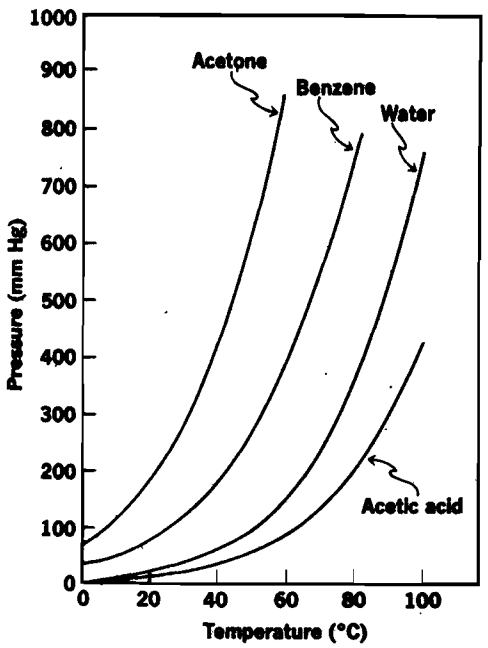


Fig. 2–3. The variation of vapor pressure of some liquids with temperature.

Example 2–7. 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.

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

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

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

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

or in natural logarithms,

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

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 is seen to 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 pressure at sea level is about 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 may 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, it 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 as 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, since 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 still more abnormal because the acids form dimers through hydrogen bonding that can remain 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 brought out in Table 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 attached through hydrogen bonds, exhibit high boiling points and high heats of vaporization.

Other properties of liquids, such as surface tension and viscosity, are discussed in Chapters 14 and 17, respectively.

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. The various crystal forms are divided into six distinct crystal systems. They are, together with examples of each, cubic (sodium chloride), tetragonal (urea), hexagonal (iodoform), rhombic (iodine), monoclinic (sucrose), and triclinic (boric acid).

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

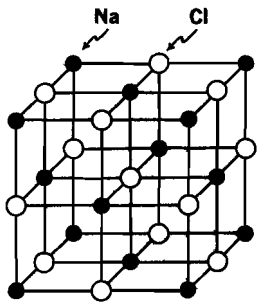


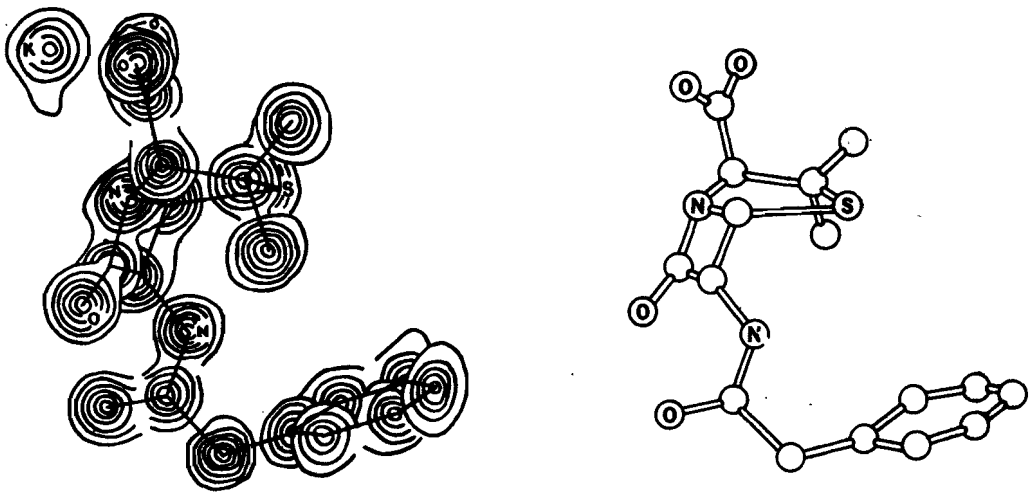
Fig. 2–4. The crystal lattice of sodium chloride.

The units that constitute the crystal structure can be atoms, molecules, or ions. The sodium chloride crystal, shown in Figure 2–4, 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 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, while 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 low melting points.

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.

X-Ray Diffraction. X-rays are diffracted by crystals just as visible light is dispersed into a color spectrum by a ruled grating (i.e., a piece of glass with fine parallel lines of equal width drawn on it). This is due to the fact that x-rays have wavelengths of about the same magnitude as the distance between the atoms or molecules of crystals. The x-ray diffraction pattern is photographed on a sensitive plate arranged behind the crystal, and by such a method the structure of a crystal may be investigated. Employing a later modification of this principle, involving reflection of the x-ray beam from the atomic planes of the crystal, it has become possible to determine the distances of the various planes of the crystal lattice. The structure of various compounds can be determined in this way.

Where whole crystals are unavailable or unsuitable for analysis, a powder of the substance may be



(a) (b)

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

investigated. Comparing the position and intensity of the lines on such a diagram with corresponding lines on the photograph of a known sample allows one to conduct a qualitative and a quantitative chemical analysis.

The electron density and, accordingly, the position of the atoms in complex structures such as penicillin may be determined from a mathematical study of the data obtained by x-ray diffraction. The electron density map of crystalline potassium benzylpenicillin is shown in Figure 2–5. The elucidation of this structure by x-ray crystallography paved the way for the later synthesis of penicillin by the organic chemist. Certain aspects of x-ray crystallography of pharmaceutical interest have been reviewed by Biles[7] and by Lien and Kennon.[8]

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 heat absorbed when a gram 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, since 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 may be obtained by using one form of the Clapeyron equation. It is written

$$\frac{\Delta T}{\Delta P} = T\frac{V_l - V_s}{\Delta H_f} \qquad (2\text{–}17)$$

in which V_l and V_s are the molar volumes of the liquid and solid, respectively. Molar volume (volume in cm^3 per 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.

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

Example 2–8. 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, $\Delta H_f \cong 1440$ cal/mole, the molar volume of water is 18.018, and the molar volume of ice is 19.651, or $V_l - V_s = -1.633$ cm³/mole. To obtain the result in deg/atm, using equation (2-17), we first convert ΔH_f in cal/mole into units of erg/mole by multiplying by the factor 4.184×10^7 erg/cal

$$1440 \text{ cal/mole} \times 4.184 \times 10^7 \text{ erg/cal}$$
$$= 6025 \times 10^7 \text{ erg/mole or } 6025 \times 10^7 \text{ dyne cm/mole}$$

Then multiplying the equation by the equivalent, 1.013×10^6 dyne/cm² per atmosphere (p. 4), gives the result in the desired units.

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

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

Hence, an increase of pressure of 1 atm lowers the freezing point of water by about 0.0075°, or an increase in pressure of about 133 atm would be required to lower the freezing point of water 1°. (When the ice-water equilibrium mixture is saturated with air under a total pressure of 1 atm, the temperature is lowered an additional 0.0023°.) 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/cm³ as compared with 0.9988 g/cm³ for water at 0° C) accounts for the fact 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.* According to *Example 2–8*, an increase of pressure of 1 atm reduces the freezing (melting) point of ice by 0.0075°. 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 cm².

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/sec²) and divided by the area of the skate blades (0.085 cm²).

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

Changing to atmospheres (1 atm = 1.01325×10^6 dyne/cm²) yields a pressure of 464.7 atm. The change in volume ΔV from water to ice is 0.018 liter/mole − 0.01963 liter/mole, or −0.00163 liter/mole for the transition from ice to liquid water.

Use equation (2–17) 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:

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

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

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) to convert cal to liter atm. We now have

$$\ln T = (-2.74 \times 10^{-5}\text{atm}^{-1})(465.7 - 1 \text{ atm}) + \ln(273.15)$$
$$T = 269.69° K$$

The melting temperature has been reduced from 273.15° K 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^{-1}, must be multiplied by the conversion factor, 1 liter atm/24.2 cal, to yield 59.504 liter atm.

$$\frac{\Delta T}{\Delta P} = \frac{T\Delta V}{\Delta H_f} = \frac{(273.15° \text{ K})(0.0180 - 0.0196) \text{ liter mole}^{-1}}{59.504 \text{ liter atm mole}^{-1}}$$

$$\frac{\Delta T}{\Delta P} = -0.00734° \text{ K/atm}$$

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.

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 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.

Paraffins crystallize as thin leaflets composed of zig-zag 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 observed in Figure 2–6. This phenomenon presumably is due to the fact that alkanes with an odd number of carbon atoms are packed in the crystal less efficiently.

*Modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, p. 93; and R. Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd Ed., Macmillan, New York, 1977, p. 162.

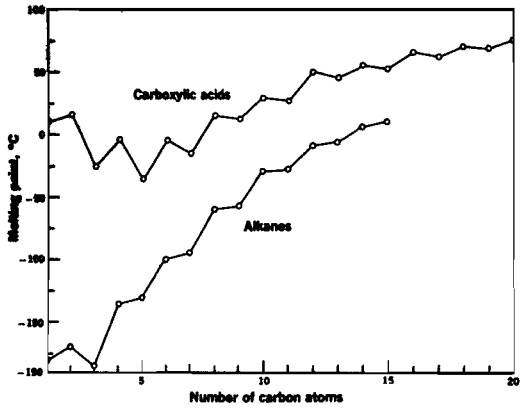


Fig. 2–6. The melting points of alkanes and carboxylic acids as a function of carbon chain length. (Modified from C. R. Noller, *Chemistry of Organic Compounds*, 2nd Ed., Saunders, Philadelphia, 1957, pp. 40, 149).

