Solid-State Chemistry of Drugs

SECOND EDITION

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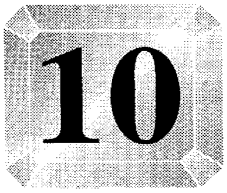


Polymorphs

As discussed in Chapter 1, polymorphs exist when two crystals have the same chemical composition but different internal structure, including different unit cell dimensions and different crystal packing. Compounds that crystallize as polymorphs can show a wide range of different physical and chemical properties, including different melting points and spectral properties. Polymorphs can also differ in their solubility, density, hardness, and crystal shape. While some compounds may exist in only two polymorphs, others may exist in many polymorphs (*e.g.*, progesterone has five polymorphs and water has nine polymorphs). Control of polymorphism is particularly important for pharmaceuticals where changing the polymorph can alter the bulk properties, dissolution rate, bioavailability, chemical stability, or physical stability of a drug. The clearest indication of the existence of polymorphs comes from the X-ray crystallographic examination of single crystals of the various samples that are known to have the same composition. Often, however, X-ray powder diffraction is sufficient to establish the existence of polymorphs.

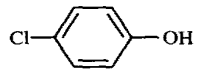
There is, unfortunately, no standard numbering system for polymorphs. In the literature, the various polymorphs have been designated by Roman numerals (preceded by the word "Form," *e.g.*, Form I), Greek letters (with the suffix "-form," *e.g.*, α-form), or in some cases, capital letters (similar to the Roman numeral system). To add to the confusion, some of numbering schemes of polymorphs also include solvates (*e.g.*, the α- and γ-forms of indomethacin are anhydrates, yet the β-form is the benzene solvate). Furthermore, some polymorphs have been identified only by their crystallographic classification (*e.g.*, the two polymorphs of (±)-β-promedol are designated the monoclinic form and the rhombohedral form). It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point. This of course would lead to confusion upon the discovery of a new polymorph having intermediate stability or melting point and thus requiring renumbering of the existing polymorph system. It has also been suggested that polymorphs be numbered consecutively in the order of discovery, but this requires knowledge of their history and a timely access to that information. Whatever the numbering system, it is imperative that it be consistent. Thus, when a new polymorph is discovered and characterized, the designation of the new polymorph should be the next increment in the

previous system. However, this is not always practical when more than one laboratory is involved in the development process at the same time.

10.1 Classic Examples of Polymorphism

This section summarizes several classic examples of polymorphism which have appeared in the chemical literature.

A. 4-Chlorophenol



4-chlorophenol

The crystal structure of both the thermodynamically stable (α) and unstable (β) forms of 4-chlorophenol have been determined (Perrin and Michel, 1973a–b). Both forms belong to the same space group ($P2_1/c$); they both have the same number of molecules per unit cell ($Z = 8$) and nearly identical densities, yet they have different cell parameters (see Table 10.1). The crystal structure of the β-form projected on the (100) plane is shown in Figure 10.1. The packing consists of tetramers of molecules connected by hydrogen bonding. The crystal packing of the α-form (shown in Figure 10.2) also consists of tetramers connected by hydrogen bonds, but the arrangement of the rings is slightly different than that of the β-form. Although the β-form converts to the α-form, no detailed studies of this transformation have been reported.

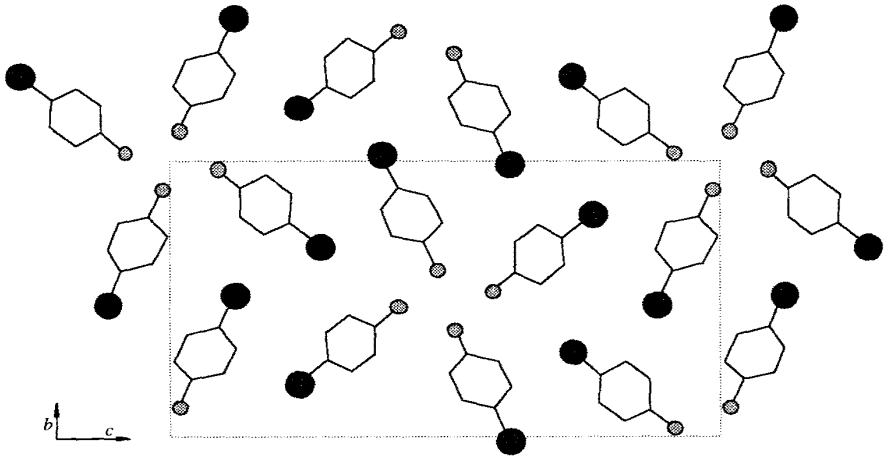


Figure 10.1 Projection of the crystal structure of the β-form of 4-chlorophenol (● chlorine atom, ◎ hydroxyl group) (Perrin and Michel, 1973b).

