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Analysis of Organic Polymorphs
A Review

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Summary of Contents

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Introduction and Definition of Polymorphism

Polymorphism[1–7] in the chemical sense of the word* is a phenomenon of the solid state, associated with the structure of the solid. It has proved difficult to define precisely although the basic concept is readily understood. The definitions which have been offered vary in breadth but the implication of all of them is that polymorphs involve different packings of the same molecules in the solid.[4] The question of how similar the same molecules must be and of how dissimilar the different packing arrangements must be in order to qualify as polymorphs is more than a matter of semantics but goes to the root of our understanding of the organic molecular solid state.

McCrone has defined a polymorph as 'a solid crystalline phase of a given compound resulting from the possibility of at least two crystalline arrangements of the molecules of that compound in the solid state' and has listed those types of solid phenomena which are excluded from this definition.[1] Later writers who have accepted this definition have tended to substitute their own list of exclusions,[5] if they have addressed the matter at all. Buerger's tentative definition[3] 'ideally, two polymorphs are different forms of the same chemical compound which have distinctive properties' is broader and appears not to accept the need for separate phases and to include amorphous forms. The nature of the amorphous state[8,9] will be discussed later.

Polytypism[10] is one-dimensional polymorphism, referring to different stacking of the same layers. It is most familiar in inorganic systems, particularly silicon carbide, but has been recognized in organic crystals, both as ordered[11–13] and as disordered stacking.[14] There is no special term for two-dimensional polymorphism, although some liquid crystal systems display it. Liquid crystals are notorious for their ability to exist in different phases both in the mesomorphic and in the solid state[15–17] and this has led to the suggestion that the term polymorphism should apply to liquids as well as solids,[18] but it is only the solid dimensions of liquid crystals which can adopt distinct packing arrangements. Liquid-crystal polymorphism will not be dealt with specifically in this review except where it is related to the polymorphism of solids. The long standing question[19] of whether allotropy and polymorphism are distinct[20] is not an issue in the case of organic compounds. Inorganic polymorphs have been excluded because the extended structures of which most inorganic crystals are composed raise concepts not discussed here.[21,22] Protein polymorphism usually refers to minor molecular sequence changes[23,24] rather than to packing, but different crystal packing of protein molecules is also known.[25] Polymorphism of thin films[26,27] and polymers, both of biological[28,29] and of synthetic[30] origin, although of the same nature as the concept of polymorphism considered here, will not be discussed.

There is a profusion of words in the English language for the phenomena discussed in this review, yet not enough because of the overlapping usage. 'Polymorph' (dimorph, trimorph) 'form' and 'modification' are all used to describe polymorphic phases, but 'form' and 'modification' are also used in reference to crystal habit. 'Polymorph' and 'form' have been used to describe solvates, whilst 'pseudopolymorph' doubles for both solvates and for those solids which are otherwise not considered true polymorphic forms. The term 'pseudopolymorphic solvate' applied to crystals losing solvent molecules without change of crystalline form offers yet another source of confusion in terminology. Genetic polymorphism which is now the major use of the term is often described as 'polymorphisms' but this is occasionally seen also in chemical senses. In view of the almost universal use of 'polymorphic' as the appropriate adjective, the word 'polymorphous' seems superfluous despite dictionary support. There is an urgent need for consistent usages so as to be able to delineate the phenomena under consideration.

There is no clear choice as to the best method of designating polymorphs. Arbitrary systems are to be discouraged, but numbering based either on order of melting point or of room temperature stability have been recommended. Both are susceptible to change as a result of later identification of new polymorphic forms. Numbering based on order of discovery is unchangeable, but requires a knowledge of the history of the compound. The addition of the crystal class, as has been suggested for minerals[31] is not very practicable, since crystallographic classes are rarely determined from optical microscopic or X-ray powder diffraction studies for organic compounds. The assignment of a space group is even less realistic.

* An on-line search of Chemical Abstracts will reveal more than 47000 entries under 'polymorphism'. Over 90% of these relate to genetic polymorphism, which at least in its origins can claim the true etymology of the word. Some selectivity between biological and chemical uses can be achieved, but there is no certain searching strategy. Searching under 'phase transition' and related concepts will generate a further 44000 entries, most of which refer to inorganic systems, and cannot be easily disentangled. Nevertheless, these represent only a proportion of the papers containing information on polymorphs and polymorphism. Hence it is not possible to state how many publications relate to those aspects of polymorphism described here.

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In any case the distribution of organic molecules amongst crystal classes and space groups is extremely limited, as is discussed later.[32,33] The addition of a melting or upper transition point to a Roman numeral is probably the best compromise,[1] although care must be taken to distinguish the melting point of the polymorph and that of the transformed product.

Significance of Polymorphism

The continuing investigation of polymorphism by the Innsbruck school (Kofler, Kuhnert–Brandstätter, Burger) over more than half a century has shown that around one-third of organic substances show crystalline polymorphism under normal pressure conditions.[34,35] A further third are capable of forming hydrates and other solvates.

Much of the literature on the polymorphism of organic compounds relates to pharmaceutical products.[1,36–40] The incentive for this interest in polymorphism began with the need to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new chemical entities.[36,37] Of the several contributory factors to the bioavailability of finished products, the inherent solubility and rate of dissolution of the drug substance itself are of major importance. The solubility is dependent on the polymorphic state, as different polymorphs have different energies and therefore different solubilities.[40] It has been pointed out, particularly by Burger,[36] that the difference in solubility between polymorphs is likely to result in significant bioavailability differences, in practice, only in exceptional cases. Although some may think that this represents an extreme view, the consequences of polymorphism on bioavailability are commonly overstated. Chloramphenicol palmitate, over which the original concerns were voiced,[41] is unique in that the solubility is related to the rate of enzymic attack on the solid.[42] This and novobiocin,[43] which involves consideration of the amorphous state, are among the handful of examples of marketed products showing major bioavailability differences as a result of polymorphism.

As formulations have become more sophisticated and as the tolerances on products have become tighter, the need to identify polymorphic behaviour at an early stage of development has become important in the pharmaceutical industry as a means of ensuring reliable and robust processes[44] and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tabletting problems and subsequent tablet failure,[45,46] crystal growth in suspensions[47,48] and resultant caking, precipitation from solutions and problems with suppositories,[49] as well as chemical production problems such as filtrability[1] and to ensure analytical reproducibility. By extension such considerations relate to the control of quality in manufacture and product reliability in any industry by ensuring that the processes are well understood and under control so that unpleasant surprises do not occur.[50] This point is most dramatically illustrated in the explosives industry, where the wrong polymorph can have greatly increased sensitivity to detonation.[51,52] Pigment colour and solubility are polymorph dependent,[53–59] as are photographic and photolithographic sensitizers.[60] The performance of industrial products, particularly those based on natural fats and waxes[61,62] and derived soaps,[63] and on petroleum products[64,65] is in many cases related to polymorphic composition and degree of crystallinity. The same is true of the processing, acceptability and deterioration of foods and confectionery containing fats,[66,67] sugars,[68–72] polysaccharides[73] and other constituents.[74–75] A comprehensive summary of the solid-state properties of lipids has recently appeared.[76]

It is also worth establishing the polymorphic behaviour of a compound for the sake of good order in documentation so that reference works, for example, pharmacopoeias, do not contain conflicting data[34,77] such as a spectrum of one polymorph, but the melting point of another.

A major incentive to the study of polymorphism in the pharmaceutical industry during development has become strikingly apparent recently in the use of subsidiary patents on desirable polymorphic forms[78] to prolong the patent life of major products. Much recent pharmaceutical patent litigation has concerned polymorphs and particular interest has been taken in Glaxo's patent on the polymorph of ranitidine[79] (Zantac) which if held valid will extend the patent protection from 1995 to 2002 in many countries.[80] For a compound with annual sales of over 2 400 million pounds sterling,[81] the financial incentives to investigate polymorphs are obvious.

Finally, the very existence of polymorphism tells us something about the solid-state. Investigation of polymorphic systems, especially those with a large number of forms can help in understanding solid-state and molecular behaviour and intermolecular interactions[82] and the relationship between crystal structure, crystal growth and crystal habit[83] and their influence on bulk properties. Apart from knowledge for its own sake, this is of clear application in the development of organic electronic[84,85] and other specialty products[86–88] and in understanding the function of biological membranes.[89]

Distinction From Related Phenomena

At one time polymorphism was regarded only as different arrangements of rigid molecules in the solid state.[90,91*] A clear dichotomy existed between this and arrangements of molecules in different forms, such as could be imagined would occur with isomeric, tautomeric, zwitterionic and chiral structures and later with different conformers.[92] The early crystallographic studies on rigid aromatic molecules tended to reinforce the distinction. This simple division could only be maintained whilst details of the rich variety of solid-state structures were inaccessible. The early examples of dynamic isomerism and tautomerism were few[93,94] and the proposition that they could not be part of polymorphism was copied by reviewers until even the examples were forgotten.[95] A quoted example of a tautomeric solid-state structure, that of 3,5-dichloro-2,6-dihydroxy dimethyl terephthalic acid was shown in 1972 not to be tautomeric, but to involve conformational change with hydrogen bonding differences.[96] One would have expected examples of tautomerically related solid structures to be exceedingly numerous, since the molecular energetic requirements can easily be fulfilled as is shown by the widespread occurrence of tautomerism in solution.[97] Tautomeric polymorphism is surprisingly rare, but a well investigated example is now known, that of 2-amino-3-hydroxy-6-phenylazopyridine.[98]

There are a few papers in the literature either where tautomeric polymorphism is invoked[99–105] or where examination of the IR spectra is suggestive of forms whose difference resides in transfer of hydrogen between one part of the molecule and another.[106] The instances of 1,3-cyclohexadienone and squaric acid (3,4-dihydroxy-3-cyclobutene-1,2-dione are more difficult to place unambiguously in the category of tautomeric polymorphism. Proton transfer between donor and acceptor oxygen sites results in little change in over-all structure.[107]

Both tautomeric equilibrium and the neutral $\longleftrightarrow$ zwitterionic equilibrium formally involve such an intramolecular hydrogen transfer. The nominal difference is that a charge separation is produced in zwitterions which cannot be extinguished intramolecularly by a double-bond rearrangement cascade. The difference may be even smaller in practice because charge stabilization of zwitterions can occur intermolecularly, for example, in solution through solvation, whilst tautomeric structures can retain a substantial part of their charge as shown by dipole moment and IR spectroscopic studies.[108,109] Anthra-

* Earlier literature can be accessed *via* references 1, 2 and 10.

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nilic acid exists as two metastable forms containing only uncharged molecules and a form stable at room temperature, half the molecules of which have been shown from crystallographic studies to be zwitterionic and half uncharged.[110] A related phenomenon is the changing of allegiance of hydrogen-bonded hydrogens between electron donor atoms, which is a prolific source of polymorphism.[111] The role of hydrogen-bonding networks in determining crystal structure has been discussed extensively.[112] Conformational differences between molecules of different structures have been admitted, perhaps reluctantly, and distinguished by the title conformational polymorphism.[113] The original examples form one extremity where molecules in distinctive conformations pack similarly,[92] but it is now obvious from the plethora of crystal structures, as could always have been deduced from elementary considerations of energy minimization, that any change of packing will cause geometrical change in molecules and conversely that any change in geometry will invite different packing of the molecules.[82] The extent will depend on the rigidity of the molecules. Although some floppy ring systems maintain their shape in different forms[114,115] even nominally rigid structures such as the ring systems of steroids[116] can show substantially different conformations in different polymorphs. Heteroaromatic[117–121*] and benzoquinone[122] planes are frequently bent and even benzene rings[123] may be. Thus it seems pragmatic to accept conformational polymorphism as a normal sub-set of polymorphism and the term will only be used here when it is necessary to distinguish cases of substantial conformational change.

The distinction between polymorphism and chirality is made in most accounts of polymorphism; yet it has recently been pointed out that if conformational polymorphism is accepted, then racemates and conglomerates of rapidly interconverting chiral systems are in fact polymorphs.[5] Such systems are generally ones with an easy conformational change where the trivial distinguishing feature from other conformational polymorphism is that the result of such a change is a reflection of an asymmetrical structure across a mirror plane. Although this seems difficult to accept, the dextrorotatory and laevorotatory forms of such systems are then equally polymorphs.[124] The narrow line of demarkation between polymorphism, conformational polymorphism and chirality first seems to have been recognized by Eistert *et al.*.[125] Examples of rapidly interchanging enantiomers in solution capable of independent existence in the solid state are known[126,127] but uncommon.

A further extension of the concept of conformational polymorphism is to be found where there is rapid interconversion between isomers.[128] As in the chiral examples, one molecular species or the other becomes exclusively incorporated in the crystal because the mechanism of crystal growth acts as such an exquisitely discriminatory process.[129]

Since a hydrate and an anhydrous form are constitutionally distinct, they cannot bear a strictly polymorphic relationship on the basis of any definition. However, the observation of material of different melting point or other properties during recrystallization may be due (apart from chemical reaction with solvent or decomposition) to solvation or polymorphism and the methods of examination are similar in either case. Hence the term 'pseudopolymorphism' has become common[130] particularly in the pharmaceutical industry. The term seems unnecessary and could lead to confusion[131] with its use to describe all other phenomena related to polymorphism[1] and so will not be used here. It must be emphasized, however, that the distinction between solvates and polymorphs is not as clear-cut as might be imagined, either conceptually or practically.

* In the case of phenothiazines[121] the point of interest is not that the ring system is bent, but that the heteroatoms are out of the plane of the aromatic rings and in the opposite sense to expectation.

The traditional narrow view of polymorphism, rigidly excluding chirality and isomerism, has caused considerable difficulty[128] to the investigators of the systems described above and it is suggested that the way to avoid these problems is to adopt the gloss originally proposed by McCrone and co-workers[1,37] on his definition of polymorphism, namely that the criterion is that the component molecules must have the same structure in solution irrespective of the polymorph from which they were derived; but, as has been suggested by Dunitz,[5] without excluding tautomerism, isomerism or conformers *per se*. Thus, rapidly interconverting species would be accepted, whilst slowly interconverting species would be excluded, as was surely within the original contemplation. Despite appearances, this proposal is likely to multiply examples of polymorphism very little and it avoids what otherwise must be artificial situations of accepting phases as polymorphs based on impeccable polymorph behaviour until their crystal structure reveals excluded molecular forms.[98,110,132] If, as asserted, the transition between polymorph I and polymorph II of 1,3-cyclohexadiene occurs by transfer of hydrogen from one oxygen to another, then this is nominally an example of tautomeric polymorphism.[107] If, on the other hand, the same change occurs or can be made to occur by a movement of the whole molecule then it is an example of regular polymorphism. The boundaries between the various alternative solid structural concepts are too subtle and too vague to be used to define polymorphism.