The melting points of normal carboxylic acids also show this alternation, as seen in Figure 2–6. This can be explained as follows. Fatty acids crystallize in molecular chains, one segment of which is shown in Figure 2–7. The even 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,[9] further exemplify the relationship between melting point and molecular structure. Solubilities, like melting points, are strongly influenced by intermolecular forces, as will be discussed later in Chapter 10. It will be observed by reference to Table 2–6 that methylation of theophylline to form caffeine, and lengthening of the side chain from methyl (caffeine) to propyl in the 7 position results in a decrease of the melting points and an increase in solubilities. These effects presumably are due to a progressive weakening of intermolecular forces.

Polymorphism. Some elemental substances, such as carbon and sulfur, may exist in more than one crystal-

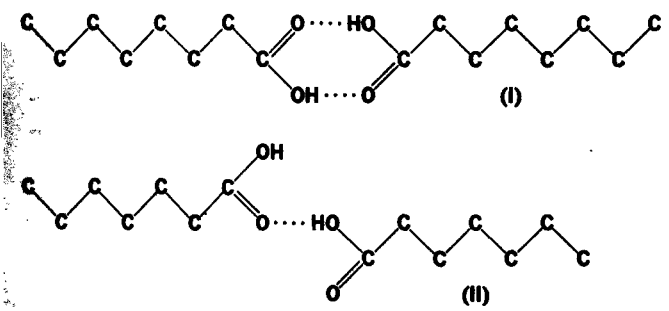
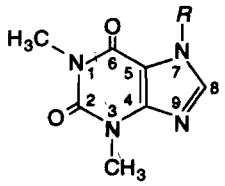


Fig. 2–7. Configuration of fatty acid molecules in the crystalline state. (Modified from A. E. Bailey, *Melting and Solidification of Fats*, Interscience Publishers, New York, 1950, p. 120.)

TABLE 2–6. *Melting Points and Solubilities of Some Xanthines



Basic structure

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-Ethyltheophylline (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.

line form and are said to be *polymorphic*. Polymorphs generally have different melting points, x-ray diffraction patterns, and solubilities, even though they are chemically identical.

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. Since it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°–36° C). Theobroma oil is capable of existing in four polymorphic forms, the unstable gamma form melting at 18°, the alpha form melting at 22°, the beta prime form melting at 28°, and the stable beta form melting at 34.5° C. Riegelman[10] has 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° 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 recent years owing to the fact that different polymorphs exhibit different solubilities. In the case of slightly soluble drugs, this may afffect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug. Aguiar et al.[11] have shown the polymorphic state of chloramphenicol palmitate to have a significant influence on the biologic availability of the drug. Khalil et al.[12] 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.

Polymorphism can also be a factor in suspension technology. Cortisone acetate has been found to exist in at least five different forms, four of which were found to be unstable in the presence of water and which change to a stable form.[13] Since 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.[14]

It is difficult to determine the crystal structure and molecular conformations of different polymorphs of a single drug, and the reports of such work are not common. Azibi et al.[15] 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 2–8a, and the molecular conformations* of the two polymorphs, I and II, are shown in Figure 2–8b. The difference between the two polymorphs is in the positioning of the atoms in the side chains, as seen in Figure 2–8b, 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.[16] 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. 2–9) and bromperidol. Variability in hydrogen bonding also contributes to polymorphism in the sulfonamides.[17]

Goldberg and Becker[18] 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 2–10. Of the two forms found, the stable polymorph, referred to as *form B*, is held in its molecular conformation in the solid state 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 and to stabilize the molecular crystal 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.[19] made physical, chemical, and x-ray studies of 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 cyclo-

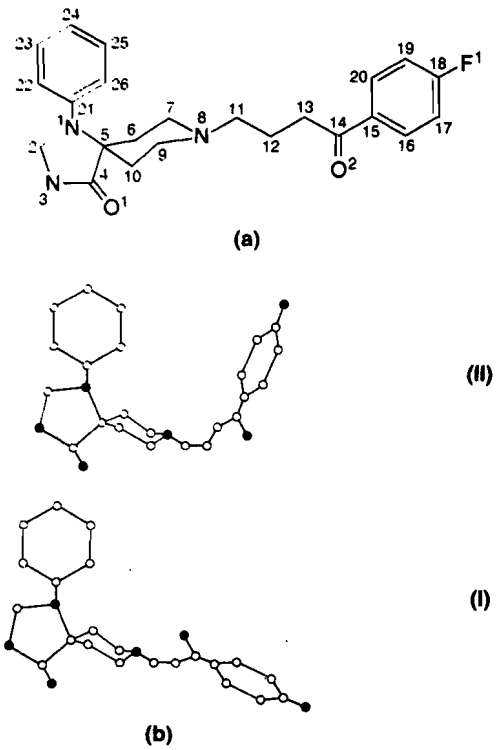


Fig. 2–8. *(a)* Structure and numbering of spiperone. *(b)* Molecular conformation of two polymorphs I and II of spiperone. (M. Azibi, et al., J. Pharm. Sci., 72:232, 1983. Reproduced with permission.)

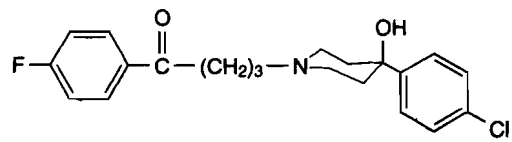


Fig. 2–9. Haloperidol.

*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.

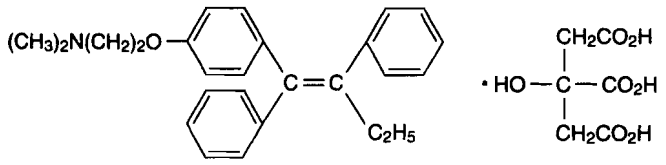
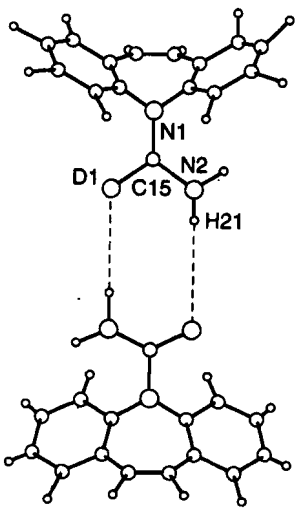


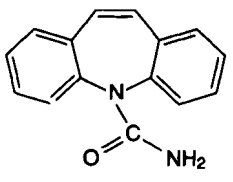
Fig. 2–10. Tamoxifen citrate.

hexane. A rather thorough study of the two polymorphic forms of carbamazepine was made using infrared spectroscopy (p. 89), thermogravimetric analysis (p. 49), hot-stage microscopy, dissolution rate (p. 330–332), and x-ray powder diffraction (p. 30). The hydrogen-bonded structure of the α polymorph of carbamazepine is shown in Figure 2–11a, together with its molecular formula (Fig. 2–11b).

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 has been reported to exist in several polymorphic forms. However, Ishida et al.[20] have now shown 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*.[21]



(a)



(b)

Fig. 2–11. *(a)* Two molecules of the polymorph, α-carbamazepine, joined together by hydrogen bonds. (M. M. J. Lowes, et al., J. Pharm. Sci., 76:744, 1987. Reproduced with permission.) *(b)* Carbamazepine.

Other related estradiol compounds may exist in true polymeric forms.

Behme et al.[22] 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.[22]

The transition temperature in polymorphism is important because it helps to characterize the system and determine the more stable form at low temperatures. At their transition temperatures, polymorphs have the same free energy, 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 (p. 152) 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.[23] This temperature can also be obtained from the phase diagram of pressure versus temperature and by using differential scanning calorimetry.[24] An example of the solubility method is given as *Problem 2–20*.

Biles,[25] as well as Haleblian and McCrone,[26] have discussed in some detail the significance of polymorphism and solvation in pharmaceutical practice.

Amorphous Solids. Amorphous solids may be considered as supercooled liquids in which the molecules are arranged in a random manner somewhat 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 Chapter 17, it will be learned that the rheologist classifies as a solid 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, 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, as already mentioned, contains both crys-

talline and amorphous constituents. Some amorphous materials, such as glass, may crystallize after long standing.

Whether or not 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.[27]

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 since materials in this state are in many ways intermediate between the liquid and solid states.

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 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.

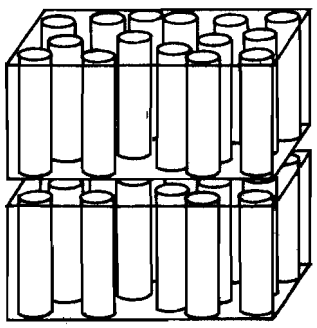
The two main types of liquid crystals are termed *smectic* (soap- or grease-like) and *nematic* (thread-like). In the smectic state, molecules are mobile in two directions and can rotate about one axis (Fig. 2–12*a*). In the nematic state, the molecules again rotate only about one axis but are mobile in three dimensions (Fig. 2–12*b*). A third type (cholesteric crystals) exist but may be considered as a special case of the nematic type.

The smectic mesophase is probably of most pharmaceutical significance since it is this phase that usually forms in ternary (or more complex) mixtures containing a surfactant, water, and a weakly amphiphilic or nonpolar additive (see Chapter 18).

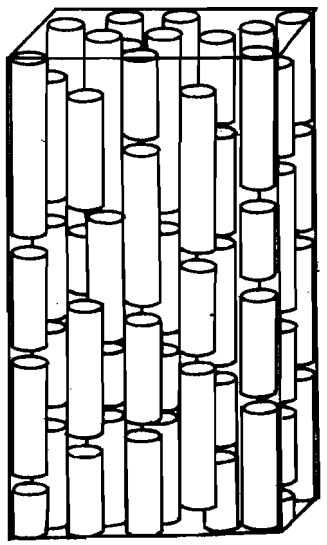
In general, molecules that form mesophases (1) are organic, (2) are elongated and rectilinear in shape, (3) are rigid, and (4) possess strong dipoles and easily polarizable groups. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action 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 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 are sensitive to electric fields, a property used to advantage in developing display systems. The smectic mesophase has applica-



(a) Smectic mesophase



(b) Nematic mesophase

tion 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. Bogardus[28] 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 (TEA) 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 (pp. 43, 45, 46) were used by Friberg et al.[29] to show the regions of the liquid crystalline phase when either polar (polyethylene glycols) or nonpolar (squalene, etc.) compounds were present as the solvent.

