Melting Point and Heat of Fusion

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

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

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

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

$$\frac{\Delta T}{\Delta P} = T \frac{V_l - V_s}{\Delta H_f}$$

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

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

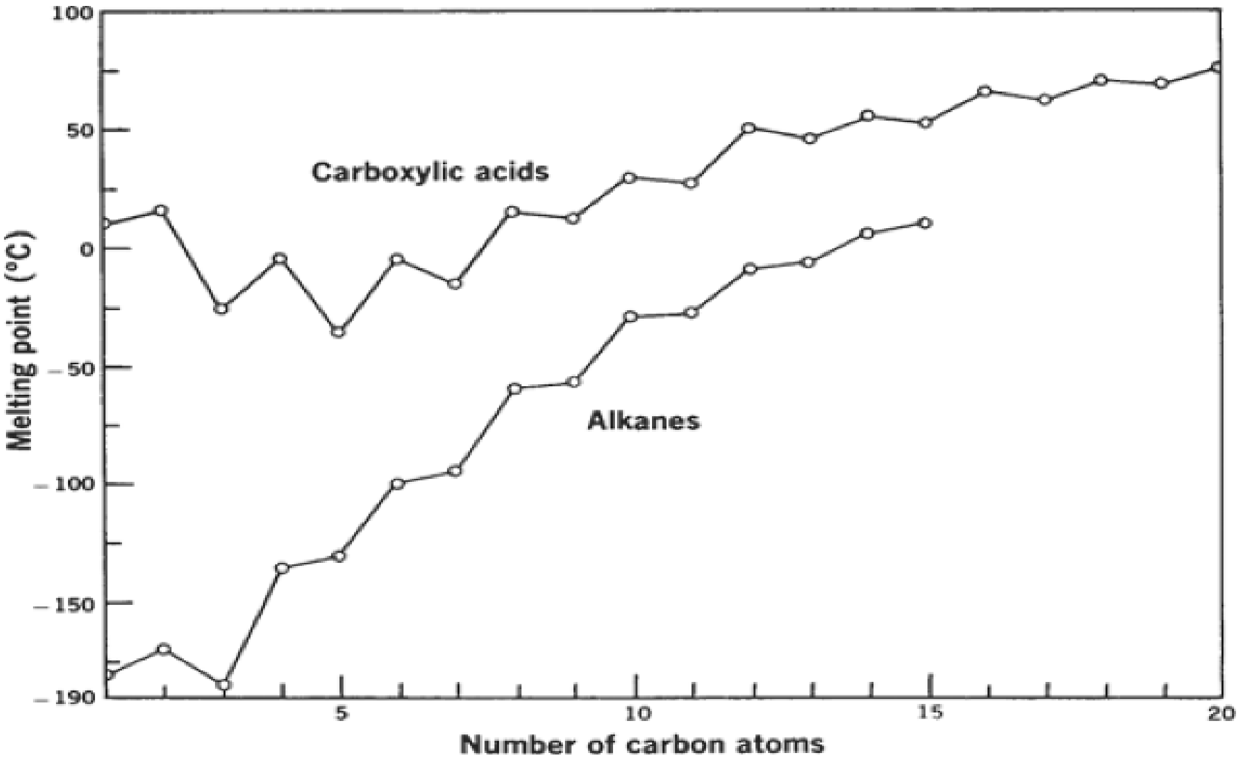
Melting Point and Intermolecular Forces

The heat of fusion may be considered as the heat required to increase the interatomic or intermolecular distances in crystals, thus allowing melting (increased molecular motion) to occur.

