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# Analysis of Organic Polymorphs

## A Review

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**Keywords:** Polymorphism; phase transitions; amorphous materials; solvates; microscopy; thermal analysis; infrared spectroscopy; Raman spectroscopy; solid-state nuclear magnetic resonance spectroscopy; X-ray diffraction

### Introduction and Definition of Polymorphism

Polymorphism<sup>1-7</sup> 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.<sup>4</sup> 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.<sup>1</sup> Later writers who have accepted this definition have tended to substitute their own list of exclusions,<sup>5</sup> if they have addressed the matter at all. Buerger's tentative definition<sup>3</sup> '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<sup>8,9</sup> will be discussed later.

Polytypism<sup>10</sup> 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<sup>11-13</sup> and as disordered stacking.<sup>14</sup> 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<sup>15-17</sup> and this has led to the suggestion that the term polymorphism should apply to liquids as well as solids,<sup>18</sup> 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<sup>19</sup> of whether allotropy and polymorphism are distinct<sup>20</sup> 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.<sup>21,22</sup> Protein polymorphism usually refers to minor molecular sequence changes<sup>23,24</sup> rather than to packing, but different crystal packing of protein molecules is also known.<sup>25</sup> Polymorphism of thin films<sup>26,27</sup> and polymers, both of biological<sup>28,29</sup> and of synthetic<sup>30</sup> 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<sup>31</sup> 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.

In any case the distribution of organic molecules amongst crystal classes and space groups is extremely limited, as is discussed later.<sup>32,33</sup> The addition of a melting or upper transition point to a Roman numeral is probably the best compromise,<sup>1</sup> 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.<sup>34,35</sup> 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.<sup>1,36-40</sup> 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.<sup>36,37</sup> 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.<sup>40</sup> It has been pointed out, particularly by Burger,<sup>36</sup> 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,<sup>41</sup> is unique in that the solubility is related to the rate of enzymic attack on the solid.<sup>42</sup> This and novobiocin,<sup>43</sup> 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<sup>44</sup> and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tableting problems and subsequent tablet failure,<sup>45,46</sup> crystal growth in suspensions<sup>47,48</sup> and resultant caking, precipitation from solutions and problems with suppositories,<sup>49</sup> as well as chemical production problems such as filtrability<sup>1</sup> 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.<sup>50</sup> This point is most dramatically illustrated in the explosives industry, where the wrong polymorph can have greatly increased sensitivity to detonation.<sup>51,52</sup> Pigment colour and solubility are polymorph dependent,<sup>53-59</sup> as are photographic and photolithographic sensitizers.<sup>60</sup> The performance of industrial products, particularly those based on natural fats and waxes<sup>61,62</sup> and derived soaps,<sup>63</sup> and on petroleum products<sup>64,65</sup> 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,<sup>66,67</sup> sugars,<sup>68-72</sup> polysaccharides<sup>73</sup> and other constituents.<sup>74-75</sup> A comprehensive summary of the solid-state properties of lipids has recently appeared.<sup>76</sup>

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<sup>34,77</sup> 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<sup>78</sup> 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<sup>79</sup> (Zantac) which if held valid will extend the patent protection from 1995 to 2002 in many countries.<sup>80</sup> For a compound with annual sales of over 2 400 million pounds sterling,<sup>81</sup> 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<sup>82</sup> and the relationship between crystal structure, crystal growth and crystal habit<sup>83</sup> and their influence on bulk properties. Apart from knowledge for its own sake, this is of clear application in the development of organic electronic<sup>84,85</sup> and other specialty products<sup>86-88</sup> and in understanding the function of biological membranes.<sup>89</sup>

### Distinction From Related Phenomena

At one time polymorphism was regarded only as different arrangements of rigid molecules in the solid state.<sup>90,91\*</sup> 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.<sup>92</sup> 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<sup>93,94</sup> and the proposition that they could not be part of polymorphism was copied by reviewers until even the examples were forgotten.<sup>95</sup> 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.<sup>96</sup> One would have expected examples of tautomeric 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.<sup>97</sup> Tautomeric polymorphism is surprisingly rare, but a well investigated example is now known, that of 2-antino-3-hydroxy-6-phenylazopyridine.<sup>98</sup>

There are a few papers in the literature either where tautomeric polymorphism is invoked<sup>99-105</sup> 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.<sup>106</sup> 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.<sup>107</sup>

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.<sup>108,109</sup> Anthra-

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

nic 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.<sup>110</sup> A related phenomenon is the changing of allegiance of hydrogen-bonded hydrogens between electron donor atoms, which is a prolific source of polymorphism.<sup>111</sup> The role of hydrogen-bonding networks in determining crystal structure has been discussed extensively.<sup>112</sup> Conformational differences between molecules of different structures have been admitted, perhaps reluctantly, and distinguished by the title conformational polymorphism.<sup>113</sup> The original examples form one extremity where molecules in distinctive conformations pack similarly,<sup>92</sup> 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.<sup>82</sup> The extent will depend on the rigidity of the molecules. Although some floppy ring systems maintain their shape in different forms<sup>114,115</sup> even nominally rigid structures such as the ring systems of steroids<sup>116</sup> can show substantially different conformations in different polymorphs. Heteroaromatic<sup>117-121\*</sup> and benzoquinone<sup>122</sup> planes are frequently bent and even benzene rings<sup>123</sup> 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.<sup>5</sup> 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.<sup>124</sup> The narrow line of demarcation between polymorphism, conformational polymorphism and chirality first seems to have been recognized by Eistert *et al.*<sup>125</sup> Examples of rapidly interchanging enantiomers in solution capable of independent existence in the solid state are known<sup>126,127</sup> but uncommon.

A further extension of the concept of conformational polymorphism is to be found where there is rapid interconversion between isomers.<sup>128</sup> 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.<sup>129</sup>

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<sup>130</sup> particularly in the pharmaceutical industry. The term seems unnecessary and could lead to confusion<sup>131</sup> with its use to describe all other phenomena related to polymorphism<sup>1</sup> 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.

The traditional narrow view of polymorphism, rigidly excluding chirality and isomerism, has caused considerable difficulty<sup>128</sup> 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<sup>1,37</sup> 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,<sup>5</sup> 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.<sup>98,110,132</sup> 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.<sup>107</sup> 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,<sup>133,134</sup> melt, solution<sup>126,135</sup> 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.<sup>90</sup>

### Stability of Polymorphs

Polymorphs, or strictly dimorphs where only two forms are under consideration, may be in an enantiotropic or monotropic relationship.<sup>19,136</sup> 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.<sup>137</sup> 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.<sup>8</sup> Forms outside their range of stability are described here as metastable<sup>138</sup>. 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.<sup>139</sup> 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.<sup>140</sup> The distinction between thermodynamic and kinetic transition points also needs to be drawn.<sup>141</sup>

\* In the case of phenothiazines<sup>121</sup> 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.

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