Although the requirement of the same structure in solution has been canvassed above, one-component phase diagrams are constructed on the basis of equilibrium with vapour, rather than liquid. It is just in the instance of conformational, configurational or hydrogen mobility that molecular differences between vapour,[133,134] melt, solution[126,135] and solid are found. The mobilities are inevitably of different magnitudes in different states. We shall be increasingly obliged to decide where to draw the boundaries of polymorphism as more comparative studies involving polymorphs and molecular structure in different states are undertaken.

One negative consequence of accepting the wider view of polymorphism should be noted, namely that the thermodynamic relationships discussed later are likely to be less certain for the wider polymorphic family.[90]

Stability of Polymorphs

Polymorphs, or strictly dimorphs where only two forms are under consideration, may be in an enantiotropic or monotropic relationship.[19,136] An enantiotropic relationship implies that each form has a range of temperature over which it is stable with respect to the other and a transition point at which the forms are equistable and in principle interconvertible.[137] Above that temperature the thermodynamic tendency is to the formation exclusively of the form stable at the higher temperature. Below the transition temperature the low- temperature form is the only stable one with respect to the other, although there is usually a greater tendency for the high temperature form to become frozen-in than for a low- temperature form to persist beyond its stability range.[8] Forms outside their range of stability are described here as metastable[138]. In the case of a monotropic relationship one form is metastable with respect to another at all temperatures. There is no observable transition point, although the thermodynamic description implies a theoretical transition point above the melting point which is therefore unattainable.[139] The use of the terms enantiotropic or monotropic in reference to a phase, as opposed to a transition, is ambiguous and likely to lead to confusion, since a polymorph can have a monotropic relationship to a second polymorph, but be enantiotropic in relation to a third polymorph. Flufenamic acid provides such an example.[140] The distinction between thermodynamic and kinetic transition points also needs to be drawn.[141]

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Polymorphs only exist in the solid state: melting or dissolution destroys any distinctions. It is therefore important in examining polymorphs analytically not to submit them to conditions under which they melt, dissolve or are rendered more likely to interconvert. Heating and grinding[142–144] are obviously potentially hazardous operations in this context, but often cannot be avoided. The presence of solvent, even one in which the substance appears insoluble, will speed up the interconversion.[145] Trace moisture, acid or alkali on vessels can be similarly effective in interconverting polymorphs or in catalysing competing and confusing phenomena such as ring-opening reactions, for example, in 3,5-dihydroxy-3-methylvaleric acid derivatives,[146], or group transfer reactions.[147]

It might be supposed that a transition during grinding would always be from less stable polymorph to the polymorph more stable at that temperature, but in our experience, as well as from the literature,[145] this is not always true, presumably because the transformation takes place at a local temperature generated by the grinding and the unstable form becomes frozen-in by rapid cooling outside the immediate area of grinding.[148] This can only occur in cases in which the transition temperature does not lie too far above ambient. There may be alternative explanations, namely interconversion *via* amorphization or that a less stable polymorph may become the more stable one when in the form of small crystallites, as a result of surface effects. The latter phenomenon has been observed and investigated theoretically in the case of phthalocyanine pigments.[149] The possibility of growing unstable forms in microdrop conditions has been known for some time,[34] but recently the value of emulsions for this purpose has been suggested.[150] Although it would be desirable to have more compelling evidence than that obtained by differential scanning calorimetry (DSC) alone to establish the relationship between forms grown in this way, it does appear that new forms can be produced as well as metastable ones which are otherwise only accessible *via* the melt. The product of a polymorphic transition can also depend on particle size.[151,152]

Mnyukh and Petropavlov, in extensive studies of the transformation of individual crystals, observed that strict orientation of axes between mother and daughter phases was not preserved upon transformation.[153] They have concluded that only reconstructive transitions, *i.e.*, those involving the growth of new crystals in place of the old, take place for organic compounds. Even rapid transitions, described as atypical, were observed to follow the same patterns. No displacive (martensitic, co-operative) mechanism involving concerted structural change is therefore possible for organic compounds in Mnyukh's scheme. Whilst it would now appear that the reconstructive mechanism is the usual one, there are many examples involving preservation of axial orientation at phase transitions[4] some of which appear to be topotactic rather than only epitaxial.[154–157].

Irrespective of the mechanism and the rate of conversion at the point of transition, the stability in practice of a metastable polymorph at room temperature varies enormously,[158] from examples where the transformation is so rapid that the only evidence of the transient existence of a polymorph is its pseudomorphic outline,[1] to those which can be kept indefinitely and indeed refuse to transform in the absence of heat, high humidity or solvents.[152] The majority of systems are in fact quite robust to handling. It may therefore be thought that some of the present work presents over-concern with the possibility of transforming polymorphs during analytical examination. However, the modifications of some compounds show extraordinary sensitivity to handling in so many different ways. For example, with octakisphenylthionaphthalene, pressure on a cover-slip causes the yellow form to change to red;[159] with ethylenediamine hydrochloride, mere contact with KBr is stated to cause transformation;[160] with D,l-pantolactone 2,4-dihydroxy-3,3-dimethylbutyric acid γ-lactone, absorption of IR radiation in the spectrometer is sufficient for transformation;[161] and with meprobamate, high humidity may rapidly transform an otherwise indefinitely stable polymorph.[162] The problem is that this sensitivity may not be apparent until after the measurements have been made and then only if the analyst is alert, so that it is not possible to be too careful at the outset. Three of the commonest methods, IR spectroscopy, X-ray powder diffraction and differential scanning microscopy are unreliable for comparison of identity unless the sample is examined as a fine powder, but grinding can mislead into belief of identity if it induces transformation. This is why optical microscopy is so valuable for the initial examination. On the other hand, where transformation is sluggish, solubility determinations will be of more value than instrumental measurements for establishing the stability relationships.[34]

The existence of enantiotropically related polymorphs is indicative of the fact that the relative stabilities and therefore the Gibbs energies of the forms are very similar.[163,164] For this reason the empirical forecasting of polymorphism of a given compound is unlikely to be reliable.[88,165] Despite this, groups of compounds such as sulfonamides, barbiturates and steroids are known to be extraordinarily susceptible to polymorph formation.[39] Around 70% of these are now known to be polymorphic. Other examples include theophylline derivatives,[35] coumarins,[87] alkanes,[64,65] fatty acids and their derivatives[61,62] molecules which form liquid crystals,[15–17] and molecules which pack badly.[166] With the advent of molecular modelling techniques for crystal growth prediction, interest has been generated in the computer prediction of polymorphism.[87] The task is difficult because of the lacunae in our understanding of polymorph structure.

Methods for the Examination of Polymorphs

Polymorphs can be sought deliberately by cooling or quenching of melts, by condensation of vapour, or by crystallization under different conditions, although they are often encountered by chance. In the process of crystallization from solution, the expected effect of crystallization temperature may be overshadowed by other factors, particularly deliberate or adventitious seeds.[167] The importance of crystallization control during process development and the attitudes when unexpected polymorphic forms are encountered has been described by Bavin:[42] 'the process of crystallization is taken for granted by most chemists and it takes a reaction vessel clogged with an unstirrable mass to provoke serious thought'.

All the solid-state properties of the different polymorphic modifications of a compound will be different, but often only marginally so, to the point of instrumental indistinguishability. For this reason, it is important to look at potentially polymorphic systems by a variety of techniques to avoid erroneous conclusions. Failure to recognize a polymorph is the more obvious situation but it is also possible to identify polymorphs where none exist, if reliance is placed on too few techniques.[168] Substances with multiple forms can require substantial effort for their complete elucidation, especially when previous studies have characterized the forms inadequately.[142,148,151,169,170]

The techniques which have been available for a long time for the examination of polymorphs include those listed in Table 1. Which are the commonest methods depends to some extent on the area of interest, but in industrial practice, microscopy, IR spectroscopy, DSC, X-ray powder diffraction, solubility and density measurements have been the most widely used techniques. Within the past decade several new techniques and instrumental accessories have become widely available. These ease the manipulation of polymorphs and so lessen the danger of interconversion, or enable new properties to be investigated and allow measurements to be made which would have formerly

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been impossible on the specimen under examination because of its size or microcrystallinity, for example. These developments are listed in Table 2. In general, the application of these newer techniques to polymorphism has not been adequately reviewed. Much of this article will therefore be devoted to a description of these methods in relation to examples taken from the literature on polymorphism. Some attention will also be devoted to aspects of the traditional techniques which have been given surprisingly little coverage in the reviews. Apart fom the techniques discussed below, there have of course been many other methods applied to particular aspects of polymorphism and solid–solid phase transitions. Examples include scanning tunnelling microscopy,[64] electron diffraction,[53] atomic force microscopy,[171] crystal etching,[172] electron microscopy[64,173] and thermobarometric measurements.[174]

The analytical strategy in approaching a polymorphism study will be dictated by the availability of instrumentation, time and material. At the beginning of a study, the fact that minimal quantities of a compound are required by IR spectroscopy, DSC and, particularly microscopy can be a significant consideration. Since thousands of compounds are put into pre-development in the pharmaceutical industry for each successful marketed product[175]* the cost of extensive investigation of polymorphism also needs to be borne in mind.

Microscopy

Although a theme of this review is that no one technique should be used in isolation, hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.[1] In the hands of experts, surprisingly comprehensive accounts of polymeric behaviour have been generated from microscopy alone,[37,39,140,176] but it is a technique which requires experience for rapid study and the drawing of confident conclusions. A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage[177–179] will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, the generation of stable and unstable polymorphs and the recording of their optical properties.[140,180,181] The identification of solvates and the observation of sublimates and of any tendency to decompose are added information.[175] This can be carried out with minute amounts of material. The field has been excellently and comprehensively reviewed in the past,[1,37–39,178,179] and for that reason only the developments since then will be considered in detail here. The basic hot-stage methods have changed little in the intervening years, although there have been considerable improvements in the design of microscopes in terms of greater stability, versatility, ease of use and optical excellence. The availability of phase[182,183] and differential interference contrast (Nomarski) methods[184] and of interference microscopy has enabled precise refractive indices to be more readily determined.[185]

Several designs of hot-stage have been developed and are commercially available. Unfortunately, convenience is often sacrificed to temperature precision and many are unsatisfactory in maintaining temperature control whilst allowing for the manipulation of the specimen since the housings restrict access to the specimen. In fact in some designs, access cannot be gained at all whilst the stage is in position on the microscope. Recourse to a more open design, such as the Kofler stage, a graduated hot-stage[186–188] or a purpose-built heated microscope slide[189] will be necessary for such a requirement. The simplest rotating needle stages[177,185] are similarly more useful in practice than four-axis or five-axis Federov stages, because of the open access.

Although the determination of refractive indices and optic axis angles on birefringent specimens is time-consuming,[190] these optical measurements are critically distinctive of phases[140] especially when variation methods can be justified,[177,191,192] and such measurements ought to be more widely considered when doubt remains as to whether different specimens represent different phases. Such doubt is of more frequent occurrence than is ever suggested in the literature. This is owing, at least partly, to our inadequate understanding of the molecular solid state, and the relationship of that state to its properties. X-ray crystallographic studies have shown that hot-stage microscopic investigations have tended to overestimate the number of polymorphs,[193] presumably because crystal habits have been judged as modifications and because samples of different melting or transition points have been assumed necessarily to represent distinct forms. In fairness to the early investigators it is by no means clear how samples of the same polymorph, for example, can have the same unit cell yet melt 19 °C apart where purity considerations can be excluded.[146] Crystal strain which has been invoked in other,[179] less extreme cases, seems to be a rationalization rather than an explanation.

A major advance in microscopy for the analyst confronted with potential polymorphism has been the availability of video recording.[5] A change in a specimen or perhaps only in a few crystals of the specimen under examination is often only noticed after it has occurred. The ability to replay the video and re-observe the changes, perhaps in slow motion and to compare the timing of the changes in different crystals of the specimen can be exceedingly useful in making judgements of whether sample

Table 1 Techniques which have been available for many years for the examination of polymorphs

Hot-stage microscopy
Thermal methods—
DTA
DSC
Thermogravimetric analysis
Solution calorimetry
Infrared spectroscopy
Solubility measurements
Density measurements—
Flotation
Pyknometry
Dilatometry
X-ray powder diffraction
X-ray single-crystal diffraction

Table 2 Techniques of particular value for the examination of polymorphs which have become readily or more widely available within the past decade

Solid-state NMR
Diffuse-reflectance IR spectroscopy
Near-IR spectroscopy
Raman spectroscopy
Area detectors on diffractometers
Combined techniques including—
Hot-stage IR spectroscopy
IR microscopy
Video recording on the microscope

* According to Lumley and Walker[172] '5000–10000 candidate substances have to be synthesized and screened for every one new medicine that reaches the market'.

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homogeneity is in question, in determining transition temperatures or temperature ranges, in recording events in systems displaying irreproducible, erratic behaviour and in sorting out sequential but nearly concurrent events that sometimes occur. For example, a melting followed by resolidification of the low-temperature form will often accompany the transition without melting,[194], individual crystals or crystal domains within the field of view behaving independently.[110,122] A particularly valuable use is in distinguishing the movement of boundaries between domains or phases[178,195] and so distinguishing polymorphic changes from related behaviour such as crystal strain effects.[179]

A more elaborate arrangement has been described[196] in which a differential scanning calorimeter and a hot-stage microscope are linked through video recording. Commercial hot-stages with associated thermal sensors are also available which enable the optical changes and the associated changes in thermal properties to be examined simultaneously. There is a compromise[197] between optical and thermal excellence, versatility and convenience so that it is best regarded as a supplement for a microscope plus a calorimeter rather than a substitute. Close transitions or meltings are better resolved by microscopy than by DSC.[198] There are transitions which are seen by microscopy and not by DSC[106,199] and *vice versa*. The different behaviour of ethyl morpholine HCl·2H_2O under the microscope and in DSC is particularly striking.[200] Thermomicrophotometry has been recommended and shown to be effective in detecting phase transitions that were not detected either by microscopy or DSC.[201]

A triple system of DSC–microscopy–microphotometry has also been described.[202] The combination of microscopes with other instruments is discussed in the following sections.