Table 10.1 Crystallograp
4-Chlorophen

Parameter	α-
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	9
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	122

a Perrin and Michel, 1973a.

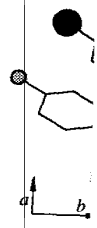
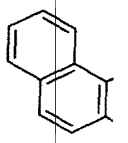


Figure 10.2 Projection of t
◎ hydroxyl gr

B. Dibenz[*a*,*h*]anthra



In an early study of polyr
[*a*,*h*]anthracene (1,2:5,6-
1947; 1956). Although th
groups (Table 10.2) and

Table 10.1 Crystallographic Parameters for Two 4-Chlorophenol Polymorphs

Parameter	α-Form[a]	β-Form[b]
Space Group	$P2_1/c$	$P2_1/c$
a (Å)	8.84	4.14
b (Å)	15.726	12.85
c (Å)	8.790	23.20
β	92.61°	93.00°
Z	8	8
ρ_{calc} (g cm^{-3})	1.40	1.38
V (Å^3)	1220.7	1232.5

a Perrin and Michel, 1973a. *b* Perrin and Michel, 1973b.

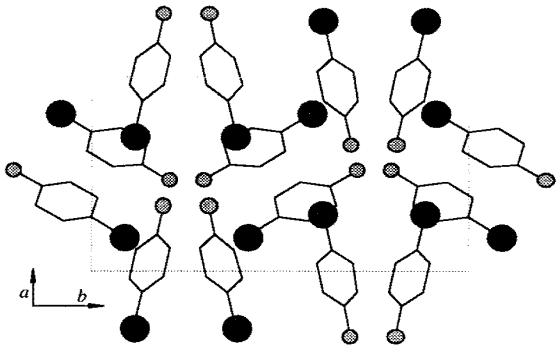
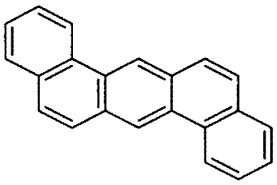


Figure 10.2 Projection of the crystal structure of the α-form of 4-chlorophenol (● chlorine atom, ◍ hydroxyl group) (Perrin and Michel, 1973a).

B. Dibenz[*a*,*h*]anthracene



dibenz[*a*,*h*]anthracene
(1,2:5,6-dibenzanthracene)

In an early study of polymorphism, the crystal structures of Forms I and II of dibenz-[*a*,*h*]anthracene (1,2:5,6-dibenzanthracene) were determined (Robertson and White, 1947; 1956). Although the forms have the same density, they belong to different space groups (Table 10.2) and have quite different packing. The crystal packing of Form I

(orthorhombic form) is shown in Figure 10.3 and the crystal packing of Form II (monoclinic form) is shown in Figure 10.4.

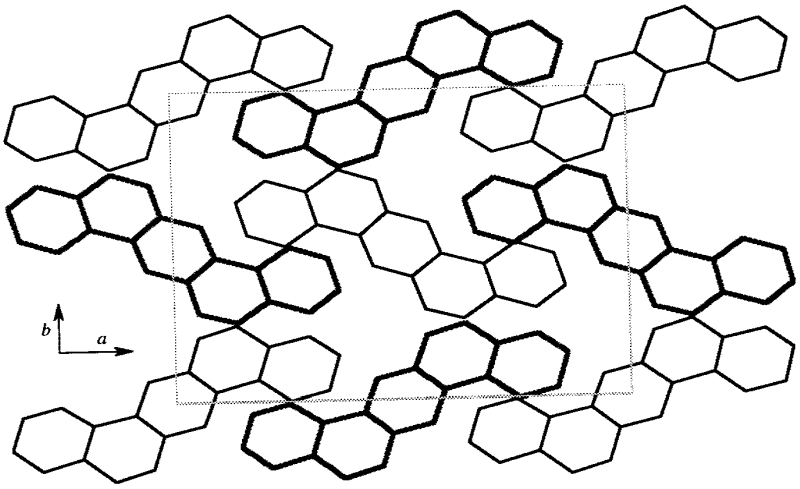


Figure 10.3 Crystal packing of Form I (orthorhombic form) of dibenz[*a*,*h*]anthracene (Robertson and White, 1947).