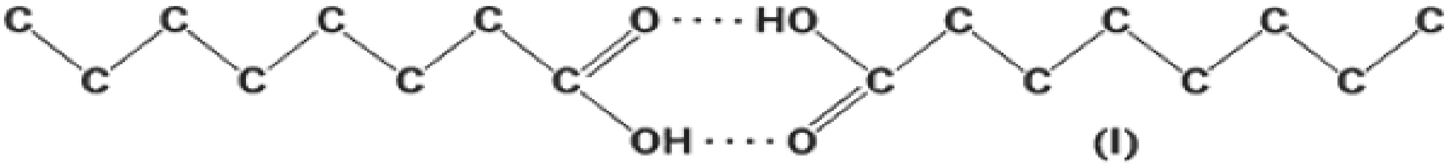
A crystal that is bound together by weak forces generally has a low heat of fusion and a low melting point, whereas one bound together by strong forces has a high heat of fusion and a high melting point.

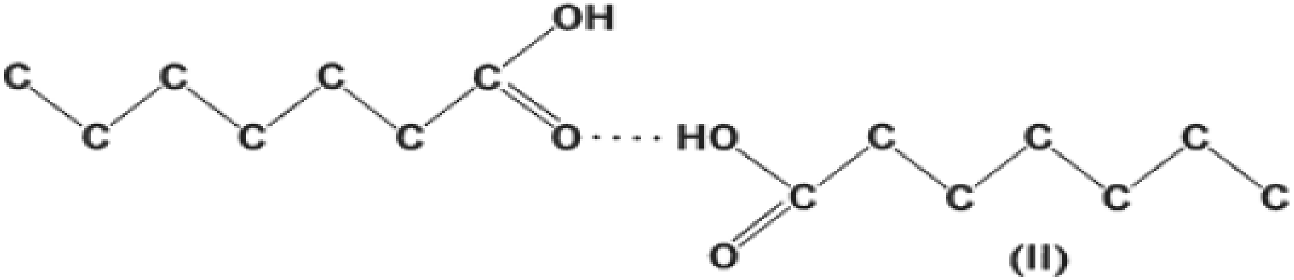
Because polymorphic forms represent different molecular arrangements leading to different crystalline forms of the same compound, it is obvious that different intermolecular forces will account for these different forms. Then consider polymorph A, which is held together by higher attractive forces than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

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



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


(I)


(II)

Solubilities, like melting points, are strongly influenced by intermolecular forces. This is readily observed in Table below, where the methylation of theophylline to form caffeine and the lengthening of the side chain from methyl (caffeine) to propyl in the 7 position result in a decrease of the melting point and an increase in solubility. These effects presumably are due to a progressive weakening of intermolecular forces.