Infrared Spectroscopy

The first intimation of polymorphism not previously noticed as a melting point discrepancy or sought deliberately by hot-stage microscopy is often from inconsistencies in solid-state IR spectra. Infrared spectroscopy has had, of course, enormous exposure in the literature through books,[203] reviews[204] and papers but there are surprisingly few descriptions of the precautions to be taken when recording or interpreting the IR spectra of polymorphs. For example, in the case of non-matching spectra, a wide variety of causes might be suspected, including mis-labelling of a homologue,[205*] sample purity, crystal size,[206,207] crystal habit and orientation,[208,209] instability to comminution,[210] formation or partial decomposition of a salt,[211] solubility in the mulling medium, hydration,[212] dehydration[213] or other solvent loss under vacuum, level of impurities in the mulling or disk medium and instrumental variables[214] including the inadequate elimination of background peaks. The latter can be more of a problem with the Fourier transform instruments now in almost universal use, because of the high (often unnecessarily high) resolution which can be achieved in routine use. Experience of the expected levels of instrument and sample reproducibility is the best prophylactic against the discovery of non-existent polymorphs or the disregard of actual polymorphs.

The choice of routine sample presentation methods now includes mulls[215–217], disks[215–219], diffuse reflection[220,221] and attenuated total reflection (ATR).[222,223] All present hazards particularly for amorphous forms and for crystals of limited stability. The running of solution spectra is, of course, excluded for distinguishing between polymorphs, but can be used to check the molecular identity and purity of the specimens and so distinguish polymorphism from solvation, isomerism and other phenomena. The key factor in determining the sample procedure is simply the stability of the polymorph to the chosen conditions. Disks or mulls are usually most appropriate for routine use, but diffuse reflectance spectra are particularly suited for preliminary examination because the preparation technique will minimize polymorphic interconversion in most cases. For particularly sensitive compounds, the choice between ATR, photoacoustic spectroscopy or microspectroscopy will probably be determined by the availability of the appropriate accessories. Interconversion depends on the nature of the compound as well as the vigour of the preparatory stages of the examination. It is desirable to establish the sensitivity of the forms to grinding at an early stage of the investigation, but it is rarely indicated in the literature that this is ever considered.

In general the preparation of a mull is less likely to produce polymorphic changes than that of a disk,[224,225] presumably because the heat of grinding is carried away more efficiently by a liquid than by a solid. However, Nujol itself can cause polymorphic change.[128,143] There is also the belief that the pressure itself during disk formation can bring about polymorphic transitions.[226,227] KCl and KI have been recommended in place of KBr for various reasons,[206,211] but KBr is now most commonly used. It is softer than KCl[228] and so safer for this reason. On the other hand, it is less neutral and so can cause salt formation. Ethylenediamine dihydrochloride is so sensitive to KBr that merely placing a Nujol mull in contact with a KBr disk causes transformation, as previously noted, although a KCl disk is inert in the same circumstances.[160] Different alkali halides have different refractive indices.[204,228] Although not often a problem with organic materials, mismatch of refractive index of medium and sample can cause distorted spectra due to the Christiansen filter effect,[229] which in extreme cases also produces an apparent band shift to lower frequencies. Sometimes, with strong bands, substantial shifts in the opposite direction result[204] a phenomenon which has never been satisfactorily explained. This reinforces the importance of always comparing spectra run under the same conditions.

The use of a grinding or dispersion promoter such as acetone for disk making is excluded, as polymorphic changes are catalysed by solvents.[145] This raises the caveat that non-polar polymorphic systems should not be examined as paraffin mulls.[128,143] In an extreme case, there is the possibility of observing the solution spectrum of the compound being mulled. The further problem with mulls is that they are less quantitatively reproducible and parts of the spectra are obscured owing to the bands of the mulling agent which makes comparison of spectral identity or differences more difficult.[230] For this reason, the use of alternative mulling agents such as hexachlorobutadiene or Fluorolube[98] may be attractive if only the high-frequency region of the spectrum is of interest. This is only likely to be the case for hydrogen-bonded molecules. The most pronounced band shifts are, however, often to be found below 800 cm^{-1} and into the far IR (FIR) region.[231,232]

In the diffuse reflectance (DRIFTS)[233,234] technique the substance to be examined is dispersed in a matrix of a powdered alkali halide and placed in a sample cup in the diffuse reflectance accessory. The sample is illuminated by a wide cone of radiation and the reflected radiation collected over a wide angle. The effects of multiple scatter and multiple reflection within the sample over a wide range of permutations of angles of incidence and reflection tend to reduce orientation effects accompanying insufficient grinding of needle or platey crystals. The observed spectrum results primarily from the transmission of radiation through crystals rather than from reflection from individual faces. Acceptable spectra of polymorphs can generally be obtained by this technique, with much gentler grinding than either for disks or for mulls. For this reason it is to be regarded as the presentation method of choice[146,226,234] for the initial examination of the IR spectra of polymorphs. KCl has

* The fact that a homologue and a polymorph can produce similar degrees of difference was first noted by Jones as quoted by Rosenkrantz and Zablow.[205]

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been recommended as the best diluent.[226] For quantitative work, it may be necessary to grind the sample thoroughly, but this may be avoidable for an initial examination. Care must be taken to ensure reproducible dispersion and packing of the sample in the sample cup.[235–237] The use of diffuse reflection is now becoming more commonly reported for the examination of polymorphic systems and the reader is referred to the literature[226,234] for details of the preparation of samples.

In ATR spectroscopy, also called frustrated total reflection or internal reflection spectroscopy, the evanescant wave that penetrates the low refractive index medium under total internal reflectance conditions at a high refractive index/low refractive index boundary is minutely absorbed. This is because the depth of penetration is only of the order of magnitude of the wavelength of the radiation or less. In practice IR radiation is directed through a thallium bromide iodide crystal which represents the high refractive index medium against which the sample is pressed. ATR spectroscopy is widely used for the examination of materials which present problems when examined by other methods. It is particularly valuable for samples which are strongly absorbing or which must be examined *in situ* or at least neat. ATR would thus appear at first sight to be the ideal way of obtaining the IR spectra of polymorphs[238-240] which is possibly why it has been preferred by some of the pharmacopoeias and authorities, for example, in Australia. In principle neither grinding nor any preparation other than possibly sprinkling the sample on to transparent sticky tape is required. However, ATR spectra are particularly susceptible to packing and crystal orientation problems. This, combined with the difficulty in obtaining sufficiently strong and acceptably reproducible spectra, without finely grinding the sample and pressing it to the face of the ATR crystal, makes the technique less attractive and it is rarely used in polymorphism studies. The potential presence of a dispersion component superimposed on the absorption component can also make the comparison of subtle differences less certain.[241] Nevertheless, if a sample proves susceptible to grinding, as in the case of phenylbutazone[239] or sulfathiazole,[242] ATR spectroscopy may be a valuable resort.

Sulfathiazole is one of the few substances in the literature for which spectra run as KBr disks,[243] Nujol mulls[169] and ATR[242] are displayed. The differences in scale make comparisons difficult. Therefore, in Fig. 1 a set of spectra of sulfathiazole polymorph III is displayed, to highlight typical differences. These are mostly in the background and in intensity variation; the position of bands, except those associated with hydrogen bonding, remain at the same wavelengths. Diffuse reflectance spectra of sulfathiazole forms are illustrated in Fig. 2 to give an idea of typical spectral differences between polymorphs. Comparison with spectra in the literature[169,242,243] reveal differences due, apart from the variation in sample presentation technique, to the possibility of interconversion during preparation for spectral examination and to the difficulty in producing pure polymorphs or even reproducible specimens. The spectra of III and IV show only minute differences. This is a consequence of the inherent similarity of the crystal structures and is reflected in the ease of conversion of IV to III. The largest spectral differences between polymorphs I and III are in the NH stretching region, reflecting the substantially different hydrogen bonding networks. Despite the curious appearance of the spectrum of polymorph II above 1700 cm^{-1}, all the features are genuine, but have become exaggerated because of the crystallinity of the sample. This illustrates the dilemma in examining polymorphs. Grinding would improve the appearance of the spectrum but at the risk of promoting a transition. The IR spectra of polymorph III shown[243] or implied[169] in the two most carefully conducted studies in the literature are those of an approximately (1 + 1) mixture of polymorphs III and IV, as are some samples of the commercial material. By near IR difference measurements (see below) the specimen of polymorph III used here was estimated to contain 8% of IV and the specimen of IV to contain 9% of III. The polymorphs of sulfathiazole must be

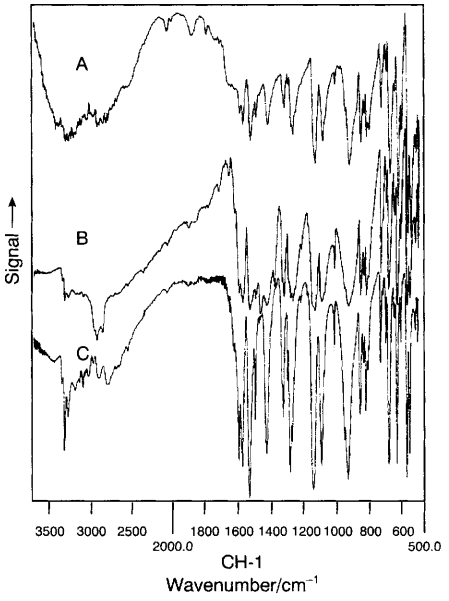

Fig. 1 The IR spectrum of polymorph III of sulfathiazole A, by attenuated total reflection; B, as a Nujol mull; and C, as a KBr disk, for comparison with the diffuse reflection spectrum, Fig. 2. Polymorph III is believed to be stable to grinding, hence any differences are due to orientation effects or to the optical differences inherent in the sample presentations. The intensity differences along the wavelength scale are due to the change in depth of radiation penetration.

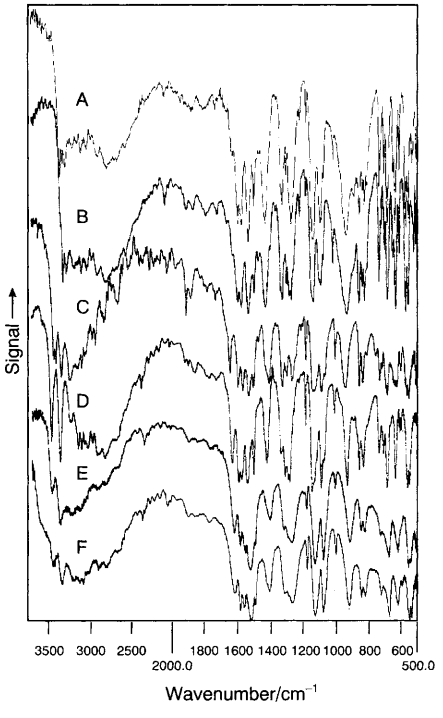

Fig. 2 Diffuse IR spectra of forms of sulfathiazole, admixed into a KBr matrix using minimal grinding. A, polymorph IV prepared inadvertantly; B, polymorph III, commercial sample; C, polymorph II by boiling an aqueous saturated solution to dryness; D, polymorph I by heating polymorph III above 175 °C; E, melt; and F, amorphous form produced by quenching the melt in liquid nitrogen. The spectrum of the melt (in a KBr matrix) is shown for comparison with the amorphous form.

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regarded as amongst the most difficult to make and keep as pure specimens, as the number of papers on this topic reflect.[243]

Photoacoustic spectroscopy (PAS) relies on the detection of the acoustic signals generated by the absorption of modulated radiation[244,245] and is therefore not subject to the blacking out effect that occurs when IR spectra of too strongly absorbing samples are recorded by any other technique. Hence spectra can be obtained from neat samples and as such it might be expected to have been more widely explored for polymorphic systems.[246] Control of particle size is, however, important in ensuring reproducibility.[247] PAS has been used to obtain IR spectra of 2*R*,4*S*-6-fluoro-2-methylspiro(chroman-4,4′-imidazoline)-2′,5-dione because the forms were too sensitive to grind.[248] Comparisons of DRIFTS and PAS have been made.[249–251]. There is a difference in the over-all intensity relationship with wavelength between these techniques and transmission methods related to the variation of depth of penetration with wavelength and this needs to be taken into account in comparing spectra obtained by the different methods.