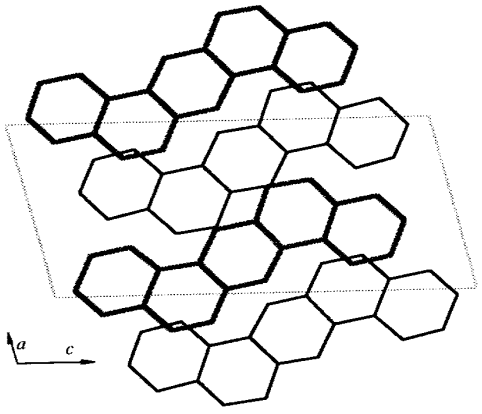


Figure 10.4 Crystal packing drawing of Form II (monoclinic form) of dibenz[*a*,*h*]anthracene (Robertson and White, 1956).

Table 10.2 Crystallographic
Dibenz[*a*,*h*]anthra

Parameter	Fo
Space group	
a (Å)	
b (Å)	1
c (Å)	1
β	9
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	141
V/molecule	35

Robertson and White, 1947; R

C. Acridine

Acridine crystallizes in fi
Schmidt, 1955). The crys
and are shown in Figures
forms appear to be quite si

Table 10.3 Crystal Parameter

Parameter	α-For
Space group	$P2_1/c$
a (Å)	16.18
b (Å)	18.88
c (Å)	6.08
β	95.67°
Z	8
ρ_{calc} (g cm^{-3})	1.27
V (Å^3)	1848.2
V/*Z* (Å^3)	231.0
Habit	Needle

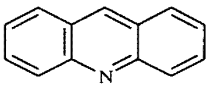
Herbstein and Schmidt, 1955

Table 10.2 Crystallographic Parameters for Two Dibenz[*a*,*h*]anthracene Polymorphs

Parameter	Form I	Form II
Space group	*Pcab*	$P2_1$
a (Å)	8.22	6.59
b (Å)	11.39	7.84
c (Å)	15.14	14.17
β	90.0°	103.5°
Z	4	2
ρ_{calc} (g cm^{-3})	1.29	1.29
V (Å^3)	1417.5	711.9
V/molecule	354.4	355.9

Robertson and White, 1947; Robertson and White, 1956.

C. Acridine



acridine

Acridine crystallizes in five polymorphs as shown in Table 10.3 (Herbstein and Schmidt, 1955). The crystal structures of the α- and γ-forms have been determined and are shown in Figures 10.5 and 10.6, respectively. The crystal packing of these forms appear to be quite similar although the cell parameters are obviously different.

Table 10.3 Crystal Parameters of the Various Polymorphs of Acridine

Parameter	α-Form	β-Form	γ-Form	δ-Form	ε-Form
Space group	$P2_1/a$	*Aa*	*Pnab*	$P2_12_12_1$	$P2_1/n$
a (Å)	16.18	16.37	17.45	15.61	11.37
b (Å)	18.88	5.95	8.89	6.22	5.98
c (Å)	6.08	30.01	26.37	29.34	13.64
β	95.67°	141.33°	90.00°	90.00°	98.67°
Z	8	8	16	12	4
ρ_{calc} (g cm^{-3})	1.27	1.29	1.15	1.24	1.29
V (Å^3)	1848.2	1826.3	4090.8	2848.7	918.2
V/*Z* (Å^3)	231.0	228.3	255.7	237.4	229.5
Habit	Needles	Plates	Laths	Laths	Prisms