Ibrahim[30] 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 has written a monograph on liquid crystals.[29] For a more detailed discussion of the liquid crystalline state, refer to the review by Brown,[31] which serves as a convenient entry into the literature.

PHASE EQUILIBRIA AND THE PHASE RULE

The Phase Rule. J. Willard Gibbs is credited with formulating the *Phase Rule*, a useful device for relating the effect of the least number of independent variables (e.g., temperature, pressure, and concentration) upon the various phases (solid, liquid, and gaseous) that can exist in an equilibrium system containing a given number of components. The phase rule is expressed as follows:

$$F = C - P + 2 \qquad (2\text{–}18)$$

in which F is the number of degrees of freedom in the system, C the number of components, and P the number of phases present.

Looking at these terms in more detail, we may 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, since 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.

The *number of degrees of freedom* is the *least* number of intensive variables (temperature, pressure, concentration, refractive index, density, viscosity, etc.) that must be fixed 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. Even though this volume is known, it would not be possible for one to duplicate this system exactly (except by pure chance) unless the temperature, pressure, or another variable is known that may be varied independently 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. Since we need to know two of the variables to define the gaseous system completely, we say that the system has two degrees of freedom. This is confirmed by the phase rule since, in this instance, $F = 1 - 1 + 2 = 2$.

Next consider a system comprising a liquid, say water, in equilibrium with its vapor. By stating the temperature, the system is completely defined 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) is now $F = 1 - 2 + 2 = 1$.

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 is $F = 1 - 3 + 2 = 0$; in other words, there are no degrees of freedom. If we attempt to vary the particu-

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	$F = C - P + 2$ $= 1 - 1 + 2 = 2$	System is *bivariant* ($F = 2$) and lies anywhere within the *area* marked vapor, liquid, or solid in Figure 2–13. We must fix two variables, e.g., p_2 and t_2, to define system *D*.
Gas–liquid, liquid–solid, or gas–solid	2	$F = C - P + 2$ $= 1 - 2 + 2 = 1$	System is *univariant* ($F = 1$) and lies anywhere along a *line* between two phase regions, i.e., *AO*, *BO*, or *CO* in Figure 2–13. We must fix one variable, e.g., either p_1 or t_2, to define system *E*.
Gas–liquid–solid	3	$F = C - P + 2$ $= 1 - 3 + 2 = 0$	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 2–13.

lar 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.

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 this data by reference to Figure 2–13, which shows the phase equilibria of water at moderate pressures.

The student should appreciate that as the number of components increases, so do the degrees of freedom. Consequently, 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 the degrees of freedom. Thus:

liquid water + vapor

$$F = C - P + 2$$
$$= 1 - 2 + 2$$
$$= 1$$

liquid ethyl alcohol + vapor

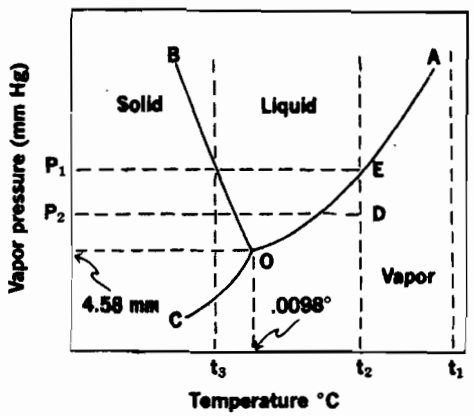


Fig. 2–13. Phase diagram for water at moderate pressures.

$$F = C - P + 2$$
$$= 1 - 2 + 2$$
$$= 1$$

liquid water + liquid ethyl alcohol + vapor mixture

$$F = C - P + 2$$
$$= 2 - 2 + 2$$
$$= 2$$

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

liquid water + liquid benzyl alcohol + vapor mixture

$$F = C - P + 2$$
$$= 2 - 3 + 2$$
$$= 1$$

(*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 alcohol–water system.)

Systems Containing One Component. We have already considered a system containing one component, namely, that for water, which is illustrated in Figure 2–13 (not drawn to scale).

The curve *OA* in Figure 2–13 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 identical with the curve for water seen in Figure 2–3. 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 have 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 dotted 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, since the compression brings the molecules within the range of the attractive van der Waals 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, the three phases are in equilibrium, that is, they all have the same vapor pressure at this temperature of 0.0098° C.

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 becomes

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

Therefore we must fix two conditions, namely temperature and pressure, to specify or describe the system completely. This statement means that if one 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 obtained 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 lines, where two phases exist in equilibrium, $\mathbf{F} = 1$ (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 have seen that $\mathbf{F} = 0$.

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, the freezing point is lowered by about 0.0075° (*Example 2–8*). The freezing point is then lowered an additional 0.0023° by the presence of dissolved air in water at 1 atm. Hence, the normal freezing point of water is 0.0075° + 0.0023° = 0.0098° below the triple point. In summary, the temperature at which a solid melts depends 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; whereas 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, $\mathbf{F} = 1 - 1 + 2 = 2$. 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. Since, in practice, we are only 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.

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). Such a system is phenol and water, and a portion of the condensed phase diagram is plotted in Figure 2–14. 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, the addition of 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 a minute amount of a second phase appears. The concentration of phenol and water at

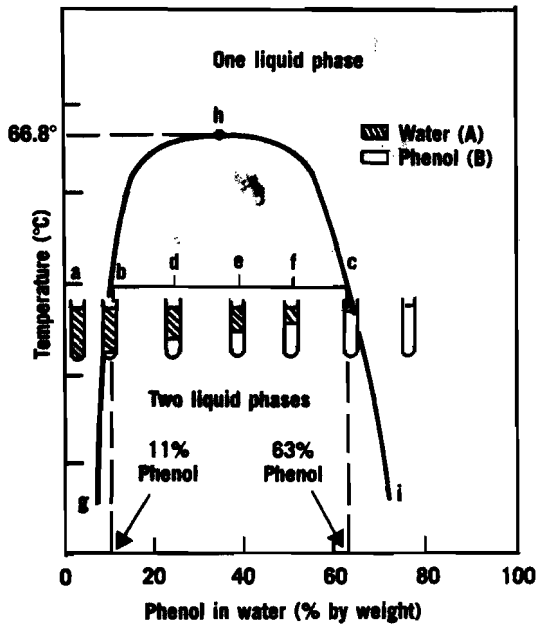


Fig. 2–14. Temperature-composition diagram for the system consisting of water and phenol. (From A. N. Campbell and A. J. R. Campbell, J. Am. Chem. Soc. 59, 2481, 1937).

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 2–14. At the same time, the amount of the water-rich phase (*A*) decreases. Once the total concentration of phenol exceeds 63%, at 50°, a single phenol-rich liquid phase is formed.

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° (point *h* in Fig. 2–14). 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 composition is *b* and *c*. The *relative amounts* of the two layers or phases vary, however, as seen in Figure 2–14. 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) while the lower layer, *B*, contains 63% phenol (point *c* on the diagram). Phase *B* will lie below phase *A* since 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* then 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 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 2–14. For example, since 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. 2–14), the ratio of phase *A* to phase $B = fc/bf = (63 - 50)/(50 - 11) = 13/39 = 1/3$. 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°, 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 $(11 \times 75)/100 = 8.25$ g of phenol, while phase *B* contains a total of $(63 \times 25)/100 = 15.75$ 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 2–14.

Applying the phase rule to Figure 2–14 shows that with a two-component condensed system having one liquid phase, F = 3. Because the pressure is fixed, F reduces 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, since F reduces to 1.* From Figure 2–14, 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. Mulley[32] 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° 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.

Figure 2–15 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 2–16 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 that interaction between the components that brings about complete miscibility only at lower temperatures.

Two-Component Systems Containing Solid and Liquid Phases: Eutectic Mixtures: We shall 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 components. Examples of such systems are salol–thymol and salol–camphor.

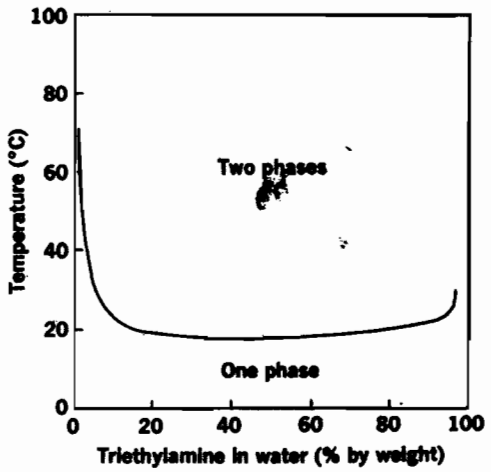


Fig. 2–15. Phase diagram for the system triethylamine–water showing lower consolute temperature.