Spectra at low temperatures are more highly resolved and so more characteristic than those at room temperature, owing to suppression of the thermal motion. Low temperature spectra have been recommended for the examination of antibiotics.[252] The relative ease of obtaining spectra at −196 °C has been stressed and the technique has been applied to polymorphic steroids to achieve greater resolution and distinguishability.[116]

The absorption of polarized radiation is dependent on molecular orientation and therefore potentially of value in examining packing modes of molecules,[253] but appears to have been little explored for enhancing the distinguishability of polymorphs. The transformation of polymorphs of fatty acids has, however, been recently investigated. Monoclinic phases of fatty acids pack in layers with oblique orientation of the hydrocarbon chains within a layer. An orthorhombic polytypic phase of both the B and the E forms is known, in which alternate layers have the contrary orientation.[254] Polarized IR spectroscopic studies have been used in establishing the relationship between the orientation of crystal axes in crystals undergoing transformation.[255]

Recording the IR spectra on thin films made by rapid cooling of melts between salt plates or pressed KBr disks is a valuable way of investigating polymorphic propensities.[256,257] Ostwald's principle[257] predicts that the form involving the least loss of Gibbs energy, that is, the modification least stable at low temperatures will be first formed on cooling and if it can be trapped by rapid cooling, it may be possible to follow a whole series of polymorphic changes with time and temperature by IR spectroscopic examination of the film. This can be achieved by warming the centre of the disk with a hot rod,[258] although it is more elegantly carried out on a hot-stage. This technique of making thin films can only be used for substances stable at moderate melting temperatures because of the possibility of fracture of the salt plates from thermal shock.[230]

Commercial heated stages for IR spectrometers have been available for some time, but have not always had sufficient temperature control or insulation to enable differential scanning calorimetric or hot-stage microscopic observations, for example, to be matched with the spectral changes. An alternative is to adapt a hot-stage to fit the IR cell compartment. The expectation of sharp changes in the spectrum at the transition points is not always borne out in practice,[259] because the degradation of the resolution and signal-to-noise ratio at high temperatures may obscure the small changes being sought. Thermal emissivity, convection currents and change in focus may be the main causes of the problem. Detailed studies have established generally the decrease in intensity of IR bands of condensed phases with temperature[260] and a sudden decrease at transition points for alkanes.[261] It is important to make allowances for these variations when comparing spectra taken at different temperatures, as may be necessary when the polymorphs interconvert readily and so cannot be examined outside their range of stability. To overcome these problems and render small changes more visible, it was advantageous to record difference spectra,[262] but now chemometric methods have been brought to bear.[263] Gu[264] has used Malinowski's criteria of number of components to determine the number of transitions and temperature of transition points for glycerides. Two-dimensional correlation plots applied to variable temperature DRIFTS have also been used to pair-up bands in the spectra and so identify the spectroscopic components of the different phases.[265] Partial least squares computation has also been used in conjunction with variable temperature DRIFTS.[234]

The most exciting development in the application of IR spectroscopy to the study of polymorphism has been that of the IR microscope.[208,253,266–269] Normally a single crystal or crystalline powder of sufficient area to fill the sample aperture of an IR spectrometer cannot be examined by transmission because of excessive absorption and can be examined only with difficulty by reflectance because of the mixture of diffuse and specular reflectance components. Although there are techniques and computer programs for the transformation based on the Kronig–Kramers relationship[241] (Hilbert transformation[270,271]) the residual uncertainties make the technique unsatisfactory for comparing subtly differing spectra. With an IR microscope, however, individual small crystals can be examined directly in transmission. The pigment naphthazarin (5,8-dihydroxy 1,4-naphthoquinone) has been examined in this way.[225] Thicker crystals can be examined by seeking thinner areas of acceptable absorptivity near the edges.[272] Apart from the virtue of minimizing polymorphic transformation and of allowing measurements to be made on minimum sample quantities, the difference in the spectra of individual crystals can be ascertained, since it is not unknown for a crystallization to produce a mixture of polymorphs.[85,199,273] Microphases can also be examined.[274] Naturally a great deal more time and manipulation is required for IR microscopy, so in the usual instance, in which sufficient sample is available, an IR macro spectrum would normally be taken first under standard conditions.

Despite all the potential problems, many of which have been discussed above, in most cases IR spectroscopy provides a simple and reliable tool for the investigation of polymorphism. The distinction between spectra of different phases is rarely large, although there are exceptions.[160,275–277] Small changes in peak positions, peak shapes, and absence or presence of a few bands may be all that can be distinguished. This may be enough to characterize a whole series of polymorphs, for example all nine polymorphs and solvates of phenobarbitone prepared by Mesley *et al.* were clearly distinguishable by IR spectroscopy.[151] On the other hand, IR spectra of polymorphs have been frequently reported as virtually identical.[116,160,277–281] In some instances such indistinguishability may be an artefact[282] of interconversion. Reports of identity or difference in IR spectra and in X-ray diffraction patterns in many publications are not borne out upon examination of the accompanying spectra or diffractograms where these have been reproduced at sufficient size to make an informed comparison.

A valuable application of IR spectra (and X-ray diffractograms) of polymorphs is as the basis of a patent claim.[78,80] The use of the NH and OH stretching band positions in establishing stability relationships in hydrogen bonded polymorphic systems is discussed in the section on solubility and density measurement.

Near IR (NIR) spectra due to overtone and combination bands[283] are less resolved than spectra in the fundamental region in the mid-IR. The multivariate methods which are routinely used in this region[284,285] minimize this disadvantage and enable small differences between spectra to be distinguished. The spectra are also much less intense, but provided

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that sufficient sample is available, this is an advantage, because saturation of the absorption will not occur and so neat samples can be used. NIR microscopy has also been tried[286] and should show the same advantages for polymorph investigation as IR microscopy. For the normal macro technique, the same problems of reproducible packing and effects of crystal size and orientation as discussed under diffuse reflection apply, but are reduced because of the larger illuminated area. The absence of diluent also removes three variables: the distribution of the analyte, the particle size of the carrier; and the bands due to the carrier or its impurities,[287] particularly moisture. The question of the particle size and reproducible packing discussed above for the mid-IR region are equally important here, although chemometric methods have been applied to try to minimize their effects.[288,289] Since the bands in the NIR region are due to OH, NH and CH stretching vibrations, it would be expected that the spectral changes would be most noticeable in hydrogen-bonded systems[290] and in conformational polymorphism. The published reports[291] are too few to confirm this, although the NIR spectra of many pharmaceutical polymorphs have been recorded. Therefore Fig. 3 shows the NIR spectra of a typical set of polymorphs of a substance, sulfathiazole, in which hydrogen-bonding networks play a significant role. Note that the differences in the spectra of polymorph III and polymorph IV, for example, are greater in the NIR region than in the mid-IR region, in line with the expectations expressed above. The technique is non-invasive, these spectra being obtained by placing a fibre optics probe on the outside of the glass tubes containing the samples. A further advantage of NIR spectra is the ease with which data manipulation, such as spectral differences, can be performed without generating unrealistic results.

Raman Spectroscopy

The Raman effect depends on the inelastic scattering, with loss of vibrational energy, of radiation in the near-UV, visible or NIR region of the spectrum.[292–294] It is inherently very weak and needs an intense, monochromatic excitation source and good filters to remove the excitation line from the collected radiation.[295]

Although commercial Raman spectrometers have been available for a long time, visible excitation sources tend to produce swamping fluorescence from many compounds.[296,297] Where this is due to impurities it may be possible to burn them out,[298] but otherwise the Raman spectrum is difficult or impossible to record against the background. In this case also there is a tendency to char the sample.[299]. There have been numerous mechanical[293] and electronic devices[299] proposed to minimize these effects, but they all have disadvantages. It is only since the advent of NIR Fourier transformation Raman (NIR–FT Raman) spectrometers using the Nd. YAG laser source at 1064 nm with efficient cut-off filters to remove Rayleigh scattering from the laser line,[300] that routine Raman spectra have become reliably available from most organic solids.[296] Although the spectra obtained are broadly similar to IR spectra, the difference in selection rules makes the information complementary.[294,301] Polar groups such as carbonyl and hydrogen-bonded hydroxy groups which are strongly apparent in the IR, are weak in Raman, whereas non-polar symmetrical or nearly symmetrical bonds such as carbon–carbon single and double bonds are strong in Raman.[292] Furthermore, the Raman effect, being a polarizability, falls off as the sixth power of the distance, whereas IR coupling, being a polarization, falls off only as the cube of the distance.[302] Therefore Raman spectra of molecular organic solids in the bond stretching and bending region would be expected to show little influence from neighbouring molecules. The effect is enhanced because the typical organic molecule consists of a non-polar backbone with polar groups on the periphery, so minimizing further the coupling of Raman active bands.

The effect of this is firstly that Raman spectra of solids tend to have narrower bands than IR spectra. In one polymorphic set that we examined, the typical bands in the IR in the 700–1500 cm^{-1} region had bandwidths at half height of about 15 cm^{-1}, whereas the equivalent Raman bandwidth was about 11 cm^{-1}. Secondly, IR spectra are influenced by neighbouring molecules both directly by hydrogen bonding[303,304] and indirectly by the above spatial distance effect. One would therefore expect that conformational polymorphism would show up more distinctly in Raman spectroscopy and that packing effects especially of hydrogen-bonded molecules would show up most clearly in the IR spectra. There is little in the literature to test this, but we have encountered examples which support this contention. For rigid, non-hydrogen bonded molecules, the largest differences would be expected to occur in the region of the low-frequency lattice modes.[231,232] Comparison of coincidences in IR and Raman bands of symmetrical molecules can lead directly to a decision between alternative structures. The possible centrosymmetric structures for polymorphs B and C of naphthazarin were eliminated in this way.[305] This study shows that the Raman spectra of even deeply coloured solids can be obtained with NIR–FT Raman spectroscopy.[306]

The chief advantage of Raman spectroscopy is that no sample manipulation is required[294] and therefore in the case of polymorphs which are, or are suspected to be, susceptible to transformation, the spectra can be obtained with complete certainty of the identity of the sample under examination. The multiple scattering taking place in powder samples[307] tends to eliminate orientation effects in the same way as occurs in DRIFTS. Because glass is transparent to the excitation and emitted radiation and gives no interfering bands, spectra can even be obtained without removal of the specimen from the sample tube. Consequently, Raman spectra of polymorphs are now actually easier to obtain than IR spectra and deserve to be more widely recorded than the handful of papers[169,233,308,309] in the literature would indicate.

A disadvantage of the NIR–FT Raman system is that commercial instruments do not allow spectra to be recorded to very low frequencies, so that the region where the greatest difference between polymorphs might be expected to be seen,[231,232,310,311] is inaccessible. As this region is also outside

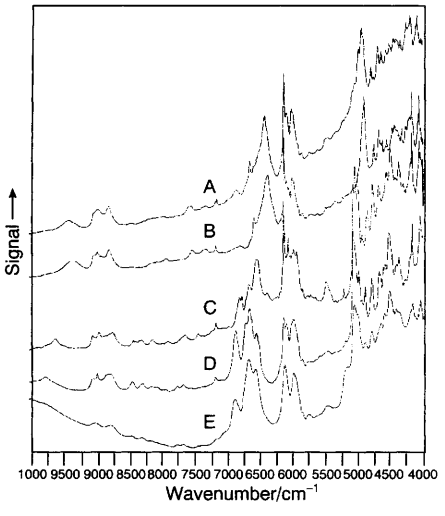

Fig. 3 Near IR spectra of sulfathiazole forms. A, Polymorph IV; B, polymorph III; C, polymorph II; D, polymorph I; and F, amorphous. The spectral differences appear larger than in the mid-IR region because NIR spectroscopy is insensitive to ring and chain modes and records only the XH modes, in this case particularly the NH stretchings.

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the range of most IR instruments, recourse must be made to conventional Raman spectrometers. As a result, there are few examples in the literature of the examination of organic polymorphs in this low-frequency region,[312–314] reflecting the difficulty of measurement.

Raman microscopy offers in principle even greater advantages than IR microscopy because the theoretical limit of resolution, related to the wavelength of the incident radiation, allows samples of an area less than 1 μm^2 to be examined.[296,297,315] The limit for IR is in the region of 50 μm^2 dependent on the wavelength range of interest.[316] However, in practice, the optical throughput due to the instrumental aperture characteristics, render it difficult to reach the theoretical limit of resolution with FT–NIR systems.[296,297] Conventional instrumentation with argon-ion laser sources at 488 nm, which can be used to examine smaller areas, produce the problems for organic compounds mentioned earlier of fluorescence and charring. The latter is particularly troublesome because of the high intensity at the focus of the beam. Even when charring is not observed, the possiblity of phase transition due to local heating needs to be taken into account.

Ultraviolet and Fluorescence Spectroscopy

Although electronic reflection spectroscopy has been rarely invoked for the examination of polymorphs, it has long been known that different polymorphs of coloured compounds[317–319] including certain dyes and pigments,[58,59] in particular, phthalocyanines,[149,320–323] display different hues. Bandshifts of up to 170 nm in the solid state as a result of packing differences of the molecules have been reported.[324–326] Furthermore, it is remarkable how many organic crystals deepen in colour on transformation to a higher melting polymorph,[98,122,155,159] so it must be presumed that many, probably most, uninvestigated colourless polymorphs would also show a spectral change in the UV region on transformation. The information that can be extracted from UV reflection is less than from the techniques whose spectral characteristics are more readily related to structure, and the measurements are more difficult. The electronic spectrum may, however, be recording more subtle solid-state changes. It has been recently ascertained that the yellow to red transformation of pyridinium picrate which has been known since 1929 does not occur at the temperature of the only transition point recorded by variable temperature X-ray diffraction studies.[327] The use of polarized near-normal UV spectral reflectance from different faces of single crystals has been applied to the conformational polymorphism of dichlorobenzylidene anilines to relate solution and crystal properties and to elucidate the relationship between molecular conformation and electronic properties.[4] The origin of these colour differences has been discussed only briefly, but must be presumed to be due to intermolecular charge-transfer effects.

Ultraviolet spectra of solids can also be obtained by transmission from the mull or KCl disk technique[328] (KCl is transparent to shorter wavelengths than KBr), provided that a thinner matrix is used and account is taken of the vast difference in molar absorption coefficients in the IR and UV regions. The UV spectra of polymorphs of 2(2-methyl-3-chloroanilino)nicotinic acid have been investigated by diffuse reflectance from Nujol mulls.[132]. A detailed comparison of the relative merits of photoacoustic spectroscopy and diffuse reflectance in the UV, visible and NIR regions has been made.[329]

The colour of cyanine dyes is related to the aggregated state in solution, concentrated solutions yielding the more deeply coloured solid-state forms containing the more extensive molecular aggregates.[330] The absorption spectra, the fluorescence spectra and the electronic properties of solid cyanines[331] display marked differences between the polymorphs. The fluorescence spectral differences in this and other cases[332] have been ascribed to a type of excimer formation. Fluorescence spectra have otherwise been little reported although they have been investigated for possible quantitative analysis of polymorph content.[333] Polymorphs may also differ in their thermoluminescent characteristics.[334,335]

Solid-state Nuclear Magnetic Resonance and Nuclear Quadrupole Resonance Spectroscopy

An NMR spectrum on a solid run under similar conditions to those used for solutions will result only in a broad hump of extremely low signal intensity. For the investigation of melting phenomena or of order–disorder transitions representing the onset of molecular rotation or libration this is advantageous: the phase yielding signals of moderate width as a result of orientational, positional or configurational freedom can be measured with little interference from the signals generated from the rigid solid phase.[336,337] For detailed observation and interpretation of the molecular structure, however, it is necessary to narrow the signals.[338,339]