Herbstein and Schmidt, 1955

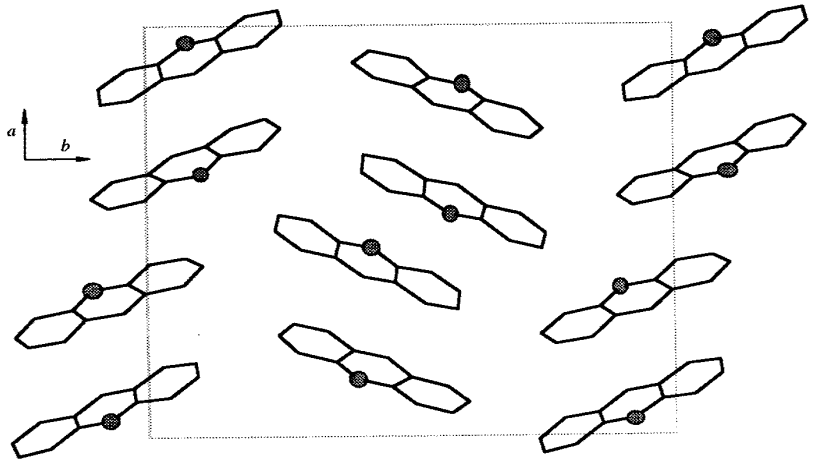


Figure 10.5 Crystal packing of acridine α-form with ● representing the nitrogen atom of the acridine ring (Phillips, 1956).

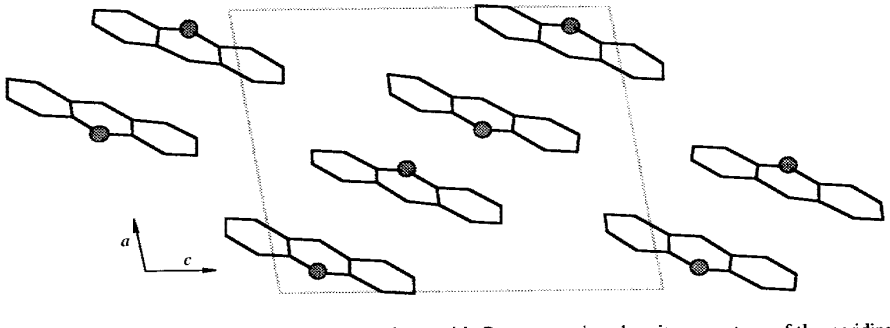


Figure 10.6 Crystal packing of acridine γ-form with ● representing the nitrogen atom of the acridine ring (Phillips *et al.*, 1960).

10.2 Conformational and Configurational Polymorphism

In this section, two special types of polymorphism will be discussed. *Conformational polymorphism* occurs when a molecule adopts a significantly different conformation in different crystal polymorphs (Bernstein, 1987). (The term "significantly different" is open to interpretation.) This term does not adequately describe cases where different types of isomers crystallize in different forms. Thus an additional term—*configurational polymorphism*—is defined. Configurational polymorphism exists when different

configurations (*i.e.*, *cis*,
forms.

Crystallization of *ci*
occurs whenever the pu
forms in separate crystal
The crystallization of equ
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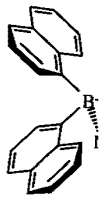
phism can be used to is
crystalline form.

A. Tri-α-Naphthylb



tri-α-naphth
For

Brown and Sujishi (1948
with the following observ

1. Two crystalli
2. The metastab
   room tempera
3. The dissociat
   stable form.
4. Removal of N
   naphthylboro

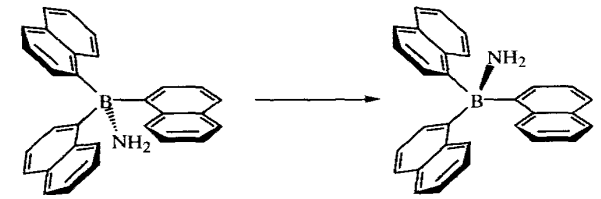
Based on these results,
above. In these forms, th
that the NH_3 is connected
and the less hindered side
ence in dissociation press
the same conformer of tri-
being the most sterically h

Unfortunately, while
formational polymorphism
The example, neverthele
polymorph formation.

configurations (*i.e.*, *cis*,*trans* isomers or tautomers) crystallize in separate crystalline forms.

Crystallization of *cis*,*trans* isomers in different crystalline forms is well known and occurs whenever the pure isomer is crystallized. Crystallization of pure tautomeric forms in separate crystals leads to what may be called *tautomerizational polymorphism*. The crystallization of equilibrating isomers in configurational polymorphs is of significantly more interest. When this occurs, the phenomenon of configurational polymorphism can be used to isolate and study the individual isomers provided they exist in crystalline form.

A. Tri-α-Naphthylboronamine



tri-α-naphthylboronamine
Form A

tri-α-naphthylboronamine
Form B

Brown and Sujishi (1948) reported an early example of conformational polymorphism with the following observations:

1. Two crystalline forms of tri-α-naphthylboronamine are found.
2. The metastable Form A is converted to the stable Form B slowly at room temperature and rapidly above 100 °C.
3. The dissociation pressure of the metastable form is higher than the stable form.
4. Removal of NH_3 from either form gives identical samples of tri-α-naphthylboron.

