1. Introduction and Definitions

1.1. POLYMORPHISM

Polymorphism (Greek: πολυ-μορφος poly = many, morph = form) specifying the diversity of nature, is a term used in many disciplines. According to the Oxford English Dictionary the term first appears in 1785 in the field of natural history, biology and pathology and was adopted for use in many disciplines during the 19th century, including, for instance, Darwin in the Origin of the Species. In the context of crystallography, the first use was by Mitscherlich [1], who recognized different crystal structures of the same compound in a number of arsenate and phosphate salts.

As in many terms of chemistry an all-encompassing definition of polymorphism is elusive. The problem has been discussed by McCrone [2], whose working definition and accompanying caveats are as relevant today as when they were first enunciated. McCrone defines a polymorph as “a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in a number of arsenate and phosphate salts.

At first glance this definition seems straightforward. What are the complications? For flexible molecules McCrone would include conformational polymorphs, wherein the molecule can adopt different conformations in the different crystal structures [3,4]. But this is a matter of degree: dynamic isomerism or tautomerism would be excluded, because they involve the formation of different molecules. The “safe” criterion for classification of a system as polymorphic would be if the crystal structures are different but lead to identical liquid and vapor states. For dynamically converting isomers, this criterion invokes a time factor [5]. As with polymorphs dynamic isomers will melt at different temperatures. However, the composition of the melt will differ. That composition can change with time until equilibrium is reached, however, and the equilibrium composition will be temperature dependent. Using these criteria, a system in which the isomers (or in the limit conformers) were rapidly interconverting would be considered a polymorphic one, while a slowly interconverting system would not be characteristic of polymorphic solids. There are many additional complications discussed in a rather comprehensive review of polymorphism [6] and although the language of chemistry is constantly developing, McCrone’s working definition of polymorphism...
appears to have stood the test of time, and is the one that would be recognized and used by most chemists today.

1.2. IMPORTANCE OF POLYMORPHISM – CONCOMITANT AND DISAPPEARING

Chemists who encounter polymorphism for the first time are often unaware of its existence and baffled by its manifestations. Experimental problems might include, for example, variable or diffuse melting point, crystal batches with inconsistent physical properties (electrical or thermal conductivity, filtering, drying, flow, tabletting, dissolution), two (or more) different colored or different shaped crystals in the same batch of (chemically) “pure” material, etc. (for example, see Brittain, [7]). These problems result because the conditions of that particular crystallization have led to the production of a number of polymorphs, which are present in the crystallizing medium or vessel at the time of harvesting or collection of the crystals. The fact that polymorphs of a substance can appear concomitantly (accompanying each other or happening together) has long been recognized but has only recently been reviewed [8].

Is the phenomenon of concomitant polymorphs a curse or a blessing? Both. It is a curse for the chemist seeking a pure substance and a robust procedure to repeatedly and consistently produce that pure material, and the existence of concomitant polymorphs corrupts that procedure. It is a blessing, however, because (the recognition of) the existence of polymorphs in general, and concomitant polymorphs in particular can provide the information and the opportunity to gain control over the crystallization process, and to achieve the desired specificity and robustness.

On the other end of the spectrum of crystallization phenomena of polymorphs is that of disappearing polymorphs [9]. There are many documented tales of difficulties in obtaining crystals of a particular known form or in reproducing results from another laboratory, or even ones own. There are cases where it was difficult to obtain a given polymorphic form even though this had previously been obtained routinely over long time periods. This phenomenon also suggests a loss of control over the crystallization process, so widely used by chemists for the purification of materials. The reasons for the sudden appearance of a new crystal modification are not always clear, even after the fact, but its presence may make the production of the previously obtained form particularly difficult, or apparently impossible. However, once a particular polymorph has been obtained it should always be possible to obtain it again; it is only a matter of finding the right experimental conditions.

Both concomitant and disappearing polymorphs depend on those experimental conditions governing the crystallization process. Two of the fundamental ones (but certainly not the only ones) are the thermodynamics and kinetics of crystallization. An understanding of the competing thermodynamic and kinetic factors governing the crystallization of polymorphs in general, or of a particular substance in particular helps to facilitate the control over the production of the desired polymorph, at the exclusion of undesired ones. Such control has important implications in a variety of industrial applications, of which pharmaceutical production and formulation is but one important example. This next section deals with the essentials of the thermodynamics involved; more detailed accounts may be found elsewhere [10-15]. The following section deals with kinetic factors.