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 based on symmetry. They are, together with examples of each, cubic (sodium chloride), tetragonal (urea), hexagonal (iodoform), rhombic (iodine), monoclinic (sucrose), and triclinic (boric acid).

The units that constitute the crystal structure can be atoms, molecules, or ions. The sodium chloride crystal, shown in Figure below 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.

In organic compounds, the molecules are held together by van der Waals forces, Coulombic forces, and hydrogen bonding, which account for **the weak binding and for the low melting points of these crystals.**

Whereas ionic and atomic crystals in general are hard and brittle and have high melting points, molecular crystals are soft and have relatively low melting points

polymorphism

Some elemental substances, such as carbon and sulfur, may exist in more than one crystalline form.

Polymorphs have different stabilities and may spontaneously convert from the metastable form at a temperature to the stable form

They also exhibit different melting points, x-ray crystal and diffraction patterns and solubilities, even though they are chemically identical.

The formation of polymorphs of a compound may depend upon several variables pertaining to the crystallization process, including 1-solvent differences (the packing of a crystal might be different from a polar versus a nonpolar solvent).
2-Temperature
3-Geometry of the covalent bond (are the molecules rigid, plane or free, flexible
4-pressure

Theobroma oil is capable of existing in four polymorphic forms: the unstable gamma form, melting at 18°C; the alpha form, melting at 22°C; the beta prime form, melting at 28°C; and the stable beta form, melting at 34.5°C.

Different polymorphs = different solubilities
Ex: slightly soluble drugs effects rate of dissolution.
Ex: chloramphenicol palmitate has a significant influence on biological activity.

The transition temperature in polymorphism is important because it helps characterize the system and determine the more stable form at temperatures of interest. At their transition temperatures, polymorphs have the same free energy (i.e., the forms are in equilibrium with each other), identical solubilities in a particular solvent, and identical vapor pressures.

Solvates

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

Amorphous Solids

Amorphous solids as a first approximation may be considered supercooled liquids in which the molecules are arranged in a somewhat random manner as in the liquid state. Substances such as glass, pitch, and many synthetic plastics are amorphous solids. They differ from crystalline solids in that they tend to **1-flow when subjected to sufficient pressure over a period of time**,
2-and they do not have definite melting points.

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

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

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

X-Ray Diffraction

X-rays are a form of electromagnetic radiation (Chapter 4) having a wavelength on the order of interatomic distances (about 1.54 Å for most laboratory instruments , the C—C bond is about 1.5 Å). X-rays are diffracted by the electrons surrounding the individual atoms in the molecules of the crystals. The regular array of atoms in the crystal (periodicity) causes certain directions to constructively interfere in some directions and destructively interfere in others.

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

The powder x-ray diffraction pattern may be thought of as a fingerprint of the single-crystal structure. Comparing the position and intensity of the lines on such a pattern with corresponding lines on the pattern of a known sample allows one to conduct a qualitative and a quantitative analysis. It is important to note that two polymorphs will provide two distinct powder x-ray diffraction patterns. The presence of a solvate will also influence the powder x-ray diffraction pattern because the solvate will have its own unique crystal structure.

One way to determine whether the presence of a change in a powder x-ray diffraction pattern is due to **a solvate or is a separate polymorph** is to measure the **powder x-ray diffraction patterns at various temperatures.** Because solvents tend to be driven out of the structure below the melting point, measuring the powder x-ray diffraction patterns at several temperatures may eliminate the solvent and reveal an unsolvated form