Based on these results, the two forms were suggested to have structures depicted above. In these forms, the conformation of the tri-α-naphthylboron is the same except that the NH_3 is connected to the boron on the more hindered side for the unstable form and the less hindered side for the stable form. Thus these structures explain the difference in dissociation pressures of the two forms and the fact that removal of NH_3 gives the same conformer of tri-α-naphthylboron. They also explain why the unstable form, being the most sterically hindered, can be converted to the stable form.

Unfortunately, while tri-α-naphthylboron was one of the first suggestions of conformational polymorphism, it was never confirmed by X-ray crystallographic analysis. The example, nevertheless, points out some of the molecular factors that influence polymorph formation.

B. Ethyl 2-[(phenylmethyl)amino]-2-butenoate

ethyl *Z*-2-[(phenylmethyl)-amino]-2-butenoate

ethyl *E*-2-[(phenylmethyl)-amino]-2-butenoate

Infrared studies (Dabrowski, 1963) and NMR studies (Dudek and Volpp, 1963) indicate that the Schiff base ethyl 2-[(phenylmethyl)amino]-2-butenoate (ethyl β-benzylaminocrotonate) exists in configurational polymorphs; the low-melting form (mp 23 °C) has the *cis*- or *Z*-conformation and the high-melting form (mp 75–80 °C) has the *trans*- or *E*-conformation. These conformers equilibrate in solution, but upon crystallization, the configurations shown are "frozen" out in their respective polymorphic structures.

The crystal structure of the *E*-isomer has been determined in our laboratory (Shieh *et al.*, 1983). Crystals of the *E*-isomer belong to space group $P2_12_12_1$ with a = 19.655 Å, b = 5.778 Å, and c = 10.632 Å. Figure 10.7 shows the structure of this isomer, and indeed it has the structure of the *E*-isomer suggested by spectroscopic evidence (Dudek and Volpp, 1963).

The NMR and IR spectra of ethyl 2-[(phenylmethyl)amino]-2-butenoate are completely consistent with this assignment. A solution-NMR spectrum of the low-melting form (prepared by dissolving crystals at low temperature) indicates that it is indeed the *Z*-isomer (Dudek and Volpp, 1963). In this experiment the isomer present in the solid state predominates in solution because of the low temperature. In our laboratory we have studied the isomerization rate of the *Z*-isomer to the *E*-isomer at ambient temperature in DMSO where it is relatively rapid. Measurement of the rate of this reaction at various temperatures gives an activation energy of 56.9 kJ/mol.

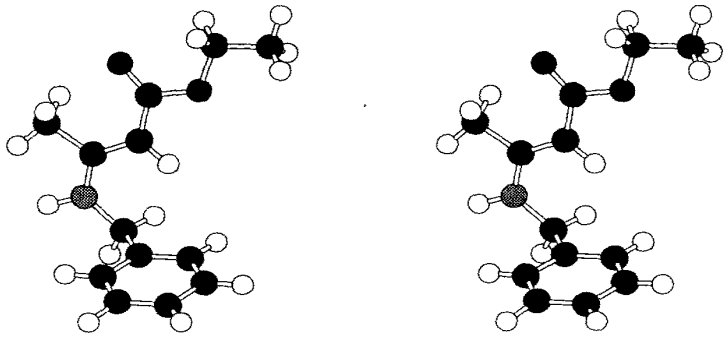
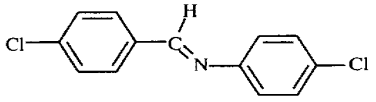


Figure 10.7 Stereoview of ethyl 2-[(phenylmethyl)amino]-2-butenoate in the high-melting *E*-isomer: H ○, C ●, N ◎, O ● (Shieh*et al.*, 1983).

The energies in kJ/mol for a number of rotamers of the *E*- and *Z*-isomers have been calculated using the *CAMSEQ* program (Weintraub and Hopfinger, 1975) which employs semiempirical potential and electrostatic functions to calculate the energies of each rotamer. These calculations indicate that the conformation of the *E*-isomer as determined by X-ray crystallography is one of the lowest energy conformations, although the *E*- and *Z*-isomers have nearly the same energy in a vacuum.