The breadth and low sensitivity of the solid state signals in ^{13}C NMR spectroscopy is due to three separate effects, each of which must be minimized.[340–342] The lines are broadened firstly by anisotropic dipole–dipole coupling and the quadrupole field gradient. Secondly, the chemical field anisotropy which is normally averaged to zero in liquids cannot be averaged out by molecular tumbling in solids. Finally, the extremely long spin–lattice relaxation times require long pulse repetition times to build up the signal. The chemical field anisotropy can be averaged by magic-angle spinning (MAS) in which the sample is rotated at speeds of 4–15 kHz.[340–342] The dipolar and quadrupolar field effects can be removed by high-power heteronuclear decoupling. Finally, the spin–lattice relaxation time is reduced by cross-polarization involving pulse sequences which transfer energy between nuclei, thus involving the 1H nucleus in the mechanism of relaxation. The net result is that NMR spectra of solids are now routinely available of acceptable signal-to-noise ratio which show adequate resolution for structural interpretation,[343–345] although longer acquisition times than for solution spectra are necessary. The detail and information content of NMR spectra should be particularly valuable in distinguishing polymorphs and in understanding the sources of their differences.[64,313,342–345] The use of NMR spectra for examination of dosage forms has been canvassed.[345,346] In practice, relatively few descriptions of the NMR spectra of polymorphs are available in the literature and in several cases where phases which have proved to be very similar by other techniques have been examined, they have also proved to show few differences by NMR spectroscopy.[5,169,281,347] This illustrates that very small packing differences are sometimes characteristic of phases or polymorphs. The interpretation of the spectra in terms of molecular structure is normally by comparison with the solution spectrum, but the assignment of carbon type can be made in the solid state with the use of appropriate pulse-sequence techniques.[348] A promising use of solid-state NMR spectra is in investigating amorphous forms.[28,349,350] The amorphous form of testosterone was assumed to have ordered packing but disordered molecular orientation from examination of the features in the NMR spectrum associated with the different portions of the molecules.[116] Conclusions could therefore be drawn as to the probable mechanism of solidification. It is not clear why a solid with positional order but rotational freedom behaves as an amorphous phase rather than a disordered one. Solid-state NMR signals can sometimes be observed to be doubled as a result of non-equivalent crystallographic molecules in the unit cell.[116,340,351]

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Nuclear quadrupole resonance spectroscopy[352] (NQR) is not troubled by the broadening effects encountered by NMR spectroscopy and has been widely used particularly for the examination of inorganic systems. It relies on the detection of the electric quadrupolar effects and is confined to those nuclei with suitable spins. For organic compounds these are principally ^{2}H, ^{14}N, ^{17}O, ^{19}F, ^{35}Cl, ^{37}Cl, ^{79}Br and ^{81}Br. It is relatively insensitive so large quantities of material are required. Chlorine and bromine can be detected by conventional radiofrequency spectroscopy but ^{14}N, which is probably the most generally useful nucleus for organic compounds,[353] requires sensitivity enhancement. Cross-relaxation experiments, similar to the cross-polarization experiments discussed above, are appropriate. ^{2}H and ^{17}O studies require isotopic enrichment. All these nuclei have been used to study phase transitions, particularly in relation to mechanism and molecular dynamics.[354,355] The use of ^{17}O to study order–disorder phenomena is discussed later. Phase transitions are detected by changes in relaxation times, couplings or multiplicity with temperature. Malononitrile[356,357] is particularly interesting, because the change in multiplicity of the ^{14}N NQR signals at −132 and 22 °C heralds a new phase in between those temperatures, although the phase below the lower temperature appears to be the same as that above the higher one. It can be seen from Fig. 4 that the Gibbs energy values for the two polymorphs are constrained to follow very similar paths. As might be expected from this, the intermediate phase has a structure which is only marginally different from the surrounding phase.

X-ray Crystallography

X-rays are reflected from crystals only when the angle between the ray and the planes in the crystal fulfil the Bragg condition $n\lambda = 2a\sin\theta$, where θ is the angle between the ray and the plane, λ is the wavelength of the radiation, a is the interplanar spacing and n is an integer. There is an infinite number of possible planes through the crystal, but only a limited number which give reflections within the accessible range $2 < \theta/\text{degrees} < 180$. With a single-crystal brought into all orientations with respect to the beam, a series of spots is generated on the surface of a sphere centred on the crystal. In the case of a powder sample a set of concentric cones is generated which can be recorded as a series of arcs on a photographic strip or as a diffraction trace *via* a

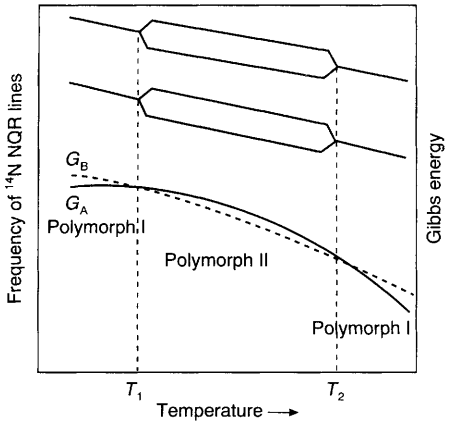

Fig. 4 Interpretation of the phase transitions of malononitrile in terms of Gibbs energy. The upper part of the diagram is a schematic representation of the variation of the ^{14}N NQR spectrum of malononitrile with temperature. T_1 and T_2 are the transition points at −132 and 22 °C, respectively. The lower part of the diagram represents the Gibbs energy situation. Instead of crossing once as in the enantiotropic system in Fig. 7, the Gibbs energy curves G_A and G_B (for polymorphs I and II, respectively) must cut twice (see text).

detector.[358] Every molecular repetition will give a unique set of reflections and so generate a unique pattern. Any change in crystal packing will lead to changes in the form of the molecular repetition. In principle, then, any polymorph will give a distinctive X-ray powder pattern. X-ray powder crystallography is therefore of great value for distinguishing and identifying polymorphs.[359]

X-ray single-crystal diffraction is, of course, even more descriptive and in principle can lead to unique definition of the packing of the molecule, the molecular interconnectivity and the three-dimensional conformation of the molecule in the crystal. However, it often proves difficult in practice to grow crystals of sufficient size and perfection for an X-ray structural analysis to be carried out whereas a powder pattern can nearly always be obtained.[73] The difficulties which may be encountered in growing crystals of the polymorph stable at room temperature are much magnified when unstable polymorphs and enantiomeric polymorphs are required and particularly when crystals of unstable polymorphs of enantiomers are involved.[248,360–363] The evidence for this packing prejudice against optically active molecules has been undermined by a detailed comparison of the density measurements recorded in the literature for racemates and enantiomers and a consideration of the statistical bias,[124] but it remains a matter of common observation during crystallization experiments that optical isomers are difficult to produce as good crystals.[364] The problems with metastable forms are easy to understand as owing to the presence of crystal strain and defects. Some crystals show such a large change in volume on transition that they generate enough strain to shatter or move violently and are therefore sometimes characterized[275,312,347,365–367] as 'jumping crystals'. Variable-temperature X-ray diffractometers[368,369] are helpful and, of course, essential for the examination of polymorphs which have no existence at room temperature but the required apparatus is infrequently available in laboratories where polymorphs are encountered. It is good practice to look at a sample under the polarizing microscope for homogeneity and for appearance of individual crystals as single and perfect, free from twinning or unusual features, before submission for single crystal X-ray examination. Occasionally, even the most beautiful and transparent crystals may be twisted, too thin to produce an adequate signal, multiply twinned, polycrystalline or otherwise defective and hence fail to give an interpretable diffraction pattern.[370] Even if the diffraction pattern is too poor for a complete structural analysis, the unit cell dimensions are a criterion for the existence of distinctive phases and the derived density a further critical reference value for the polymorph. Regrettably, crystallographers often fail to record minimum physical characteristics of specimens of polymorphs such as melting point, range of stability or relative stability[371,372] or even origin[373,374] thus limiting the usefulness of their results. For this reason it proved impossible, by examination of the Cambridge Structural Database (Cambridge Crystallographic Data Centre), to check the reliability of the rule that the polymorph stable at higher temperature has the more symmetrical structure. The structure of over a thousand pairs of organic polymorphs has been recorded, but only a small portion have adequate accompanying physical information. The theoretical basis of the rule has been described by Kitaigorodski[375] and Desiraju.[376] The total energy of a crystal is the sum of the lattice energy and the vibrational energy. Close packing minimizes the lattice energy but interferes with vibrational motion increasingly at higher temperatures. The loss of lattice energy stabilization in a more open lattice can be compensated by the entropy gain resulting from the more symmetrical structure. The close packing requirement means that the majority of organic crystal structures reside in very few space groups ($P2_1/c$, $P\bar{1}$, $C2/c$, $P2_1$, $P2_12_12_1$).[32,33] The combined effect of the vibrational and close packing requirements on organic polymorphs is that

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one of the commonest patterns for a dimorphic system on transition is monoclinic at low temperature to orthorhombic ($P2_12_12_1$) at higher temperatures. Higher symmetry space groups are adopted by disordered states.[275]. Plastic crystals generally adopt cubic space groups in the disordered phase,[8,377] reflecting the requirements for the molecular motions.

The development of area detectors for diffractometers for small molecule work means that crystals previously too small to examine can be successfully tackled, or areas of otherwise unsatisfactory crystals can be chosen.[378] This can be very effective in conjunction with the use of synchroton radiation.[312,379–382] Although there are occasional reports of incorrect conclusions being drawn from X-ray data[5,327,383,384] the most likely source of error in studying polymorphs is picking the wrong crystals.[385] As mentioned above, metastable forms often crystallize badly and in a sample of such a product it is not uncommon for the only satisfactory crystals to be interlopers of the stable polymorph. Computation of the correlation of X-ray single-crystal diffraction patterns with powder patterns is now possible and should capture such error at an early stage.[142,169,386] The contrary process, converting powder patterns of complex molecular crystals to structural information,[387] although an exciting prospect, is not yet applicable to sufficiently large molecules to be of general interest for studying polymorphs of commercially interesting compounds.

However, for the ordinary laboratory environment an X-ray powder diffractometer is of more general value. It will sometimes identify differences between samples which are too subtle to be detected up by thermal analysis[5,313] microscopy or IR spectroscopy,[388], although a few contrary examples are known.[312] One such general instance is where water or other small[389,390] molecules fill voids in a structure in a random fashion without altering the crystal packing itself as in the examples of antibiotics such as cefaloglycin and cefalexin.[391] A mixture of crystalline and amorphous material will be indistinguishable from a pure sample of the crystalline material except in absolute intensity which is rarely measured in normal use. There are other cases which are not so easy to explain.[282] For example, the X-ray patterns of the forms of D,l-norleucine are virtually identical, although the IR spectra are easily distinguishable.[160,392] Examination of the IR spectra excludes the possibility that a neutral $\longleftrightarrow$ zwitterionic transformation is involved.

A more common problem with X-ray powder diffraction is in the examination of samples consisting of larger crystals. These may produce a spotty pattern which is difficult to reduce to a series of line intensity measurements and is impossible to compare satisfactorily with diffractograms from other samples.[358] If the crystals are not roughly isometric, particularly if they are needles or platey, the pattern may show distinctive features from crystal orientation effects[169] as is shown in Fig. 5. Grinding is appropriate providing that the polymorph is stable. For soft crystals an inert powder may be mixed in,[393] in order to facilitate grinding. An alternative approach is the use of the Gandolfi camera which can be made to generate a simulated powder pattern from a single crystal. The orientational bias for platey crystals of polymorphs III and IV of sulfathiazole was eliminated in this way.[169] The calculation of powder patterns from single-crystal data mentioned above has been recommended by several groups as a means of obtaining the best reference X-ray powder pattern.[142,169,387,394]

Neutron diffraction, although of less general value than X-ray diffraction, has the advantage that the scattering factors for atoms vary little with atomic number.[395,396] Light atoms can therefore be detected and located accurately in the presence of heavy atoms, in contrast to X-ray studies. As such, it is of potential value in examining polymorphic systems for their hydrogen bonded networks[82,84,111,122,397] and in investigating tautomeric or zwitterionic polymorphism. The naphthazarin C polymorphs have been examined by neutron diffraction to establish their hydrogen-bonding characteristics and the order–disorder transition.[398] The deduced centrosymmetric structure, in contrast to the Raman results mentioned earlier, is the result of the averaging of the structure over a substantial time-scale. This factor also applies to X-ray structures[399] and needs to be borne in mind when comparing these with NMR and vibrational data. The comparative rarity of sources and the need for relatively large crystals means that neutron diffraction is likely to be infrequently used for investigation of polymorphs.

X-ray crystallography is well supported by texts at all levels, both for single-crystal work[400–404] and powder methods.[358,395,405,406]

Thermal Analysis

Although the term thermal analysis is sometimes considered to include hot-stage microscopy, it is convenient to deal with these methods separately. Microscopy is concerned with qualitative visual observations whilst instrumental thermal analysis is capable of giving quantitative measurements, but without necessarily identifying the nature of the processes responsible. Thus the techniques are complementary and best used in conjunction.[407] The main thermal techniques considered will be thermogravimetric analysis (TGA) and differential thermal analysis (DTA)/ DSC.[408] TGA measures the change in mass of a sample with temperature and is therefore particularly valuable in examining solvent loss from crystals and in identifying sublimation and decomposition processes. As it is recording dynamic processes, not only the temperature at which changes occur will vary with procedure but the very occurrence of those processes may depend on sample environment and heating conditions. The subtleties of thermal analysis are often overlooked. In the vivid words of Garn,[409] 'The apparent simplicity of the technique leads the uninformed to assume that satisfactory data may be obtained, for example, by sticking a pair of thermocouples into a sample and reference and lighting a fire under them.'

DSC and DTA are alternative ways of measuring heat capacity changes in a sample.[196,410] Although they may occasionally give significantly different thermal traces,[411] the term DSC will be used here without implying the method of acquisition of the data. Any compound will absorb heat in acquiring a higher temperature. During a transition, heat will be absorbed or emitted in effecting a change of phase. The remarks

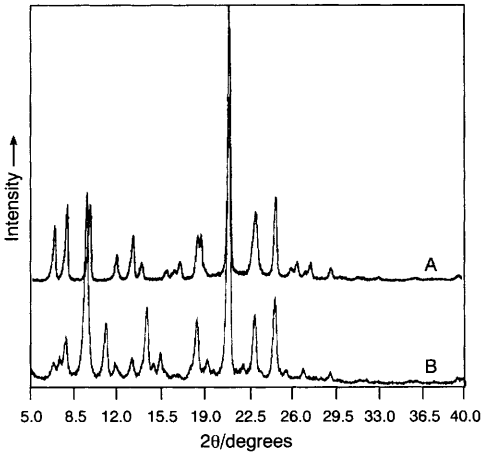

Fig. 5 Crystal orientation effects in X-ray powder diffraction. Traces due to A, the platey and B, acicular habits of the same polymorph of RP 54275 are shown. At high values of 2θ, the traces are similar, but at low values they are different. Reproduced with permission of Rhône-Poulenc Rorer Ltd.