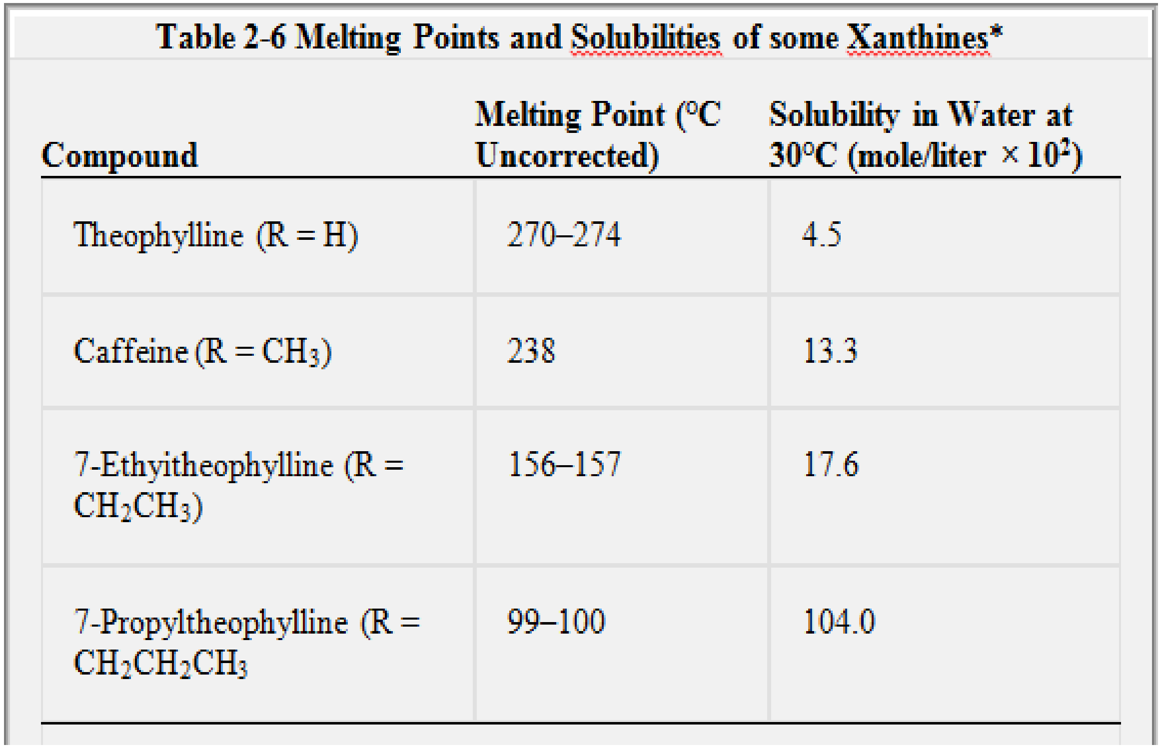
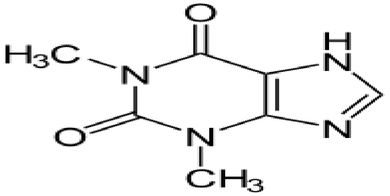
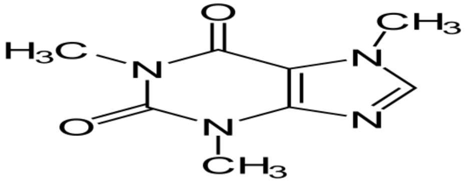


Table 2-6 Melting Points and Solubilities of some Xanthines*

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

R=H





The Liquid Crystalline State

Three states of matter have been discussed thus far in this chapter: gas, liquid, and solid. A fourth state of matter is the *liquid crystalline* state or *mesophase*. The term *liquid crystal* is an apparent contradiction, but it is useful in a descriptive sense because materials in this state are in many ways intermediate between the liquid and solid states.

Properties and Significance of Liquid Crystals

Because of their intermediate nature, liquid crystals have some of the properties of liquids and some of the properties of solids.

1-For example, liquid crystals are mobile and thus can be considered to have the flow properties of liquids.

2-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.

3-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.

4-Nematic liquid crystals may be sensitive to electric fields, a property used to advantage in developing display systems.

5-The smectic mesophase has application in the solubilization of water-insoluble materials. It also appears that liquid crystalline phases of this type are frequently present in emulsions and may be responsible for enhanced physical stability owing to their highly viscous nature.

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 1-DSC, 2-differential thermal analysis (DTA), 3- thermogravimetric analysis (TGA), 4-and thermomechanical analysis (TMA).

These methods have proved to be valuable in pharmaceutical research and quality control for the characterization and identification of compounds, the determination of, **1- purity, 2-polymorphism 3-solvent, and 4- moisture content, 5-amorphous content, 6-stability, and 7-compatibility with excipients.**