C. 4-(*N*-Chlorobenzylidene)-4-chloroaniline



4-(*N*-chlorobenzylidene)-4-chloroaniline

The Schiff base 4-(*N*-chlorobenzylidene)-4-chloroaniline crystallizes in two polymorphs (Bernstein and Hagler, 1978). Although the structures of both polymorphs are disordered, it can be seen that the conformation of the molecule is strikingly different in the two polymorphs. Hence, these forms are termed conformational polymorphs. Conformational polymorphism of drugs is discussed in more detail later in Section 10.11. In the stable (triclinic) form, the molecules are planar, whereas in the unstable (orthorhombic) form the phenyl rings are rotated by equal but opposite amounts (24.8°) with respect to the H—C=N least-squares plane of the imine. The crystal packings of these two forms is shown in Figures 10.8 and 10.9.

Molecular orbital and lattice energy calculations were used to analyze the reasons for conformational polymorphism of 4-(*N*-chlorobenzylidene)-4-chloroaniline (Bernstein and Hagler, 1978). Quantum-mechanical calculations for a single molecule

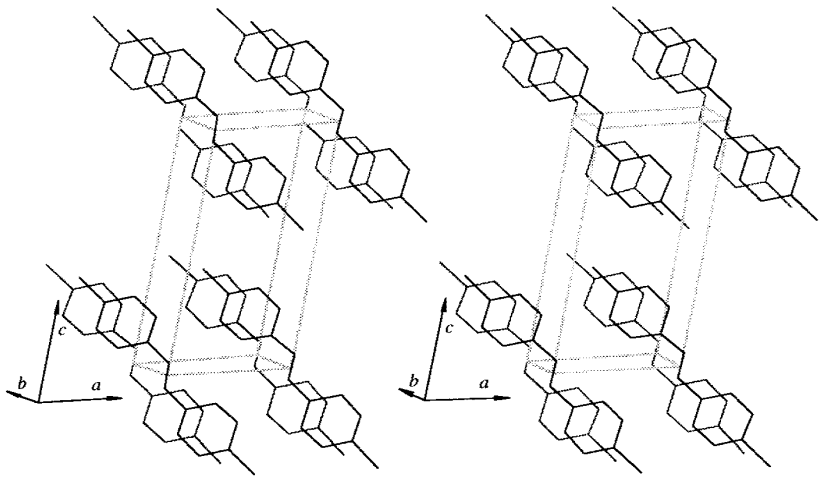


Figure 10.8 Stereoview of 4-(*N*-chlorobenzylidene)-4-chloroaniline triclinic polymorph (Bernstein and Hagler, 1978).

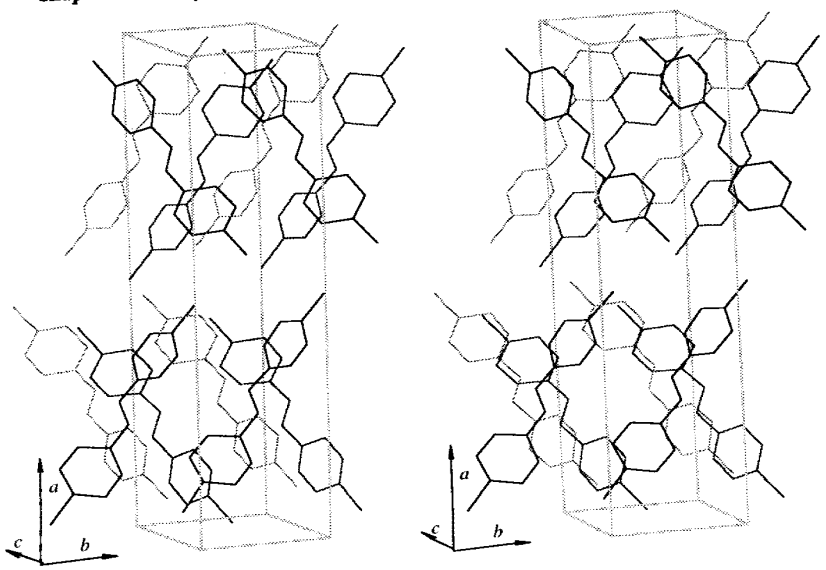
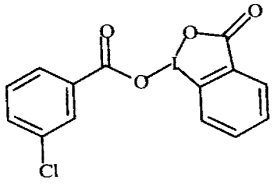


Figure 10.9 Crystal packing stereoview of 4-(*N*-chlorobenzylidene)-4-chloroaniline orthorhombic form. (Bernstein and Hagler, 1978).

showed that the nonplanar conformation was energetically favored by perhaps 2.09–6.28 kJ/mol but the lattice-energy calculations, using semiempirical potential functions, showed that the planar structure (triclinic form) gave a lower lattice energy by about 4.19 kJ/mol. These calculations explain why the triclinic polymorph is the stable crystalline polymorph even though it contains the less stable (planar) conformer.