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made above regarding the dynamic nature of TGA apply equally to DSC. In most cases where the forms are stable to grinding and the transitions are rapid the resulting curves will be sensibly reproducible. In other cases, the thermograms obtained may depend on the heating rate,[412,413] sample packing,[414] crystal size,[415,416] the ambient atmosphere[417] and encapsulation[239,367,407,418] and interpretation needs appropriate care. In particular, it is often overlooked that the history of a polymorphic crystal may be critical, for example, a later run may differ because of tempering on standing with loss or gain of seed nuclei of other forms.[200,313,367,419–421] Many instruments now run TGA and DSC simultaneously. This is valuable in that it enables a clear distinction to be made between processes involving solvent loss, sublimation and decomposition on one hand and pure phase changes on the other. The principles of thermal analysis have been set out recently in a book[422] and in an introductory video.[423]

The features to be seen in a DSC trace (Fig. 6) are endotherms, representing absorption of heat, exotherms representing the emission of heat and the so-called second-order transitions representing a change in the heat capacity without either absorption or emission of heat. A sloping baseline could represent a continually changing heat capacity, but is often due to imbalance between sample and reference, or slow loss of mass from the sample during heating. During a heating cycle endothermic processes are the most common ones. Melting and sublimation are always endothermic as are transitions involving enantiomorphs at or above transition points. Desolvation is usually endothermic and chemical reactions can be, especially at lower temperatures. Monotropic transitions, crystallization and most decomposition reactions are exothermic. On cooling, crystallization and enantiotropic transitions are exothermic, so cooling cycles normally contain only exotherms. Despite this there is often value in running the sample under both heating and cooling modes.[414] Although this has long been recommended, it is rarely indicated in the thermal analysis literature on small molecules that this has been considered.[208] By contrast it is common in lipid and polymer work to run both heating and cooling curves.[89] If it is intended to identify the material at room temperature after a phase transition, it is imperative to check on the cooling cycle that no reverse change has occurred. Heats of transformation and melting can be evaluated from the area under a DSC curve,[424,425] although not, of course, as satisfactorily as from a precision adiabatic calorimeter.[426] Conditions need to be chosen carefully in order to obtain reliable results. The greatest difficulty is in determining the most suitable base line.[427]

It is common for a polymorph to show a transition to a higher melting polymorph at the appropriate transition temperature when heated slowly, but to overshoot and melt at its own melting point under more rapid heating conditions.[194] This is often followed immediately by re-solidification to the higher melting polymorph giving a characteristic curve shape (Fig. 6, c). The polymorph thus produced may or may not be the same as that resulting from the transition at the proper transition point and in other instances the re-solidification may be delayed.[224] Dependent on the complexity of the polymorphic set, a whole series of such events may take place. Finally, the form with the highest melting point will melt if it has not previously decomposed. Several meltings may take place in the case of a

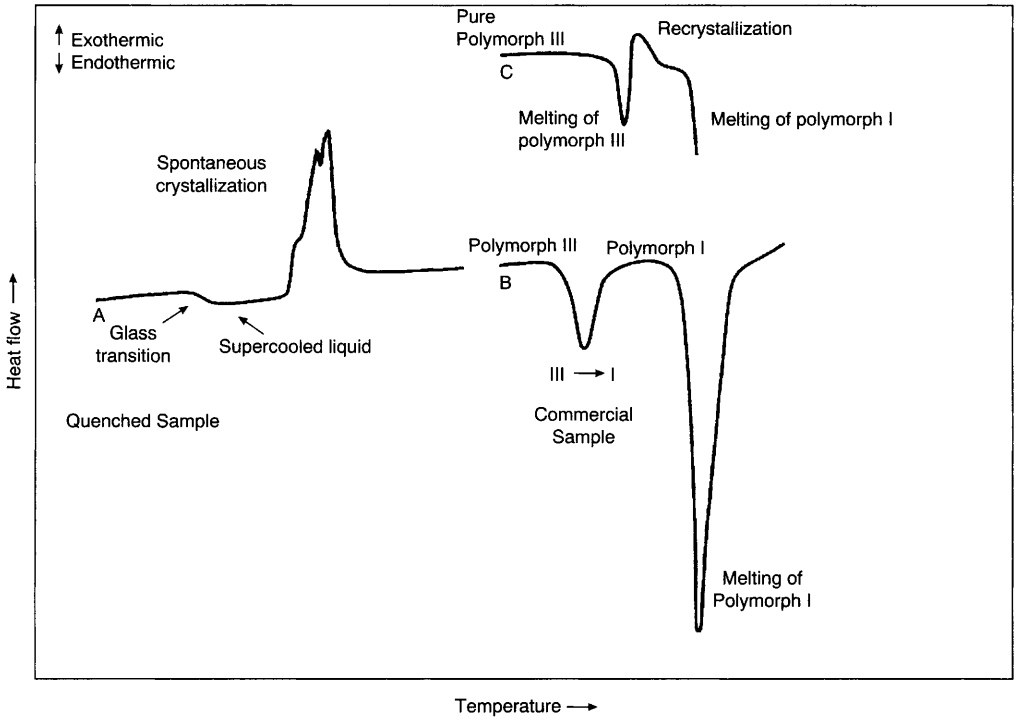

Fig. 6 Typical features in the DSC of a polymorphic system. A, Quenching the melt of sulfathiazole gives an amorphous solid, which on heating undergoes a second-order transition (glass transition) to a supercooled liquid (see refs. 422, 542–544). In a second order transition no heat is evolved or absorbed and only the heat capacity alters. This is seen as a drop in the base line. A supercooled liquid always represents an unstable phase and on heating spontaneous crystallization of this can occur. In this case it happens suddenly, causing the rapid movement away from this new base line. Irreversible processes are exothermic, but the complex exotherm which follows is unusual and probably represents several overlapping transitions. As described by Ostwald's Principle (see refs. 258 and 436) this is a cascade of transitions to successively more stable forms at that temperature. The resulting phase must be polymorph I, since it melts at 201 °C without further thermal events occurring, B, a specimen of polymorph III shows an endotherm due to the transition from polymorph III to polymorph I, followed by melting. The fact that it is endothermic indicates that polymorph I and polymorph III are enantiotropic. This endotherm always occurs around 150–175 °C although it is known that the true transition point lies many degrees below this; and C, a specimen of polymorph III which is free from seeds of polymorph I (see refs. 194 and 242), may overshoot the transition point and melt at its own melting point. This is often followed immediately by recrystallization, which is an exothermic process, of the higher melting polymorph I giving the characteristic trace shown.

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compound with liquid crystal phases, but finally a clear melt will form.

The literature on the investigation of the behaviour of phenylbutazone[239,428–432] provides an instructive example of the role of thermal analysis in polymorphism. Early work produced the not untypical situation of conflicting data on the number and properties of polymorphs.[239,428] Subsequent application of thermogravimetric analysis showed that two of the reported polymorphs were in fact solvates.[429] In a substantial re-investigation, five polymorphs were identified and characterized.[430] The IR spectra were not very useful for differentiating between the crystal forms because of their similarity.[430] The X-ray diffractograms were also reported as somewhat similar, although the earlier work[429] had relied on these to distinguish forms. The published patterns look distinguishably different[239,429,431] but it is reported that phenylbutazone shows orientation effects and is sensitive to grinding,[239] which is undoubtedly the reason for the reported similarity of the IR spectra. Dissolution rate data were also acquired, but in the absence of surface area information (see later) they cannot be regarded as definitive evidence for polymorphism. Distinction between the polymorphs relies then in this study[430] on thermal analysis. The temperatures of peak maxima are quoted for all polymorphs as well as onset temperatures of melting, the latter agreeing closely with the melting point as determined on a hot-stage microscope. The two highest melting polymorphs, A and B, show only a single peak due to melting at all heating rates, with onset temperatures of 105 and 103 °C, respectively. The remaining three polymorphs, C, D and E, each show a single melting endotherm at 96, 94 and 92.5 °C under rapid heating rate conditions of 32 °C min^{-1}. At lower heating rates they all display a melting endotherm adjacent to a recrystallization exotherm (similar to that shown in Fig. 6, c) followed by a melting endotherm at 105 °C. This was interpreted as the formation of polymorph A from the melt. Grinding or compressing the polymorphs C, D and E caused an increase in the area under this higher melting peak and a small reduction in the observed temperature of all the endotherms. In view of this and the closeness of the melting points it is difficult to be sure that A and B do not represent only one polymorph and C, D and E another, although there is some evidence of a third endotherm in some of the thermograms and evidence from the other papers of at least four forms. Subsequent studies have identified other forms[431] and confirmed the sensitivity of the results to the thermal history of the sample.[432]

By contrast, the melting points of the three polymorphs of gepirone hydrochloride[433] are substantially different and the conclusions from thermal analysis about the relationship between them unambiguous. Under slow heating conditions, samples of the low melting polymorph (mp 180 °C) showed an endotherm due to the transformation to the higher melting polymorph. At faster heating rates, a melting endotherm followed immediately by an exotherm representing re-solidification of the higher melting polymorph was observed. The higher melting polymorph then melted at 220 °C. This interpretation of the DSC measurements was confirmed by hot-stage microscopy. By prolonged heating of the lower melting polymorph it could be converted entirely to the higher melting form. The sample then showed a single endotherm at 220 °C. The endotherms of mixtures showed the disproportionate effect of small quantities of the higher melting form. The third polymorph could only be produced by crystallization as a minor component of a mixture. From DSC supported by thermomicroscopy the melting endotherm could be identified at 212 °C. Consideration of the relative thermal stabilities allowed small samples of the pure polymorph to be produced by heat treating mixtures in the calorimeter; the pure polymorph so produced showed only a single endotherm at 212 °C whereas the mixture had shown endotherms at all three melting points. From these experiments it was possible to decide on the relative thermal stabilities of the polymorphs and to calculate their heats of fusion.

The most important advance in understanding of the thermodynamic relationships between polymorphs and in interpretation of DSC curves has been through the formulation of Burger's rules.[136,434] Two of these will be discussed here and the other two in Solubility and Density Measurement. Burger's heat of transition rule implies that (*i*) if an endothermic transition is observed at a certain temperature on heating, then there must be an enantiotropic transition point at or below that temperature; but (*ii*) if an exothermic transition is observed, then the transition point must lie above that temperature, or the two forms are related monotropically.

Burger's heat of fusion rule is of value when the heat of transition cannot be observed, owing to the failure of the polymorphs to transform readily. This states that the higher melting polymorph will have the lower heat of fusion if the polymorphs are in an enantiomorphic relationship, otherwise they are monotropically related. Because of the misunderstanding of these rules which is apparent from the literature, and because of the insight into the stability relationships between polymorphs which they yield, a simplified derivation will be given here.

Fig. 7(*a*) and (*b*) are representations of the Gibbs–Helmholtz equation for enantiotropic and monotropic cases, respectively. The shape of the H (enthalpy) curves is determined by $H = H_o + \int c_p dT$. Since the specific heat C_p is always positive, they must slope upwards at an increasing rate with temperature, as shown. G, the Gibbs energy, is related to the negative summation of all the entropies, S. The value of S is again dependent on C_p. The value of S must be positive, therefore the G curves must slope increasingly downwards, again as shown. At absolute zero, $H = G$ and the curves meet. The lowest energy crystalline structure at absolute zero will have the strongest intermolecular bonds. Strong bonds imply high lattice vibration frequencies (phonon modes[396,435]) which make the smaller contribution to C_p. Therefore, the angle of divergence of the G and H curves of the polymorph most stable at low temperatures will be less than that of the less stable polymorph. Hence the G curves will tend to cross, but the H curves will not. The heat of transformation rule can be ascertained by concentrating on the H curves and noting the enthalpy consequences on going from H_a to H_b or *vice versa*, remembering that this is only possible by lowering the Gibbs energy, *i.e.*, ΔG must be positive. Hence processes which are exothermic on raising the temperature are spontaneous ones and are irreversible at or below that temperature, and *vice versa* for endothermic processes. The heat of fusion rule depends on the enthalpy curves for the polymorphs and the liquid phase being approximately parallel over the relevant region, so that the differences in C_p do not obscure differences in the heats of transition. These rules are extra-thermodynamic, in that they involve structural considerations, so they are not 100% certain. It is not clear whether there are any exceptions in practice as re-evaluation of the literature data has eliminated many of the apparent exceptions.[42]

These rules, as already implied, can be helpful in sorting out DSC results. The concept of enantiotropism as reversibility needs to be approached with caution. Mirror image curves cannot be expected on heating and cooling. Apart from Ostwald's rule[257,436] and hysteresis due to high energy barriers,[194,434] leading to offset of heating and cooling events, consider the energy–temperature diagram for a trimorphic enantiotropic system, Fig. 8(*a*). The heating cycle might produce transformations at A, B and C whilst the cooling cycle might proceed *via* any of the many paths on the diagram. A form such as polymorph II in Fig. 8(*b*) which is metastable at any temperature would be most unlikely to form on heating, but could well be the product of cooling the melt.

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For investigation of melting by DSC, small samples are usually appropriate and the temperature of melting is taken as either the peak maximum, or more precisely as a peak maximum corrected for heat flow,[425] or as the extrapolation of the leading edge back to the base line.[437] Because solid–solid transformations are often sluggish[157,438] and may reflect very small enthalpy changes, the use of larger quantities of compacted sample has been recommended, together with low heating rates and the assignment of the first discernible movement away from the base-line as the transition temperature.[197] The appropriateness of this may depend on the thermal stablity of the material under examination. Similar treatment of cooling curves then yields a transition range dependent on the hysteresis of the system. Organic compounds may be more appropriate calibrants than the almost universally used indium, as they are likely to have conductivity characteristics similar to the sample.[197,439]

It is often implied in accounts of the determination of purity by DSC that the true melting endotherm of a pure substance will be infinitely sharp,[440] but of course this cannot be so for organic powders. Apart from practical considerations of thermal conductivity, edges and surfaces are less stable than bulk and will melt first and so small crystals will melt before larger ones.[441] Melting normally starts at crystal defect sites. The observed melting will also be affected by a polymorphic transition very near to the melting temperature or decomposition at the melting point and, of course, impurities. Although it was generally thought that the melting temperature could not be exceeded without melting occurring, there are scattered reports of slow melting[442,443] and superheating[444] and increasing acceptance of the existence of this phenomenon.[445] In addition there are instrumental factors. Different instruments (DSC, DTA, melting point apparatus, hot stages, thermal photometers) measure different manifestations of the melting process and so will not necessarily give the same value.[196,199] All these factors apply also to solid-solid transformations. Even after the elimination of the possible effects, there still remain unexplained examples of anomalous melting behaviour. For obvious reasons most of these never appear in the literature but there are a few[446–449] and further examples are known to the author. Note that whilst examples of curious melting and transition behaviour ought to be carefully checked, they are not necessarily the result of inaccurate observation.