The phase diagram for the salol–thymol system is shown in Figure 2–17. 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 in Figure 2–14. Thus it is possible to calculate both the composition and relative amount of each phase from a 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

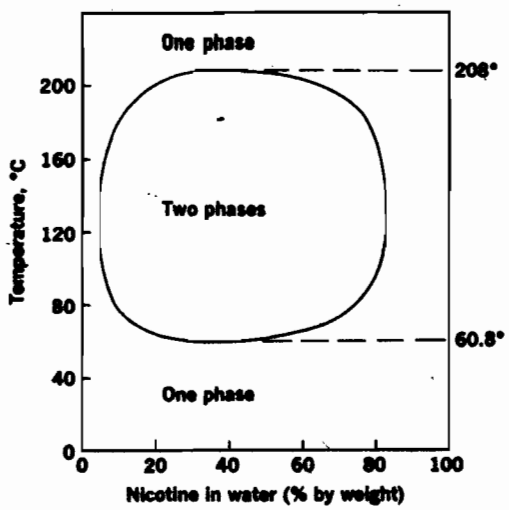


Fig. 2–16. Nicotine–water system showing upper and lower consolute temperatures.

*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.

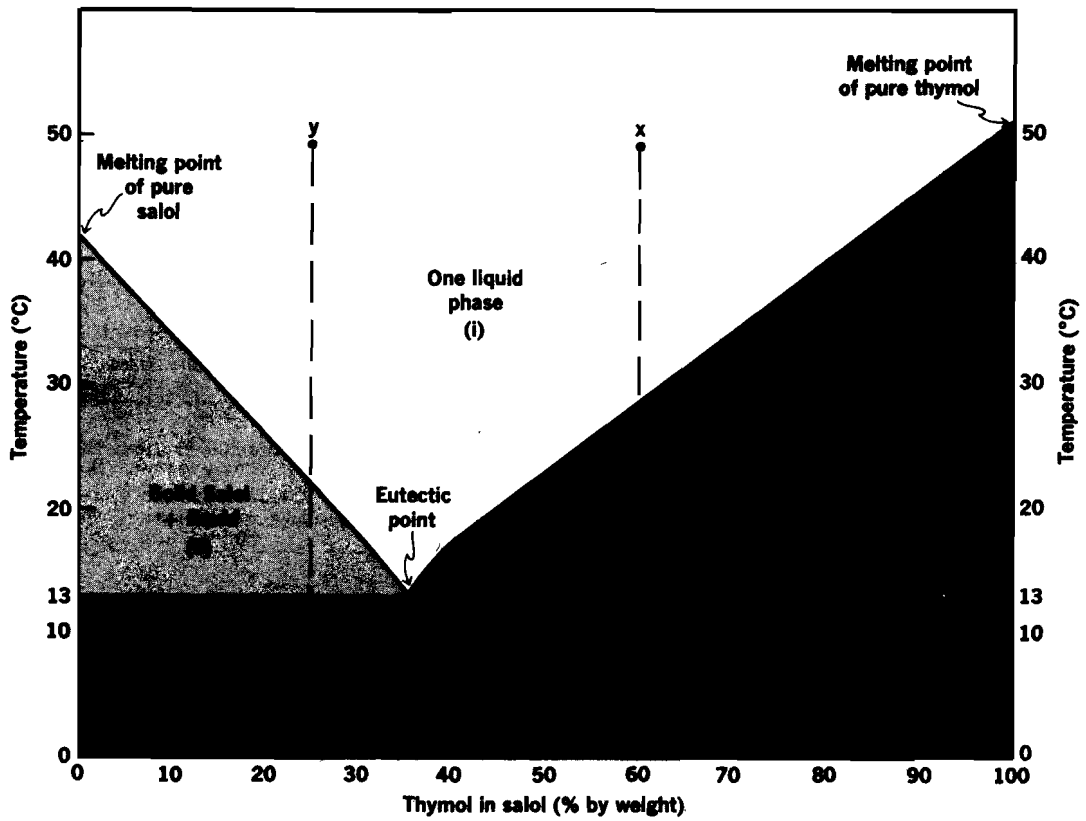


Fig. 2–17. Phase diagram for the thymol–salol system showing the eutectic point. (Data from A. Siedell, *Solubilities of Organic Compounds*, 3rd Ed., Vol. 2, Van Nostrand, New York, 1941, p. 723.)

the mixture to 50° C. Such a system is represented by point x in Figure 2–17. On cooling the system, the following sequence of phase changes is observed. 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, system x (denoted in Fig. 2–17 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), while the solid phase is still pure thymol, b_2. The phase ratio, 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 for, in a condensed system, F = 2 − 3 + 1 = 0.

Mixtures of salol and camphor show similar behavior. In this combination, the eutectic point occurs with a system containing 56% by weight of salol in camphor at a temperature of 6° C. Several other substances form eutectic mixtures (e.g., camphor, chloral hydrate, menthol, and betanaphthol).

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. Further work showed that the liquid eutectic can be emulsified in water, opening the possibility for topical bioabsorption of the two local anesthetics[33,34] (see Chapter 18, pp. 505–506).

Solid Dispersions. Eutectic systems are one example 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 is the *solid solution*, in which each solid phase contains both components, that is, a solid solute is *dissolved* in a solid solvent to give a mixed crystal.

There is widespread interest in solid dispersions since they 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. 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 reviews by Chiou and Riegelman[35] and Goldberg[36] for further details. Refer also to Chapter 19 for a discussion of newer solid dosage forms and devices.

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. Since we are dealing with a three-component system, it is more convenient to use triangular coordinate graph paper, 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 will be discussed here, however, because they are of pharmaceutical interest.

Rules Relating to Triangular Diagrams. Before discussing phase equilibria in ternary systems, it is essential that the reader become 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, while being an easy and direct method of preparing dispersions, such an approach also allows the concentration to be expressed as mole fraction or molality. The concentrations in ternary systems are accordingly expressed on a weight basis. The following statements should be studied in conjunction with Figure 2–18.

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 2–18 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, the location of a point along the line can be directly related to the percent concentration of one

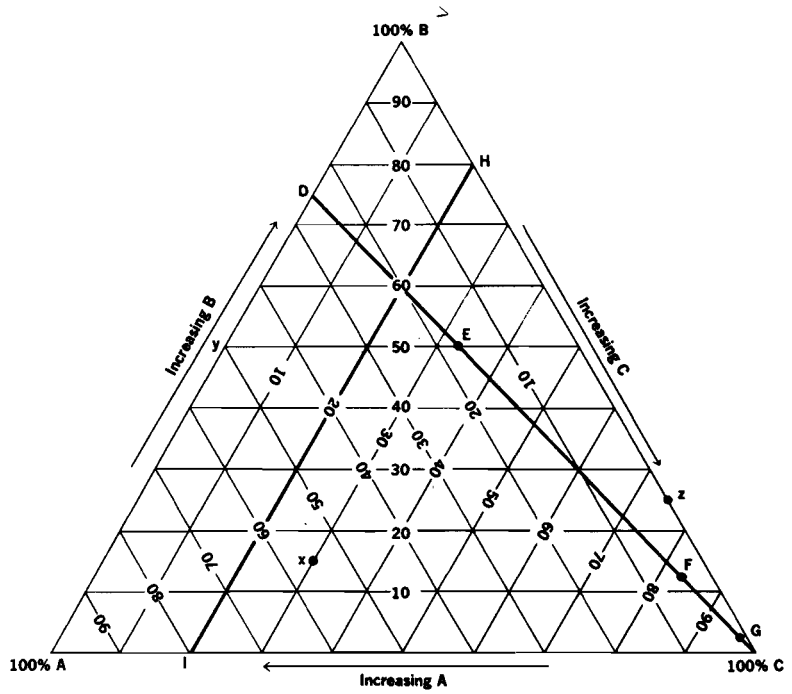


Fig. 2–18. The triangular diagram for three-component systems: preparing and interpreting the diagram.

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 quarters of the way along BC, signifies a system containing 75% of C in B.

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 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 towards 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, may be undertaken as follows.

The line AC; opposite apex B, represents systems containing A and C. 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 towards 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. 2–18), 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 have been 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 2–18, represents ternary systems 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 2–19, which depicts such a ternary system. It might be helpful for the student 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.

In Figure 2–19, let us suppose that A, B, and C represent water, alcohol, and benzene, respectively. The line AC therefore depicts binary mixtures of A and

TABLE 2–8. ***Effect of Adding a Third Component* (C) *to a Binary System Containing* A *(5.0 g) and* B *(15.0 g)***

Weight of Third Component C Added (g)	Final System			Ratio of A to B	Location of System in Figure 2–18
	Component	Weight (g)	Weight (%)		
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		

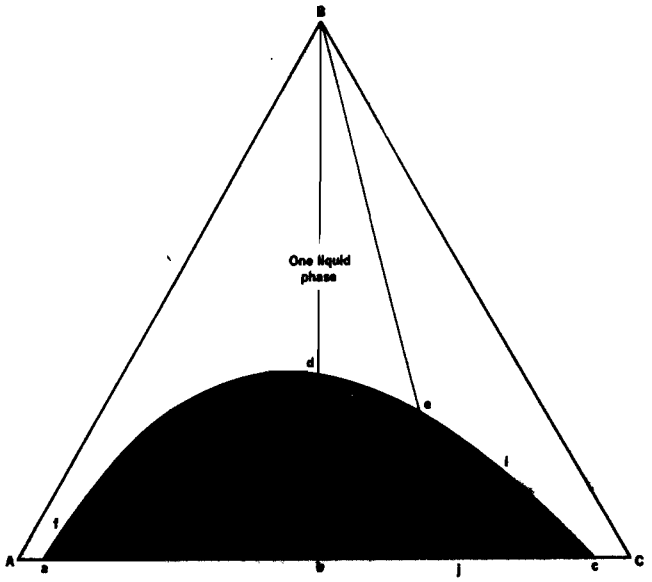


Fig. 2–19. A system of three liquids, one pair of which is partially miscible.

C, while the points a and c are the limits of solubility of C in A and 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 base line.