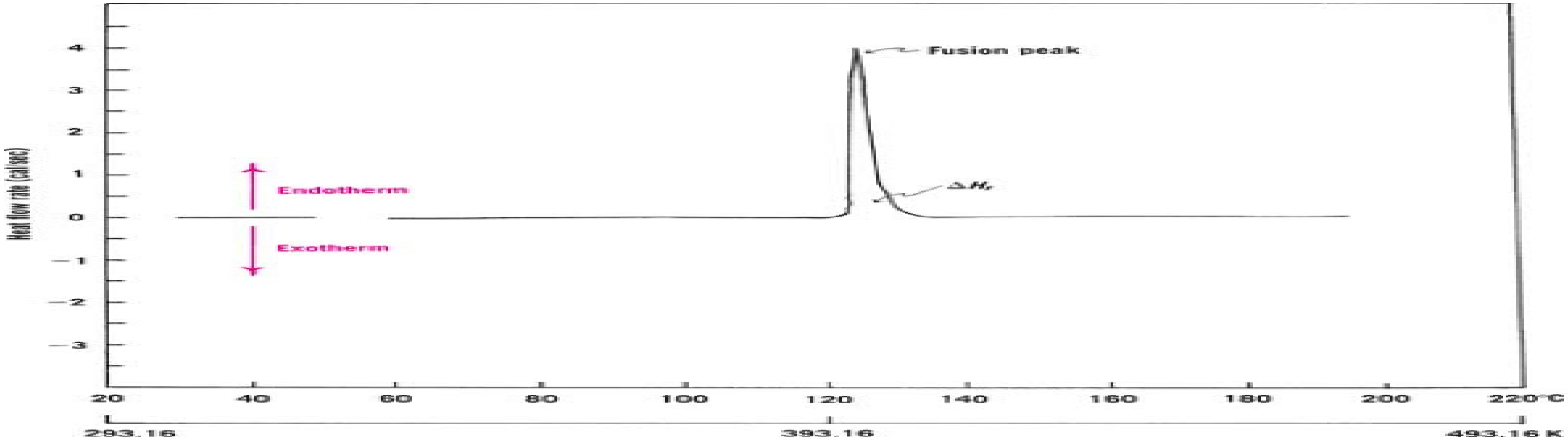
In general, **thermal methods involve heating a sample under controlled conditions and observing the physical and chemical changes that occur**. These methods measure a number of **different properties, such as 1-melting point, 2-heat capacity, 3- heats of reaction,4- kinetics of decomposition, and 5-changes in the flow (rheologic) properties** of biochemical, pharmaceutical, and agricultural materials and food.

Differential scanning calorimetry is the most commonly used method and is generally a more useful technique because its measurements can be related more directly to thermodynamic properties. It appears that any analysis that can be carried out with DTA can be performed with DSC, the latter being the more versatile technique.

Differential Scanning Calorimetry

In DSC, heat flows and temperatures are measured that relate to thermal transitions in materials. Typically, a sample and a reference material are placed in separate pans and the temperature of each pan is increased or decreased at a predetermined rate. When the sample, for example, benzoic acid, reaches its melting point, in this case 122.4°C, it remains at this temperature until all the material has passed into the liquid state.

because of the endothermic process of melting. A temperature difference therefore exists between benzoic acid and a reference, indium (melting point [mp] = 156.6°C), as the temperature of the two materials is raised gradually through the range 122°C to 123°C. A second temperature circuit is used in DSC to provide a heat input to overcome this temperature difference. In this way the temperature of the sample, benzoic acid, is maintained at the same value as that of the reference, indium. The difference is heat input to the sample, and the reference per unit time is fed to a computer and plotted as *dH/dt* versus the average temperature to which the sample and reference are being raised. The data collected in a DSC run for a compound such as benzoic acid are shown in the thermogram in Figure below.



Thermogravimetric and Thermomechanical Analyses

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

Thermogravimetric analysis instruments have now begun to be coupled with infrared or mass spectrometers to measure the chemical nature of the evolved gases being lost from the sample.

Phase Equilibria and the Phase Rule

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

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

The Phase Rule

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

$$F = C - P + 2$$

where *C* is the number of components and

P is the number of phases present.

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

The *number of components* is the smallest number of constituents by which the composition of each phase in the system at equilibrium can be expressed in the form of a chemical formula or equation. The number of components in the equilibrium mixture of ice, liquid water, and water vapor is one because the composition of all three phases is described by the chemical formula H_2O.

Systems Containing One Component

We have already considered a system containing one component, namely, that for water, which is illustrated in Figure beside . The curve OA in the *P–T* (pressure–temperature) diagram in 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. 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.