A large endotherm followed by a small melting endotherm is characteristic of the formation of a disordered phase in which the positional order of the crystal is retained, but the orientational order is lost.[8,275,426,438] This may be due to random orientation of molecules, but is most often associated in organic systems with the onset of 'free' rotation. Molecules of roughly spherical shape are particularly likely to show an order–disorder transition to a plastic crystal state.[8,224,426,450,451] At lower temperatures, crystals of such molecules sometimes show a glass transition in the crystalline state.[452,453] Order–disorder transitions have been regarded as second-order transitions,[154,180,454] but organic examples are not characterized by 'second-order' DSC traces. Although second-order transitions are widely discussed in the literature, the concept presents certain difficulties as has been well addressed by West.[154] On the whole the term is better avoided, except in reference to glass transitions, in considering the inter-relationships of organic polymorphs.

From a study involving a selection of appropriate techniques it should be possible in most cases to acquire a reliable listing of the polymorphs, their relative stabilities and their transition points, which is as far as present day economics of industry may allow. However, a study is incomplete without the drawing of a semi-schematic energy–temperature or the equivalent pressure–temperature diagram.[433] If all the relevant data have been assembled such a figure takes, except in complicated cases, only a few minutes to prepare. The discipline of setting out the results in this form leads to a great confidence that the system is understood and avoids the erroneous descriptions of polymorphic systems sometimes presented in the literature.[35] Whilst the unwelcome appearance of a further polymorph at a late stage of investigation cannot thereby be excluded, it is rendered less likely.

A development which offers greater sensitivity as well as enabling overlapping spontaneous and reversible processes to be separated is oscillating, alternating or modulated DSC.[455] The superposition on the temperature ramp of a periodic temperature function allows a computational separation *via* a Fourier transform. Although the rate of modulation in commercial instrumentation is too slow for many polymorphic transitions, it is already being found useful in pharmaceutical investigations.

Thermosonimetry[456] is a relatively unexplored technique owing to the lack of convenient instrumentation and the dearth of applicable theory. It is mentioned here because it would appear to have considerable potential for the identification of phase changes and possibly for the understanding of the crystal structure changes accompanying these. The frequency spectra of the sonic emission of solids on heating are very rich, although it is only possible to use these at present as a signature.[457,458] Phase changes are accompanied by increased activity and a change in the spectrum.

Solubility and Density Measurement

These are two of the measurements traditionally used to identify polymorphic behaviour. They remain important today: solubility because that is often the target property which is required of the polymorph in practice: and density because of its reliability and theoretical linkage with crystal structure and with stability. A pigment which bleeds, a solution of an agrochemical* which is liable to precipitate and block spray nozzles or a suspension of any product which cakes[47–49,461] during storage is probably unmarketable. The solubility also has an important thermodynamic feature: it is inversely related to the stability of the polymorph such that the most stable polymorph is always the least soluble at a given temperature.[19,34] At a transition point, the interconverting polymorphs are equally soluble. There is an implicit assumption behind these assertions that the solutions prepared from either of the polymorphs are identical. There is limited evidence against this in some cases. For example, in the case of sulfonamides the polymorph crystallizing from solution is dependent on that dissolved.[462] In principle then, the determination of the solubility over a temperature range for two or more forms of a substance will readily establish the transition points and thermodynamic stabilities.[463] It is the author's experience, however, that the measurement of solubility gives rise to more difficulty and more erroneous data than any other connected with polymorphism. The problem is threefold.

(i) The attainment of equilibrium is often slow, particularly with poorly soluble or poorly wettable substances,[464] for which several days' agitation may be required to establish a consistent value. Either through system instability, lack of awareness or time constraints this is often not done and the measured solubility is then effectively a dissolution rate measurement. This latter, whilst related to solubility *via* the Noyes–Whitley equation[465] and so roughly parallelling it in many cases, is also a direct function of surface area and therefore of particle size.[36,466] If particle size is checked only instrumentally

* Examples of polymorphs of agrochemicals in the open literature are few, *e.g.*, Borka.[459] Instability of formulations is more often related to supersaturation than to polymorphism and problems are often solved pragmatically. However, the more sophisticated formulations now being introduced demand attention to polymorphism.[460]

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(Coulter counter, Malvern analyser) over-all aggregate size rather than individual grain size may well be measured.[467] Any differences in grain and aggregate size can then result in erroneous solubility comparisons. A preliminary microscopic examination will give forewarning of such a situation, but may not indicate how to solve it. Intrinsic dissolution measurements[464,468] may provide a surrogate solution to the problem. 'Surrogate' because there are both practical and theoretical reasons why the intrinsic dissolution rate ratio of polymorphs will only approximate the relative solubilities. (For an example see Table 1 in the study by Buxton, *et al.*[469]). Wettability differences can totally destroy any correlation.[470,471] Nor can slow equilibrium be overcome by working at higher temperatures followed by cooling, because the temperature–solubility hysteresis usually determines an even longer equilibration time. The second factor is the susceptibility of the polymorphs to transformation when examined outside their stability ranges.[472] As indicated earlier, the presence of a solvent can be particularly efficacious at promoting a polymorphic transition. It is often possible to measure the solubility of a polymorph below its lower transition point, but rarely many degrees above its upper one.

(ii) The possibility of a transformation to a solvate,[473] or hydrolysis[146] or other chemical reaction. Sometimes the shape of a solubility–time curve will indicate whether a transformation is occurring, but whether or not this is so depends on the relative kinetics of the dissolution and transformation processes. One solution is to measure the solubility of the polymorphs in an inert solvent and then measure the partition coefficient rapidly.[474]

(iii) There are the consequences of pH variation in the measurement of the solubility of ionizable species.[463,475] The self-buffering capacity of organic acids and bases can often make a dramatic difference to the observed solubility. The need to match buffer capacity to the expected solubility is rarely considered.[476] Trace ionic[477] or other (oxygen, carbon dioxide) contamination can occasionally present a source of error. If the solubilities are being measured spectrophotometrically the effect of pH or complexation on the absorption spectrum also needs to be taken into account.[36,478]

When the solubilities cannot be determined in the region of the supposed transition point, it is possible to extrapolate from other temperatures using the van't Hoff isochore. This procedure needs to be applied with caution as the experimental inaccuracies and theoretical assumptions are often not appreciated.[77,162,463,479]

For molecular solids in which hydrogen bonding is not a structural feature, the stability of a form is nearly always closely related to the density. Although this relationship, as a consequence of the rapid reduction of intermolecular attractive forces with distance, has been understood for a long time, the structural implications were first explored in detail by Kitaigorodski.[480] Dipole–dipole interactions can contribute to the structural stability (surprisingly, however, they do not appear to contribute to the preferential formation of polymorphs[481]), but the only common and significant attractive force other than van der Waal's forces is hydrogen bonding. This can produce more open structures in which the loss of polarizability energy is matched by favourable disposition of the strong hydrogen bonds. This is the basis of the other two of Burger's rules,[136] namely the density rule 'the more stable polymorph at absolute zero will possess the highest density' and the IR rule 'the highest frequency OH or NH stretching band will be associated with the form least stable at absolute zero'. The highest frequency OH or NH stretching will be associated with the weakest hydrogen bond. Juxtaposition with the heat of transformation and heat of fusion rules will usually allow the deductions to be generalized to working temperatures. Consideration of the circumstances pertinent to these rules could lead to the expectation of exceptions. It is found in practice that whilst there is a small proportion of exceptions to each rule, their complementarity makes the concurrent failure of both rules less likely.[42]

Density can be measured by flotation,[482,483] by volumenometry, or by pyknometry.[483] All are time consuming. Alternatively the true density* can be calculated from the unit cell dimensions.[485] The latter must always be marginally greater than the measured density, as the crystal voids and other defects always lower the overall density of the crystals. Any discrepancy is a warning of solvates or other incorrectly assumed molecular structure. Generally, the measured density will increase marginally on grinding as a result of cracking occurring preferentially at crystal pores and defects, but on prolonged grinding it may begin to decrease owing to increased surface area and amorphization.[42,486] An attempt to check Burger's density rule against the true densities by using the Cambridge Crystallographic Data Centre data base for X-ray structures failed for the reasons mentioned earlier.

The air comparison pyknometer represents an instrumental method of measuring densities with enhanced sensitivity. Flotation is best carried out with centrifugation and it may detect the presence of interloper crystals of a different polymorph in a specimen. The main problems with flotation are in finding a liquid mixture of suitable density that does not dissolve the sample and in maintaining that density through adequate temperture control. The first requirement is particularly critical for organic polymorphs.

Solvates

Hydrates or other solvates often produce a further level of complexity in a polymorphic system.[487,488] There is the expectation of a monohydrate or monosolvate but, in fact, the accommodation in a unit cell for a small molecule can produce multiple,[489,490] fractional,[282] irrational[412] or variable[469,491] molar ratios. Amongst the polymorphs of a molecule some can be hygroscopic and others stable to water or water vapour.[489] Different hydrates can be produced from different polymorphs.[45] This is probably related to the 'stuffing' effect of impurities described by Buerger.[3] Where there are two or more hydrates of the same composition, these are in a polymorphic relationship with each other.[138] In practice it may be difficult to interconvert polymorphic solvates, because of the likelihood of preceding desolvation.[389,469] The desolvation of a solvate can sometimes produce a polymorph not obtainable in any other way.[138,389] A detailed study of celiprolol hydrochloride has shown that the hydrate is not a true one in the usual sense but appears to be a solid solution of the drug in water.[492] This leads to speculation about the exact nature of the crystal structure involved.

Thermomicroscopy in silicone oil will reveal desolvation on heating by bubble formation.[178] DSC will show features corresponding to solvent loss, but such features are notoriously sensitive to heating rate, crystal size, mass of sample, sample packing, and to the use of open as against closed or sealed pans or even pan shape.[427] When the transitions are accompanied by inhomogeneous melting (dissolution) or a mixture of inhomogeneous and homogeneous melting[282] or when the desolvation overlaps the normal melting or a phase transition, the DSC can become difficult on interpret. Another phenomenon which leads to confusion when the DSC trace is viewed in isolation is stepwise loss of solvent, especially when this occurs in irrational proportions.[492] A simultaneous TGA is of unique

* The term 'true density' is used by other authors in contrast with bulk density to describe what is here called the 'measured density'. For a discussion of different measures of density, see Lowell and Shields.[484]

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value in these cases in pinpointing the temperature or temperatures of solvent loss in the particular run. It cannot be necessarily assumed that the form resulting from recrystallization from an 'anhydrous' solvent will be the anhydrate.[494] In contrast, the anhydrous form III of cortisone acetate is reported as only obtainable in the presence of water, whilst the hemihydrate is produced from wet solvents and the monohydrate from dry solvents.[488] Erythromycin dihydrate is said to dehydrate when heated in water at lower temperatures than in air.[417,487]

Whilst X-ray powder diffraction patterns will distinguish a solvate except for the rare examples discussed earlier, they do not display any characteristic features of the solvent as such. By contrast, all of the common solvents have strong and distinct bands in the IR spectrum which generally reappear at the same or similar wavelengths in the solvate.[495] Those bands sensitive to hydrogen bonding will shift, but these shifts are again very characteristic. It could be supposed that except for very low molar ratios of solvent or high molecular mass compounds, IR spectra would be a totally reliable reflection of the presence of a solvate. The bands due to water are often difficult to distinguish from those due to hydrogen-bonded hydroxy groups in the host molecules and there are occasional reports of the indistinguishability of IR spectra of hydrates and other solvates.[365,430,496,497] There is the danger of pumping off the solvent if the sample is prepared as a KBr disk, or of rehydration.[365] Some of the literature reports may well reflect this. Hydrates have occasionally been mistaken for enolic tautomers[498] and frequently for simple polymorphs. A microanalysis, Karl–Fischer or mass loss determination will avoid such misinterpretation. Quantitative DSC has also been used to determine the degree of hydration, based on assumptions of the energy of binding of the water molecules.[499] Solid-state ^{13}C NMR spectra will show bands due to solvate guest molecules but not, of course, to water. The presence of the latter will affect the positions of other signals,[349,500] except presumably in those cases where X-ray diffraction shows no change in packing. In one such case of spectral indistinguishability, resort was made to differences in spin–lattice relaxation times.[346]

The solubility of a hydrate in water or a solvate in its own solvent is always less than that of the unsolvated form, for thermodynamic reasons. On the other hand, the solubility of the hydrate in ethanol or of an ethanolate in water will be always greater than that of the unsolvated form.[463] The vacuum microbalance which measures the mass of a sample under different pressure and humidity conditions is a valuable way of quantifying the stepwise loss and gain of solvent.[501]