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, half way along the tie line, will contain equal weights of the two phases at equilibrium.

The phase equilibria depicted in Figure 2–19 shows 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.

As we saw earlier, $F = 2$ in a single-phase region, and so we must define two concentrations to fix the particular system. Within the binodal curve, *afdeic*, $F = 1$ and we need only know one concentration term, since 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 2–19 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. 2–20*b*). Alternatively, a family of curves representing

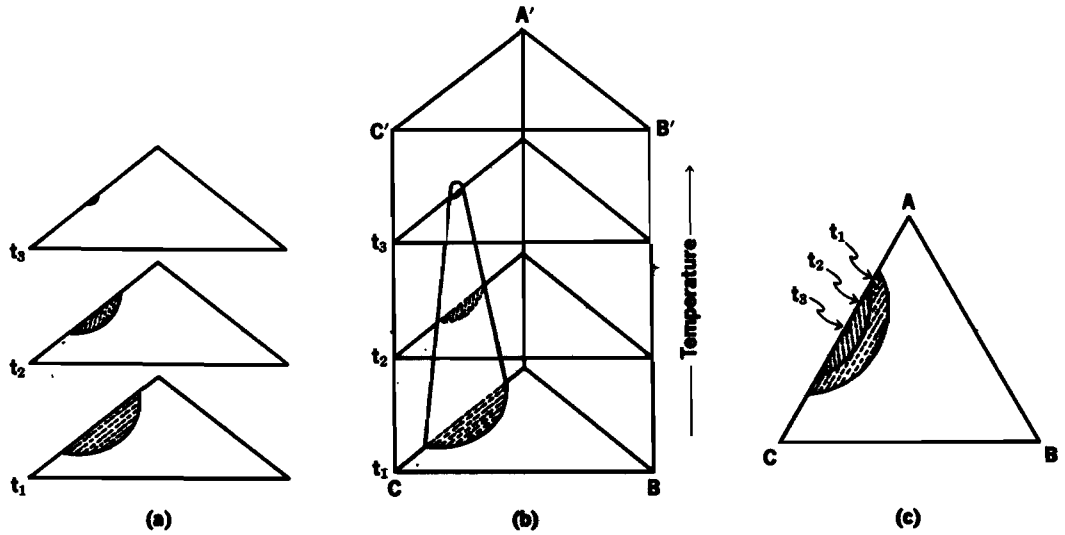


Fig. 2–20. Alterations of the binodal curves with changes in temperature. *(a)* Curves on the triangular diagrams at temperatures t_1, t_2, and t_3. In *(b)* is depicted the three-dimensional arrangement of the diagrams in the order of increasing temperature. The sketch in *(c)* represents the view one would obtain by looking down from the top of *(b)*.

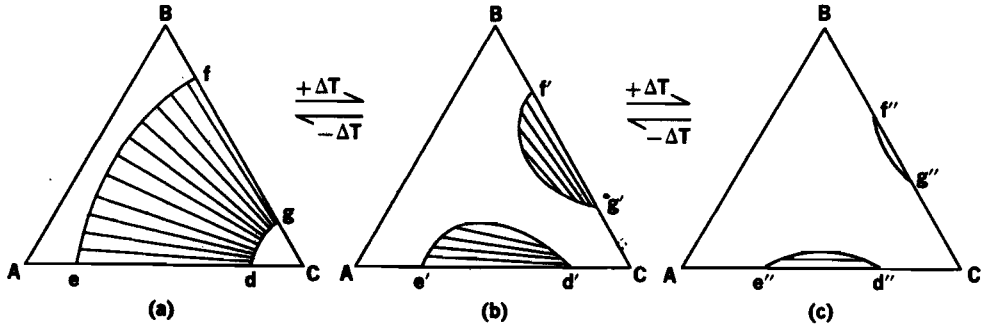


Fig. 2–21. Effect of temperature changes on the binodal curves representing a system of two pairs of partially miscible liquids.

the various temperatures may be used, as shown in Figure 2–20*c*. The three planar sides of the prism are simply three-phase diagrams of binary-component systems. Figure 2–20 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.

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 2–21*b*, 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. 2–21*c*). 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 2–21*a*. Tie lines stilll exist in this region, and the usual rules apply. Nor do the number of degrees of freedom change—when $P = 1$, $F = 2$; when $P = 2$, $F = 1$.

Systems containing three pairs of partially miscible liquids are of interest. Should the three binodal curves meet (Fig. 2–22*a*), 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 quantity that varies is the relative amounts of these three conjugate phases. Increasing the temperature alters the shapes and sizes of the regions, as seen in Fig. 2–22*b* and 2–22*c*.

We shall meet phase diagrams in later chapters (Chapters 10 and 15) in which their application in certain pharmaceutical systems will be discussed.

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 differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), and thermomechanical analysis (TMA). These methods have proved valuable in pharmaceutical research and quality control for the characterization and identification of compounds, determination of purity, polymorphism[19,20] solvent and moisture 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

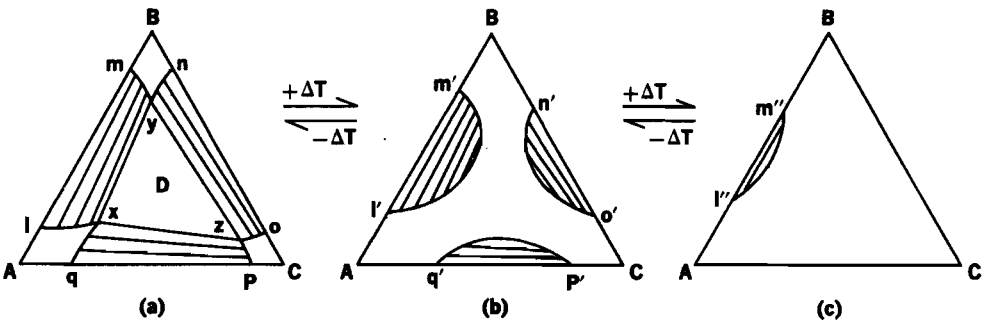


Fig. 2–22. Temperature effects on a system of three pairs of partially miscible liquids.

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 thermal analysis has been used more frequently in the past than DSC principally because the DTA instrument appeared earlier on the market and is less expensive. Differential scanning calorimetry is more useful in the research laboratory because its measurements can be related more directly to thermodynamic properties. It appears that any analysis which can be carried out with DTA can be done with DSC, the latter being the more versatile technique.

Differential Scanning Calorimetry. In differential scanning calorimetry (DSC), a sample and reference material are placed in separate pans and the temperature of each pan is increased or decreased at a predetermined rate. When the sample (e.g., benzoic acid) reaches its melting point, 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 (mp = 156.6° C), as the temperature of the two materials is raised gradually through the range 122° 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 the reference, indium. The difference is heat input to the sample, and the reference per unit time is fed to a recorder and plotted as dH/dt versus the average temperature to which the sample and reference are being raised. The differential heat input is recorded with a sensitivity of ± 0.1 millicalories per second, and the temperature range over which the instrument operates is −175° to 725° C. The data collected in a DSC run for a compound such as benzoic acid are shown in the thermogram in Figure 2–23. The DSC-3 instrument is depicted schematically in Figure 2–24. The panel with its controls and temperature readout are shown, together with dials for preset temperature and rates of temperature change. The unit

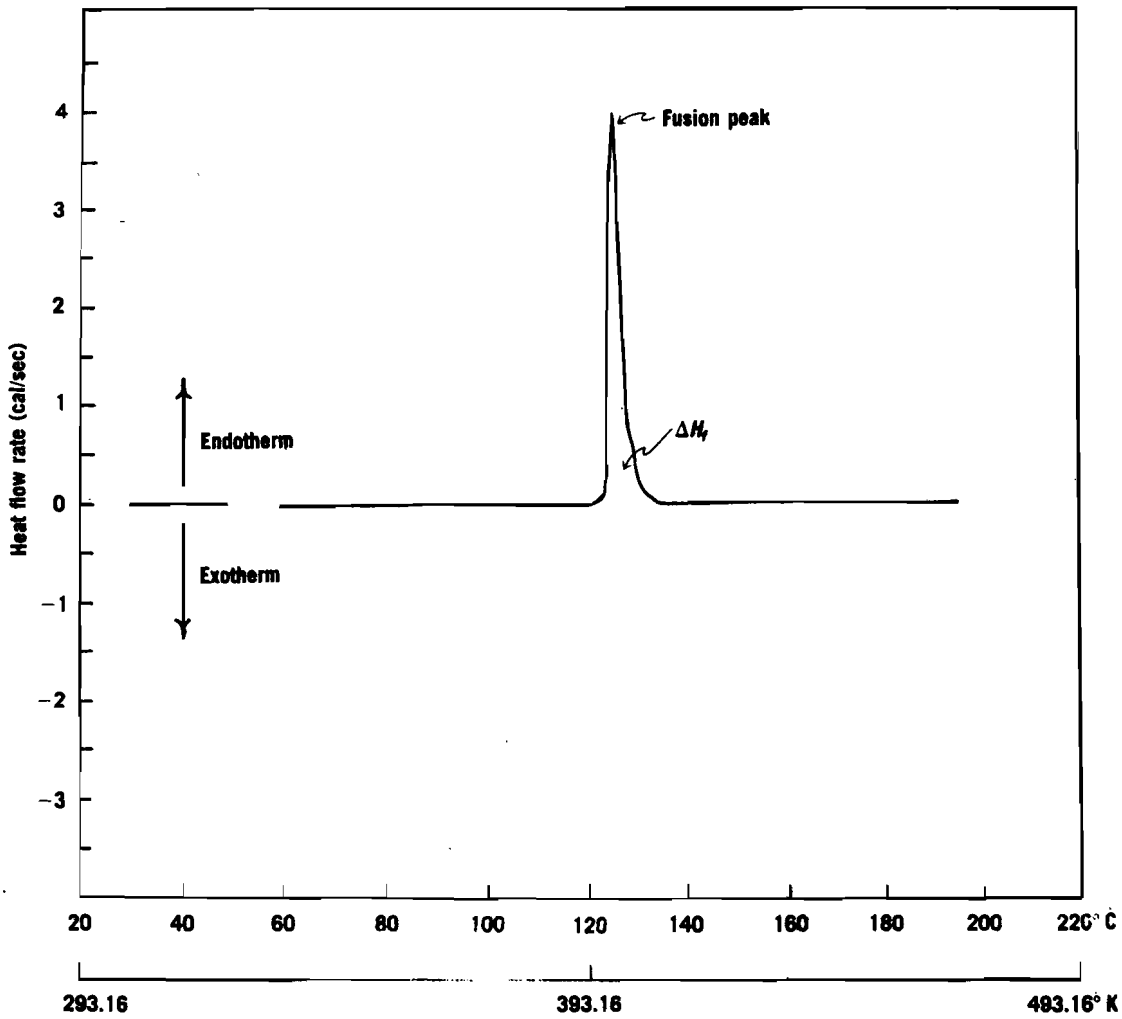


Fig. 2–23. Thermogram of a drug compound. Endothermic transitions (heat absorption) are shown in the upward direction, and exothermic transitions (heat loss) are plotted downward. Melting is an endothermic process, whereas crystallization or freezing is an exothermic process. The area of the melting peak is proportional to the heat of fusion, ΔH_f.

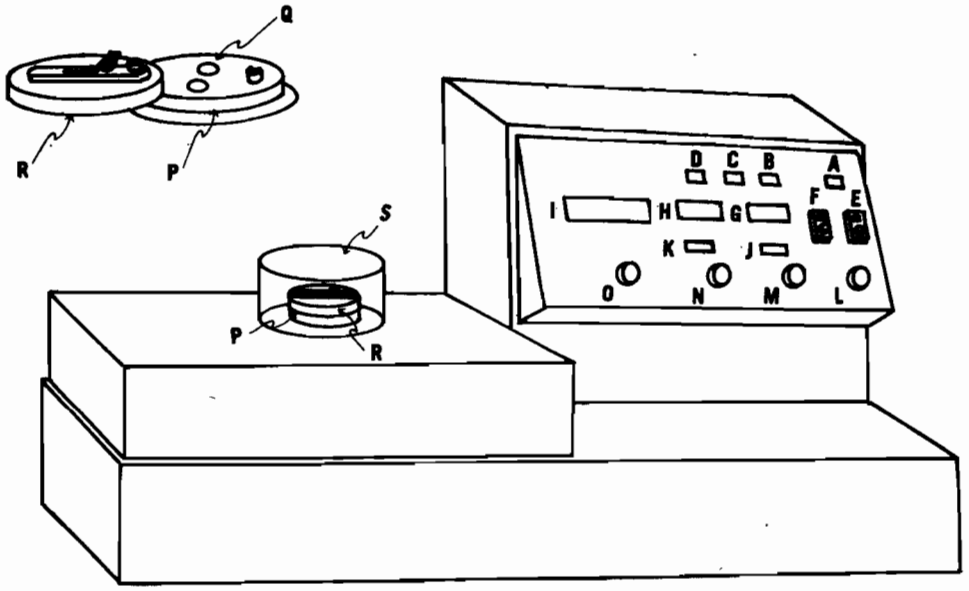


Fig. 2–24. Perkin Elmer differential scanning calorimeter, DSC-3. The dials and windows on the console at the right are used to program the increasing and decreasing temperature at definite rates and to set the baseline of the thermogram, which is plotted on an X–Y recorder. The left section of the instrument is the heating unit, with two sample holders, Q, in the heating block P. The sample cover R is closed and the heating unit is covered by a draft shield, S, during a run.

on the left provides uniform heating and cooling and contains the sample and reference in appropriate pans in the sample enclosure. A thermogravimetric analyzer (TGA) and a thermomechanical analyzer (TMA) may be added to the basic instrument. A data station may also be added to process the thermal data. The DSC-4 is slightly different in appearance from the DSC-3 shown in Figure 2–24.

Although DSC is used most widely in pharmacy to establish identity and purity, it may be used to obtain heat capacities and heats of fusion, referred to in Chapters 3 and 10. It is also useful for preparing phase diagrams to study the polymorphs discussed in this chapter, and for carrying out the kinetics of decomposition of solids (Chapter 12). Differential scanning calorimetry, as well as other thermal analytic methods, has a number of applications in biomedical research and food technology. Guillory and associates[37] have explored the applications of thermal analysis, DSC and DTA in particular, in conjunction with infrared spectroscopy and x-ray diffraction. Using these techniques, they have characterized various solid forms of drugs, such as sulfonamides, and have correlated a number of physical properties of crystalline materials with interactions between solids, dissolution rates, and stabilities in the crystalline and amorphous states.

Differential scanning calorimetry has found increasing use in standardization of the lyophilization process.[38] Crystal changes and eutectic formation in the frozen state can be detected by DSC (and by DTA) when the instruments are operated below room temperature.

For additional references to the use of DSC in research and technology, contact the manufacturers of differential thermal equipment for complete bibliographies.[39]

Differential Thermal Analysis. In differential thermal analysis (DTA), both sample and reference material are heated by a common heat source (Fig. 2–25) rather than the individual heaters used in DSC (Fig. 2–26). Thermocouples are placed in contact with the sample and reference in DTA to monitor the difference in temperature between the sample and reference as they are heated at a constant rate. The temperature difference between sample and reference 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. R in turn depends on temperature, nature of the sample, and packing of the material in the pans. Therefore, it is not possible to directly calculate

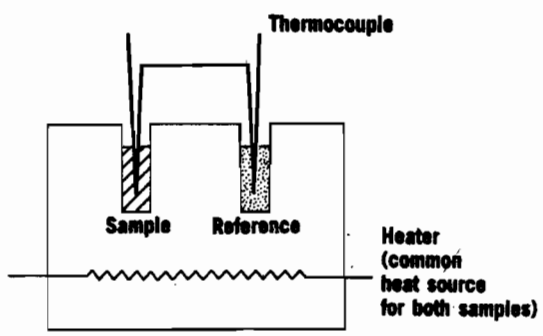


Fig. 2–25. Common heat source of DTA with thermocouples in contact with the sample and reference material.

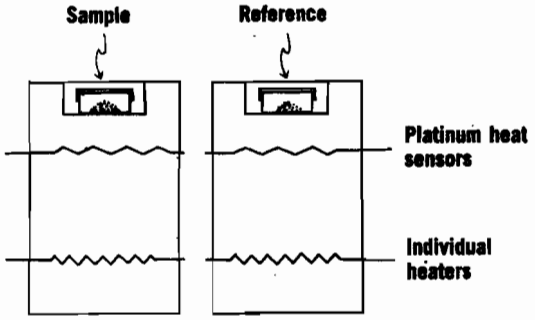


Fig. 2–26. Separate heat sources and platinum heat sensors used in DSC.

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.

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 atmosphere. The changes in hydrated salts such as calcium oxalate, $CaC_2O_4 \cdot H_2O$, with temperature are evaluated using TGA, as discussed by Simons and Newkirk.[40]

The characterization by TGA of bone tissue associated with dental structures was reported by Civjan et al.[41] Thermogravimetric analysis also may be used to study drug stability and the kinetics of decomposition.

Thermomechanical analysis (TMA) 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 may be programmed over a range from −150° to 700° C. The apparatus serves essentially as a penetrometer, dilatometer, or tensile tester over a wide range of programmed temperatures. Humphries et al.[42] have used TMA in studies on the mechanical and viscoelastic properties of hair and the stratum corneum of the skin.

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Problems*

2–1. A weather balloon rises 2 miles into the upper atmosphere. Its volume at ground level is 2.50 liters at 1 atm pressure and 24° C. What is its final volume if the atmospheric pressure is 8.77×10^{-3} atm and the temperature is −44.7° C at the 2-mile position?

Answer: 219 liters

2–2. An air bubble is blown by a fish at the bottom of an aquarium tank and it rises to the surface. As in the case of the weather balloon, *Problem 2–1*, its volume increases as the pressure on the bubble decreases. The bubble has a radius of 0.1 cm at the bottom of the tank where the pressure is 1.3 atm and the temperature is 14° C. At the surface of the tank the pressure is 750 torrs and the temperature is 27° C. What is the radius of the bubble when it comes to the surface of the tank? For the equation for the volume of a sphere, see the inside front cover of the book.

Answer: The volume of the bubble at the bottom of the tank is 4.19×10^{-3} cm³. The radius of the bubble increases from 0.1 cm to 0.11 cm as the bubble rises to the surface.

2–3. Calculate the volume in liters of 1 mole of nitrogen gas at 400 atm and 0° C, using the ideal gas equation. Give the answer in mL of N_2.

Answer: 56 mL

2–4. If 0.50 g of a drug in the vapor state occupies 100 mL at 120° C and 1 atm pressure, what is its approximate molecular weight?

Answer: 161 g/mole

2–5. The Air Protection Laboratory in a large city isolated a new gaseous pollutant that was found to exert a pressure of 1.17 atm when 6.07 gram of the substance was confined in a 2.0-liter vessel at 28° C. (a) What is the molecular weight of the pollutant? (b) If the pollutant is known by chemical test to be a sulfur compound, what do you suppose the compound might be?

Answers: (a) 64.1 g/mole; (b) the molecular weight should provide a strong clue.