Quantitative Aspects

The requirement of analytical control implies reliable methods of detecting, distinguishing and quantifying polymorphs. All the caveats in the examination of polymorphs referred to previously apply with greater force when quantification is required. A method needs to be selected in which the differences between the polymorphs is maximal, yet unlikely to be interfered with by the presence, in particular, of other potential polymorphs or solvates. X-ray powder crystallograpy,[359,393,502] IR,[234,469] NIR[291] and Raman[308] spectroscopy, DSC[234] and DTA[503] have all been investigated for the determination. They have a common feature, namely that the transfer of energy to and through the powdered sample is one of the critical factors with respect to the precision of the measurement. Whilst solution transmission properties are capable of being dealt with theoretically, powder absorption can only be tackled when simplifying assumptions are made.[251,504] The critical features are the particle size and shape of the sample and of the diluent, if one is present, and the homogeneity.[505] It is therefore necessary to grind, and to grind reproducibly. The sample then needs as a minimum requirement to be stable under the grinding conditions. Again microscopy comes into play to check whether the sample is dispersed. Care must be taken to ensure that the sample is quantitatively transferred with the matrix powder, rather than left coating the vessel.[505] This applies particularly to greasy, low melting or plastic crystals. Each compound will present its own problems. It is unlikely that any one technique will prove universally suitable. Because of the small differences that are commonly encountered, realistic limits of quantification even with the use of chemometric methods will probably be 1–10%, dependent on the individual problem. The few examples in the literature on the determination of polymorphic mixtures support most of these contentions. The precautions needed to obtain reliable results in DRIFT spectra have been explored in detail in the case of sulfamethoxazole[234] and of a new anti-inflammatory drug.[226] The potential of X-ray methods have been explored on a model system.[394] Although it has a long history,[359] quantitative X-ray analysis has often been used without attention to possible sources of error. The α-inosine content of mixtures of α- and β-inosine has been investigated by both X-ray powder diffraction and IR spectroscopy.[393] The limit of detection by the X-ray method was decidedly superior to that by IR spectroscopy, but the IR spectra display some curious features. X-ray diffraction has also been used for the detection of α-prasosin in γ-prasosin. Using a profile fitting analysis, a detection limit of 0.5% was achieved.[506] Possible interference from other polymorphs was not considered. The polymorphic composition of cortisone–acetate mixtures and of a candidate hypolipidaemic drug have been determined by Raman spectroscopy,[309] as has chlorpropamide.[507] DTA was found to be superior to X-ray powder diffraction for the determination of fatty acid polymorphs.[503]

If the enthalpy of solution of two polymorphs is sufficiently different, then solution calorimetry can be used for their determination in a mixture.[508,509] The solution obtained by dissolution of one polymorph must be the same by definition, as that obtained from another polymorph of the same substance.[19,462] The difference in heat (enthalpy) of solution therefore determines the relative enthalpies of the polymorphs.[463] the polymorph stable at lower temperatures will have the lower enthalpy (see Fig. 7). The determination can be made indirectly from solubility measurements over a temperature range with the application of the van't Hoff isochore or preferably, directly by measuring the heat of solution in an adiabatic calorimeter.[463] The enthalpy difference will be the same whatever solvent is chosen: therefore it is possible to select one in which adequate solubility is shown. The occurrence of polymorphic change during dissolution will not affect the calorimetric result, as the heat of transition will be summed in the measured heat of dissolution.[463] X-ray powder studies are most commonly used to determine the degree of crystallinity.[510] Solution calorimetry has also been applied to the determination of degree of crystallinity of partly amorphous antibiotics, proving more reliable than X-ray powder methods.[512] The values of crystallinity determined by the two methods were substantially different. The polymorphic composition of phenobarbitone[411] and phenylbutazone[512] by X-ray powder diffraction and by DSC have also been reported to be different, but no explanation of either of these observations has been offered.

Amorphous and Crystalline Solids

There are different schools of thought as to whether amorphous states ought or ought not to be included in the definition of polymorphism.[513] Crystalline solids are distinguished by the presence of periodic pattern repetition in three dimensions

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leading to long-range order*: this can be defined as the expectation of finding an identical pattern repeated at regular intervals in any direction throughout the solid.[514] Isotropic liquids and amorphous solids, on the other hand, have no long-range order so the most that can be said about the structure is that the probability of finding a particle distant from any point is given by the particle density.

The neatness of this distinction has been obscured firstly by the existence of liquid crystals[515] with one- or two-dimensional long-range order and incommensurate phases[516] and more recently by the discovery of quasicrystals[517,518] with long-range non-periodic order,[519] often characterized by pseudo five-fold crystallographic axes,[520,521] some of which enjoy greater stability than the equivalent crystalline state.[522] The term non-crystalline therefore does not imply total randomness and there is an increasing awareness of the possibility of different amorphous structures.[523–524] For example, the amorphous and liquid state are generally considered to represent the same phase, yet there are substances which exist in two amorphous forms separated by what appears to be a phase transition.[131,524]. Different amorphous structures may arise from different processes of production.[525,526] In practice many of the organic materials usually described as amorphous are the 'meringues' produced by evaporation of solvent from solutions of substances which do not crystallize readily, or the powders produced by precipitation, transition,[487] freeze drying,[527] spray drying[259,528] or grinding,[449] although the terms microcrystalline or colloidal might be more appropriate, dependent on the size of the crystalline volume.

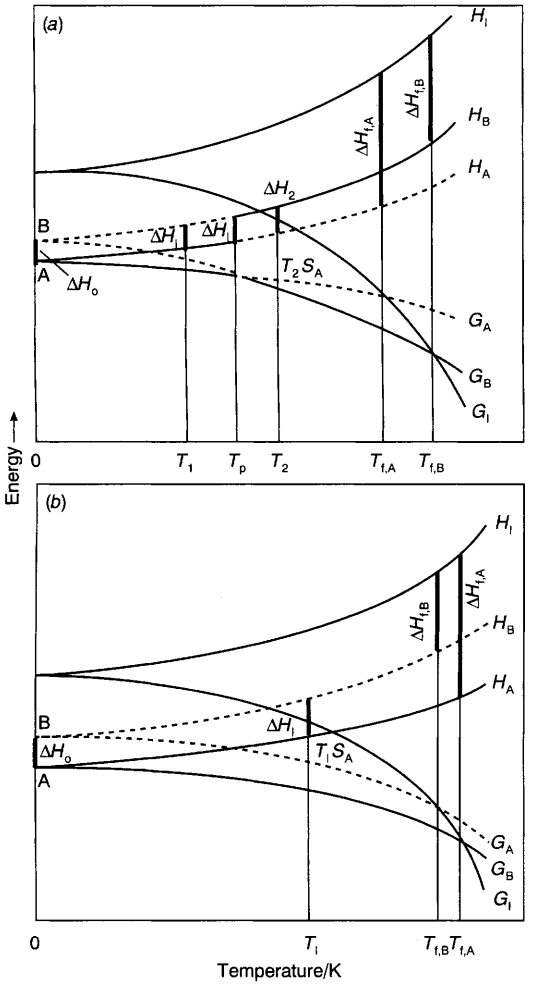

Fig. 7 Energy–temperature diagrams of dimorphic systems. Reproduced from Burger, A., and Ramberger, R., *Mikrochim. Acta*, 1979, **II**, 261 by permission of Springer–Verlag, Vienna (*a*) Enantiotropic systems and (*b*) monotropic systems. (T_p, transition point; T_f, fusion point; H, molar enthalpy; G, molar free energy; S, molar entropy; A, B: crystalline modifications; l, liquid phase).

The concept of an amorphous solid as microcrystallite clusters rather than as a continuous random network or dense random packing has fallen into disfavour, but most of the work has been done with semiconductor materials, and the conclusion may not apply to organic molecular solids. Quasicrystal clusters or 'amorphons' may need to be considered for organic states.[8,9,529] However, there is limited possibility with the analytical tools presently at our disposal of deciding the nature of the detailed structure of amorphous materials. X-ray crystallography has been the most used technique for establishing structure both in terms of long- and short-range order,[9,358,530], although calorimetric methods, vibrational spectroscopy, and increasingly NMR spectroscopy[531,532] provide structural information. Solid-state ^{13}C NMR spectroscopy can show, for example, conformational preferences of molecules even when there is no discernable X-ray pattern.[28,349] Despite this, there has been an almost total neglect of the study of organic amorphous materials. When they are reported they are usually characterized inadequately, if at all. It is not always possible even to ascertain if the reported lack of crystallinity is derived from visual examination, polarized light microscopy or X-ray examination. The significant advances in our understanding of the amorphous solid-state have come recently not in the area of structure but in recognizing the entropic relationships between liquids, crystals and the amorphous state.[533–537]

The most investigated amorphous materials are polymers[364] and inorganic glasses formed by cooling silicate melts[538] although amorphous metals and semiconductors have become the subject of intense research activity in recent years.[320,539] The solids most typically and traditionally regarded as amorphous are those produced by cooling a liquid in the absence of crystallization. During this process the material passes by continual change from a liquid state though the glass transition to a solid state, *via* a more viscous, possibly rubbery or malleable state.[540,541] The term 'supercooled liquid' gives rise to some confusion.[542] A solid is usually arbitrarily defined as a material whose shear viscosity exceeds $10^{14.6}$ poise ($10^{13.6}$ N s m^{-2}).[515] Amorphous materials have therefore been described as having the rheological properties of a solid but the structure of a liquid.[543] Given the limited knowledge of the structure of either liquids or amorphous materials, it may be felt that the latter half of that statement is ambitious. The glass transition temperature is the point at which the melt sets, accompanied by changes in many other properties. There are several methods of investigating the glass transition, including DSC.[544,545] In the idealized case, the DSC trace shows no peak, but only a step representing a change in the heat capacity. This occurs only when the heating rate is the same as the cooling rate which has produced the glass. If the heating rate is faster than the cooling rate, an exotherm is superimposed and if the cooling rate is faster, the usual case, an endotherm is superimposed.[546] These effects are due to strain as a result of the structure failing to reach equilibrium within the experimental time-scale.[9,531,540] In either case the underlying heat capacity change can be

* More precisely, the definition of a crystalline array is given by:

$$\lim |x - x'| \to \infty < \rho(x)\,\rho(x') > = F(x - x')$$

Where $<\rho(x)\,\rho(x')>$ is the density-density correlation between two points x and x' related by a basis factor. Isotropic liquids and amorphous solids, on the other hand, have no long-range order, so the probability of finding a particle distant from x is given by

$$\lim |x - y'| \to \infty < \rho(x)\,\rho(x') > \approx \bar{\rho}^2,$$

where $\bar{\rho}$ is the average particle density.

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obscured. The temperature of the glass transition is not fixed, but is lower the slower the cooling and heating rates.[422,546] Amorphous solids are always less stable than crystalline forms and so on heating will normally show an exothermic transition to a crystalline phase, although this may be preceded by a glass transition.[242,422] There are a few compounds which, as solids, are only known in the amorphous state and these display only a step corresponding to the glass transition.[547]

Many organic materials can be prepared as glasses by rapid cooling.[162] Molecules with myriad conformational possibilities, particularly polysaccharides and synthetic polymers, tend to occur as amorphous forms. Molecules whose shape precludes a packing density, that is, the ratio of the volume occupied by the molecules as such to the volume of the space in which they reside, of at least 0.60 also solidify most easily as glasses.[85,548] Directed bonds favour the more open structure implied by these low densities, so that multiply hydrogen-bonded molecules, for example, carbohydrates, are notoriously difficult to crystallize.[73,549,540]

The industrial significance of amorphous organic materials has increased enormously. Polymers are, of course, ubiquitous. In the pharmaceutical industry there are compounds, particularly antibiotics, which have long been used in that form because of the difficulty of crystallization and solubility problems of the crystalline forms.[43,512,551] More recently attention has been paid to the deliberate use of amorphous forms with a crystallization inhibitor as a means of more rapid drug delivery.[521] Interest in amorphous forms relates not only to active ingredients but to excipients including sugars[550,552] and polymers. In the food industry, carbohydrates often need to be used in amorphous forms and many food constituents exist naturally in an amorphous state.[66–73,553,554]

Amorphous material may result from grinding[449,555], deliberately or inadvertently. The effect of comminution of a crystal is to reduce the long-range periodicity and broaden the signals in X-ray diffraction patterns until in the limit the pattern is so diffuse as to be indistinguishable from that of an amorphous form produced from the melt.[524] On this argument there is no break between a crystalline and an amorphous form. If by contrast, one cools a melt so as to produce a glass, then by this process there is no break between the liquid state and the amorphous form. There may be distinction between the products of the two processes. It may be possible in principle, or in practice in favourable cases, to distinguish between limitingly small crystalline domains and large non-crystalline domains, for example by analysis of the shapes of X-ray powder diffraction lines,[358,405,556] but it would be very artificial to draw the boundaries of the coverage of this review between the two, especially as their properties for all practical purposes are likely to be identical. On balance then, the wider definition is adopted here, intended to allow the reader to decide on the inclusion of amorphous states or otherwise in the term polymorphism. On this wider definition, McCrones' view[1] that every system will be discovered to be polymorphic if studied enough, comes much nearer to verification.

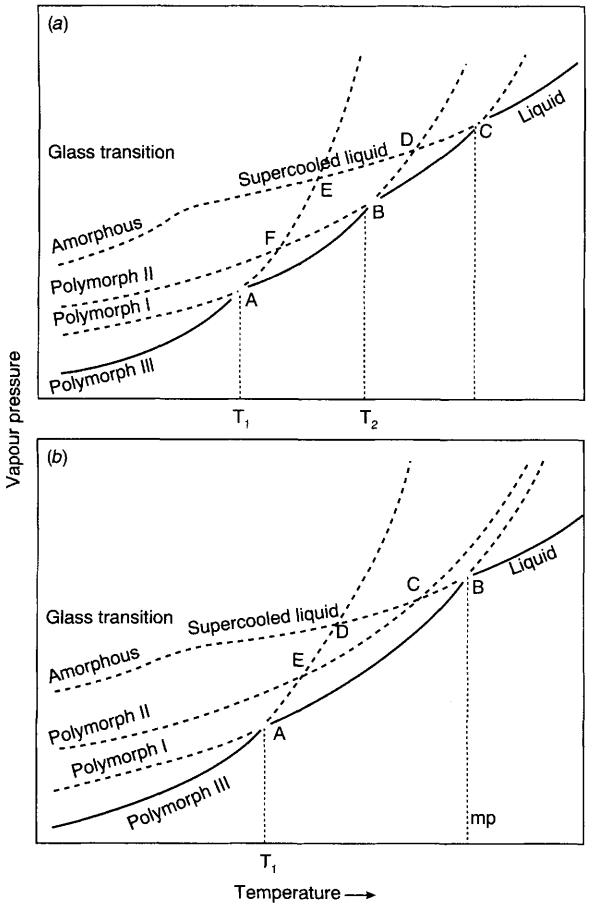

Fig. 8 Vapour pressure–temperature diagrams for trimorphic systems showing that heating and cooling curves can follow different paths *via* different polymorphs. Dashed lines represent metastable equilibria and full lines stable equilibria. The heating cycle in the system shown in (*a*) will probably proceed *via* A, B and C (but see ref. 194 and the caption to Fig. 6 whilst any propensity to undercool might give routes to polymorph III *via* CBF, CDB or CEA. In addition the paths may well end at the amorphous form or polymorphs I or II. Similarly in (*b*) heating will probably proceed *via* A and B, but cooling could follow several paths. In either case spontaneous transitions (vertical drops) are also possible.

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