2–6. Nitrous oxide (N_2O), U.S.P., is used for the rapid induction of anesthesia (80% N_2O, 20% O_2) and at lower percentages for maintenance anesthesia. (a) Using the ideal gas equation, compute the molecular weight of this gas, given that 1 liter at 0° C and 760 mm Hg pressure weighs 1.97 g. Check your results using a table of atomic weights. (b) Compute the root mean square velocity, μ, of N_2O. (c) Use equation (2–12), p. 26, to compute the density ρ of N_2O at 1 atm and 0° C.

Answers: (a) 44.15 g/mole; (b) 3.9×10^4 cm/sec; (c) density = 2×10^{-3} g/cm³

2–7. An auto tire is inflated to 30 psi gauge pressure (1 atm = 14.7 pounds per square inch and the total air pressure is the tire gauge pressure plus 14.7 psi) on a day when the outside temperature is 10° C. After running on the highway for several hours the temperature of the air in the tire has risen to 26° C. (a) What is the pressure in the tire at this time, assuming that the volume of the tire does not change appreciably with temperature? (b) Refer to a table of conversion factors in a handbook of chemistry to assure yourself that 1 atm = 14.7 lb/in.² (actually 14.6959 lb/in.²). Express the value, 14.7 lb/in.², in the SI units of Pascals. (c) Would it be wise to release some air from the car tires after traveling for hours during August in the Southwest? How high can the pressure in a tire become before it is in danger of blowing out?

Answers: (a) 47.23 psi; gauge pressure = 32.5 psig.; (b) 14.69594 lb (avoirdupois)/in.² = 101,325 kg m^{-1} s^{-2} = 101,325 N m^{-2} = 101,325 Pa; (c) check with your local service station attendant.

2–8. An experimenter wishes to determine the partial pressure of chloroform required to anesthetize a 28.0-gram mouse in a 2.37-liter container at 20° C. If 2.00 cm³ of $CHCl_3$ is introduced into the closed vessel through a valve, what is the partial pressure of the $CHCl_3$ in the container? Assume complete evaporation of the chloroform. Calculate the partial pressure using both (a) the ideal gas equation and (b) the van der Waals equation. Assuming the density of the mouse to be about 1 g/cm³, calculate its volume in liters and subtract this from the volume of the vessel to obtain the volume available to the chloroform vapor. The density of liquid chloroform at 20° C is 1.484 g/cm³, so 2.00 cm³ × 1.484 g/cm³ = 2.968 g and since the molecular weight of chloroform is 119.4 g/mole, 2.096 g ÷ 119.4 g/mole = 0.0249 mol of chloroform in the vessel. The van der Waals a and b values for $CHCl_3$ are given in Table 2–3.

Answers: (a) 0.256 atm or 194.3 torr; (b) 0.254 atm or 193.3 torr

2–9. A 0.193-mole sample of ether was confined in a 7.35-liter vessel at 295.15° 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 liter² atm mole^{-2}; the b value is 0.1344 liter mole^{-1}. To solve for pressure the van der Waals equation may be rearranged as follows:

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

Answers: (a) 0.636 atm; (b) 0.626 atm

2–10. Equations for calculating the van der Waals constants a and b are the following:

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

where T_c is the *critical temperature and* P_c is the *critical pressure.* The critical temperature and critical pressure, respectively, for chloroform are T_c = 263° C and P_c = 54 atm. R is expressed in units of liter atm °K^{-1} mole^{-1}. Calculate the a and b values for chloroform. Check your results against the values given in Table 2–3.

Answers: a = 15.12 liter² atm mole^{-2}; b = 0.1019 liter mole^{-1}

2–11. A small household fire extinguisher of 0.80-liter capacity contains CO_2 at a pressure of 12.3 atm and 25° C. (a) What is the weight of the CO_2 in kg in the extinguisher? (b) What is the volume of this mass of CO_2 at 25° C when the pressure is reduced to 1 atm? (c) Compare your result with that obtained from the density of gaseous CO_2 at 25° C (density = 0.001836 g/cm³). CO_2 is a gas, not a liquid, at atmospheric pressure. The molecular weight of CO_2 is 44.01 g/mole.

Answers: (a) 0.0177 kg; (b) 9.84 liter; (c) 9.64 liter

2–12. The vapor pressure of water at 25° C is 23.8 mm Hg. The average heat of vaporization between 25° and 40° C is about 10,400 cal/mole. Using the Clausius–Clapeyron equation, calculate the vapor pressure at 40° C. The experimentally determined value is 55.3 mm Hg.

Answer: 55.2 mm Hg

2–13. The vapor pressure of ethyl alcohol is 23.6 torr at 10° C, 78.8 torr (mm Hg) at 30° C, and 135 torr at 40° C. Using equation (2–16*a*) plot log P vs. $1/T$ (ln P of equation (2–16*b*) may be used instead of log P and the factor 2.303 will then not be needed), and obtain the vapor pressure of ethyl alcohol at 20° C. What is the heat of vaporization, ΔH_v, at this temperature?

Answer: From the graph, the vapor pressure P is 43.7 torr; ΔH_v = 10,282 cal/mole. Using linear regression, ΔH_v = 10,267 cal/mole and P = 43.9 mm. The heat of vaporization ΔH_v of ethyl alcohol in the *CRC Handbook of Chemistry and Physics*, 67th Edition, is 9673.9 cal/mole.

**Problems 2–1* and *2–2* are modified from R. Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd Edition, Macmillan, New York, 1977, p. 23. *Problems 2–8, 2–11, 2–15,* and *2–17* are modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Chemistry*, Addison-Wesley, Reading, Mass., 1977, pp. 7, 9, and 97, respectively. *Problems 2–7* and *2–18* are modified from Chang, ibid, pp. 24 and 162, and from Moncrief and Jones, ibid, pp. 79 and 92, respectively.

2–14. (a) The vapor pressure of water at 100° C is 76 cm Hg and at 90° C it is 52.576 cm Hg.[43] Using the Clausius–Clapeyron equation, calculate the heat of vaporization ΔH_v of water in cal/mole within this temperature range.

(b) For 20° C and 30° C the vapor pressures of water are 17.535 mm Hg and 31.824 mm Hg, respectively. What is the heat of vaporization ΔH_v within this temperature range? Give the results in cal/mole.

(c) At 5° C and 10° C the vapor pressures of water are 6.543 mm Hg and 9.209 mm Hg, respectively. What is the heat of vaporization ΔH_v of water within this range of temperatures? Express the result in cal/mole.

(d) The results of (a), (b), and (c) may suggest that one obtains, and should use in further calculations, different ΔH_v values for water within these three temperature ranges. To test this suggestion, prepare a table of these six vapor pressures and their corresponding temperatures recorded in Kelvin degrees. Using equation (2–16), regress log P versus $1/T$ and obtain the overall ΔH_v for the temperature range of 5° to 100° C. (Be careful to use consistent units throughout the problem.) Finally, answer the question: Does ΔH_v have a single value over the temperature range from 5° to 100° C, or is it better represented by different values over the three temperature ranges considered in this problem?

Answers: (a) 9922 cal/mole; (b) 10,525 cal/mole; (c) 10,698 cal/mole; (d) ΔH_v (5° to 100° C) = 10,310 cal/mole; $r^2 = 0.9999$

2–15. A group of hikers decide to climb a mountain and heat cans of beans and some sausages when they reach the summit, using backpacker stoves. The mountain is 3500 meters high (11,500 ft), at which height the atmospheric pressure is 506 mm Hg. The temperature at this time of year is −15° C (5° F) at the mountain top.

The heat of vaporization of butane and propane, two volatile compounds used as fuel for backpacker stoves, are 5318 and 4812 cal/mole, respectively; and their normal boiling points (at sea level) are −0.50° C and −42.1° C.

It may be noted that flammable liquids such as butane and propane will not vaporize and ignite at temperatures below their boiling points and cannot serve as cooking stoves at lower temperatures. (a) Compute the boiling point of butane and propane at the top of the mountain. Changes in temperature with vapor pressure are dealt with using the Clausius–Clapeyron equation. (b) Could either the butane or propane stove be used at the top of this mountain? (c) Can water be "boiled" on the mountain top to prepare coffee for the hikers? The heat of vaporization of water is 9717 cal/mole and its boiling temperature is 100° C at 1 atm.

Partial Answer: (a) Butane, −11.30° C; propane, −50.73° C

2–16. Isoflurane and halothane are nonflammable volatile liquids used for general anesthesia. (a) What is the vapor pressure p' of isoflurane at room temperature, 25° C? The heat of vaporization $\Delta H_v'$ of isoflurane is 6782 cal/mole at its boiling point. The vapor pressure p' for isoflurane at its normal boiling point, 48.5° C, is 1 atm according to the definition of the normal boiling point. (b) What is the heat of vaporization $\Delta H_v''$ of halothane within the temperature range 20° C to its boiling point, 50.2° C? The vapor pressure p'' of halothane at 20° C is 243 mm Hg. These two general anesthetics are slightly greater in vapor pressure than ether (ether, p = 217 torr at 20° C). But of much greater importance, they are nonflammable whereas ether is highly flammable. (c) What other advantages does halothane have over ether as a general anesthetic? Consult a book on pharmacology.

Answers: (a) p' = 329.3 torr; (b) $\Delta H_v''$ = 7112 cal/mole

2–17. (a) What pressure is necessary to keep butane as a liquid in a container on a day when the storeroom temperature is 104° F. The heat of vaporization of butane is 5318 cal/mole, and the boiling point at 1 atm is −0.50° C.

(b) Repeat the problem using propane as the volatile liquid. The ΔH_v of propane is 4811.8 cal/mole and its boiling point at 1 atm (normal boiling point) is −42.1° C.

(c) From results in (a) and (b) conclude whether you can keep these gases as liquids at 104° F in plastic containers. The maximum safe pressure for plastic containers is 1.75 kg/cm². Can these volatile compounds be kept in aluminum containers that have a maximum safe pressure of 4.2 to 4.9 kg/cm²? (One atmosphere = 1.033 kg/cm².)

Answers: (a) 3.56 atm; (b) 15.60 atm; (c) to keep propane as a liquid at 104° F requires a pressure above 15.6 atm or 16.2 kg/cm². Neither plastic nor aluminum containers are satisfactory for propane.

2–18. If the skate blade of a 175-lb man on ice is 12 in. long and 1/64 in. thick and the heat of fusion of water (ice) is 6025 J/mole, what is the melting point change that produces liquid water under the skate allowing the liquid to lubricate the skate? The molar volume of liquid water (its molecular weight divided by its density) is 0.018 liter and the molar volume of ice is 0.01963 liter. (a) Carry out the calculations, using SI units and the integrated form of the Clausius–Clapeyron equation,

$$\int_{273.15°K}^{T} \frac{1}{T}\,dT = \frac{\Delta V}{\Delta H_f}\int_{P_1}^{P_2} dP$$

(b) Repeat, using the approximation

$$\frac{\Delta T}{\Delta P} = T\,\frac{\Delta V}{\Delta H_f}$$

Answers: (a) ΔT = −0.470° K; (b) ΔT = −0.468° K

2–19. When a solid that exists in more than one crystalline form is subjected to the relatively high pressure of a tablet machine it might favor transformation to a denser polymorphic form.

Sulfathiazole can be obtained in at least two polymorphic forms, I and II, I being the lower energy state at room temperature. The densities are 1.50 g/cm³ (form I) and 1.55 g/cm³ (form II). The transition temperature $I \rightarrow II$ is 161° C and the heat of transition ΔH_t is 1420 cal/mol.[44] (a) What is the effect of a normal pressure of 1 atm on the transition temperature of sulfathiazole from form I to form II? The molecular weight is 255.32 g/mole. Use equation (2–17), p. 31, substituting ΔH_f, V_l, and V_s with ΔH_t and the molar volumes of the two polymorphs.

(b) What is the transition temperature when form I is compressed in the tablet machine at 2812 kg/cm² (2757.6 bar)? Would form I be stable during the tableting process? (One bar = 14.5038 pounds/in.² and 1 kg/cm² = 14.223343 pounds/in.²)

Answer: (a) Using equation (2–17), $\frac{\Delta T}{\Delta P}$ = −0.041 °K/atm; (b) 49.4°C. If the temperature during processing were greater than 50° C, form I might change to form II.

2–20. The temperature of transition T from one polymorphic form to another can be obtained from solubility data as explained on page 35. The solubilities m_1 and m_2 of sulfathiazole, forms I and II, at several temperatures are given in the table below. Plot the $\ln(m_2/m_1)$ on the vertical axis against $1/T$, (°K⁻¹), on the horizontal axis, and compute the transition temperature for the transformation, form I → form II.

Data for *Problem 2–20**

T (°C)	$1/T$ (°K^{-1}) × 10^3	ln (m_2/m_1)
31.50	3.01	0.2562
19.80	3.11	0.3501
14.00	3.20	0.4243
9.93	3.30	0.5198
8.15	3.37	0.5552
7.10	3.41	0.6125

*From G. Milosovich, J. Pharm. Sci. **53**, 484, 1964.

$\text{Ln}(m_2/m_1)$ is the natural logarithm of the ratios of the solubilities, m_2 and m_1, of the two polymorphic forms. Obtain the linear least-square fit of the line. Recognizing that $\ln(m_2/m_1)$ must be 0

when $(m_2/m_1) = 1$, read the value of $1/T$ (and hence T) from the graph when $\ln (m_2/m_1) = 0$. Or, better, from the least-squares equation, calculate the value of $1/T$, and therefore of T, when $\ln(m_2/m_1)$ is 0.

Answer: $0 = -2.34 + 864.5(1/T)$; $T = 369.4°$ K

2–21. A mixture containing 21% by weight of phenol in water (see Fig. 2–14) is prepared and allowed to come to equilibrium at 30° C. The two liquid phases that separate contain 7% and 70% of phenol, respectively. If the total weight of the original mixture was 135 g, calculate (a) the weight of each phase at equilibrium, and (b) the actual weight of water, in grams, in each phase.

Answers: (a) 30 g; 105 g; (b) 9.00 g; 97.65 g

2–22. *A* and *B* are two partially miscible liquids. The following mixtures (percent by weight) all formed two liquid phases below, and one liquid phase above, the temperature noted (in other words, these are temperatures at which two-phase systems became one-phase systems).

Data for *Problems 2–22* and *2–24*

A (% w/w)	*B* (% w/w)	Temperature (°C)
20	80	10
30	70	22
40	60	34
50	50	39
60	40	38
70	30	32
80	20	22
90	10	10

Plot these results on rectangular coordinate paper and describe accurately the phase changes observed as *A* is continually added to *B* at a temperature of (a) 25° C and (b) 45° C.

Answers: (a) There is a single liquid phase up to 31% w/w of *A* present, at which point two liquids are formed (compositions are 31% w/w *A* and 78% w/w *A*). As more *A* is added, the amount of the second phase *B* decreases while that of the first phase *A* increases. When the system exceeds 78% w/w *A* at 25° C the two phases disappear and the system again becomes one phase. (b) At 45° C, we are above the region of immiscibility, and hence a single phase exists for all combinations of *A* and *B*.

2–23. If a liquid mixture containing *A* (20 g) and *B* (30 g) is prepared and allowed to come to equilibrium at 22° C, (a) what are the compositions of the two phases present and (b) what is the weight of each phase? See *Problem 2–22*.

Answers: (a) 30% w/w *A* and 70% w/w *B*; 80% w/w *A* and 20% w/w *B*. These are conjugate phases; (b) 40 g of *A* and 10 of *B* g

2–24. Using the table of data in *Problem 2–22*, plot % *A* on the horizontal axis versus temperature (°C). Ten grams of a mixture containing equal weights of *A* and *B* at 50° C are cooled to 10° C. (a) At what temperature will a phase change be observed; (b) at 10° C, how much *B* must be added to produce a single phase; (c) at 10° C, how much *A* must be added to produce a single-phase system? See *Problem 2–22*.

Answers: (a) 39° C; (b) 15 g *B* (to produce a system containing 20% w/w *A* and 80% w/w *B*); (c) 40 g *A* (to produce a system containing 90% w/w *A* and 10% *B*)

2–25. Plot the following points on triangular coordinate paper for a mixture of three liquids. The area bounded by the binodal curve contains two liquid phases in equilibrium; the area outside the binodal curve contains one liquid phase.

Data for *Problems 2–25, 2–26,* and *2–27*

A (% w/w)	*B* (% w/w)	*C* (% w/w)
84	11	5
78	12	10
70	14	16
63	16	21
55	19	26
45	25	30
40	30	30
32	39	29
26	48	26
22	55	23
17	65	18
14	75	11
12	81	7
9	89	2

When a liquid system containing *A* (45 g), *B* (40 g), and *C* (15 g) was prepared and allowed to reach equilibrium, analysis of one phase gave the following data: *A* = 84% w/w; *B* = 11% w/w; *C* = 5% w/w. (a) From your knowledge of tie lines in binodal areas, what is the composition of the conjugate phase? (b) What is the weight of each of these two conjugate phases? The total weight of the components is 100 g.

Answers: (a) Approximately 21% w/w of *A*, 58% w/w of *B*, and 21% w/w of *C*. (b) 38 g; 62 g

2–26. Using the data given in *Problem 2–25*, you are required to formulate a 5-g single-phase solution containing 50% w/w *B* and 35% w/w *C* that is to be diluted to 100 g with *A* immediately prior to use. (a) What is the sequence of phase changes observed as *A* is progressively added? (b) What is the composition of the final system?

Answers: (a) A single liquid phase system contains approximately 30% w/w *A*, 41% w/w *B*, and 29% w/w *C* when a second liquid phase separates. When the composition of the system is 81% w/w *A*, 11% w/w *B*, and 8% w/w *C*, the system will revert to one liquid phase. (b) 95.75 g *A*, 2.5 g *B*, and 1.75 g *C*

2–27. Based on the data given in *Problem 2–25*, a system containing *A* (45 g), *B* (40 g), and *C* (15 g) was prepared and allowed to attain equilibrium. (a) How much of a mixture containing 30% w/w *C* and 45% w/w *A* would you need to add to produce a single-phase system from the two-phase system? (b) What would be the composition of this one-phase system? Suppose you now add increasing amounts of *B* to this phase, (c) how much *B* must you add before you produce a single-phase system again? (d) What is the composition of this phase? (e) Finally, you add *A* in increasing amounts; what amount of *A* must you add to produce a single-phase system? (f) What will be its composition? *Note:* When you add increasing amounts of a component, or a mixture of components, you prepare systems that lie on a straight line directed to the point that represents the mixture you are adding. Thus, if you continually add *A* to any mixture, you will eventually finish up at point *A* on the diagram.

Answers: (a) 60.0 g (27.0 g *A* and 33.0 g *C*); (b) 45% w/w *A*, 25% w/w *B*, and 30% w/w *C*; (c) 440 g *B*; (d) 12% w/w *A*, 80% w/w *B*, and 8% w/w *C* (approximately); (e) 4022 g *A*; (f) 89% w/w *A*, 10% w/w *B*, and 1% w/w *C* (approximate)