Programs that calculate the packing energy are now available, for example, *Cerius*[2] (Molecular Simulations, Inc., 1997). These programs alone or in combination with structure elucidations based on powder diffraction data will provide new approaches to the structure analysis of materials when suitable single crystals are not available.

D. 3-Oxo-3*H*-2,1-benzoxiodol-1-yl 3-Chlorobenzoate



3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate

As part of their extensive study of the crystal chemistry of iodoperoxides, Gougoutas and Lessinger (1974) determined the crystal structure of two polymorphs of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate. This compound crystallizes in α- and β-forms that both belong to the monoclinic crystal system (Table 10.4).

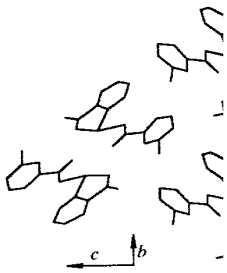


Figure 10.10 The crystal pa
(Gougoutas and

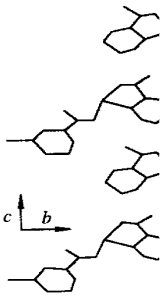


Figure 10.11 The crystal
(Gougoutas and

Table 10.4 Crystallographic
2,1-benzoxiodol-

Parameter
Space Group
a (Å)
b (Å)
c (Å)
β
Z
ρ_{calc} (g cm^{-3})
V (Å^3)

Gougoutas and Lessinger, 19

The α-form is essent
rings make an angle of a
two forms is also quite

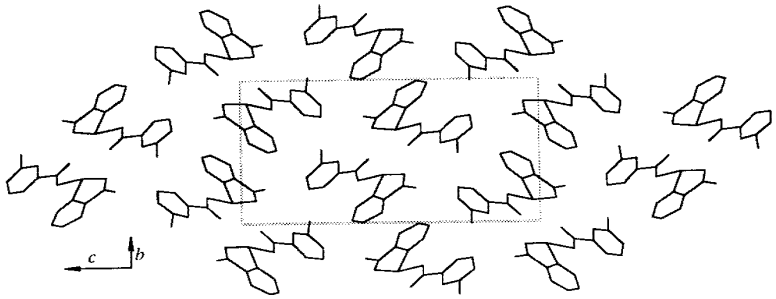


Figure 10.10 The crystal packing of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate α-form (Gougoutas and Lessinger, 1974).

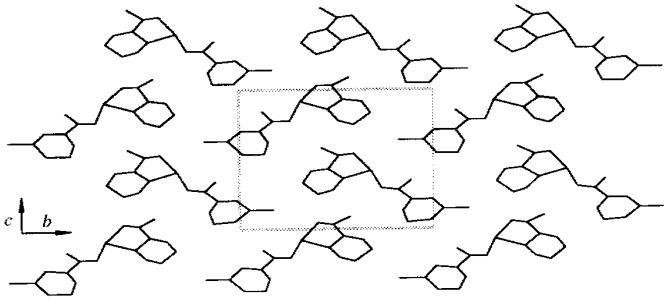


Figure 10.11 The crystal packing of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate β-form (Gougoutas and Lessinger, 1974).

Table 10.4 Crystallographic Unit Cell Parameters for 3-Oxo-3*H*-2,1-benzoxiodol-1-yl 3-Chlorobenzoate

Parameter	α-Form	β-Form
Space Group	$P2_1/n$	Pc
a (Å)	6.376	5.057
b (Å)	10.547	13.035
c (Å)	20.066	10.339
β	92.0°	99.5°
Z	4	2
ρ_{calc} (g cm^{-3})	1.984	2.009
V (Å^3)	1348.6	672.2

Gougoutas and Lessinger, 1974.

The α-form is essentially planar in the crystal while in the β-form the two phenyl rings make an angle of approximately 55° with each other. The crystal packing of the two forms is also quite different as shown in Figures 10.10 and 10.11. These two

forms have different solid-state infrared spectra (see Figure 10.12), as expected since the molecule is in different conformation in the two crystal forms.

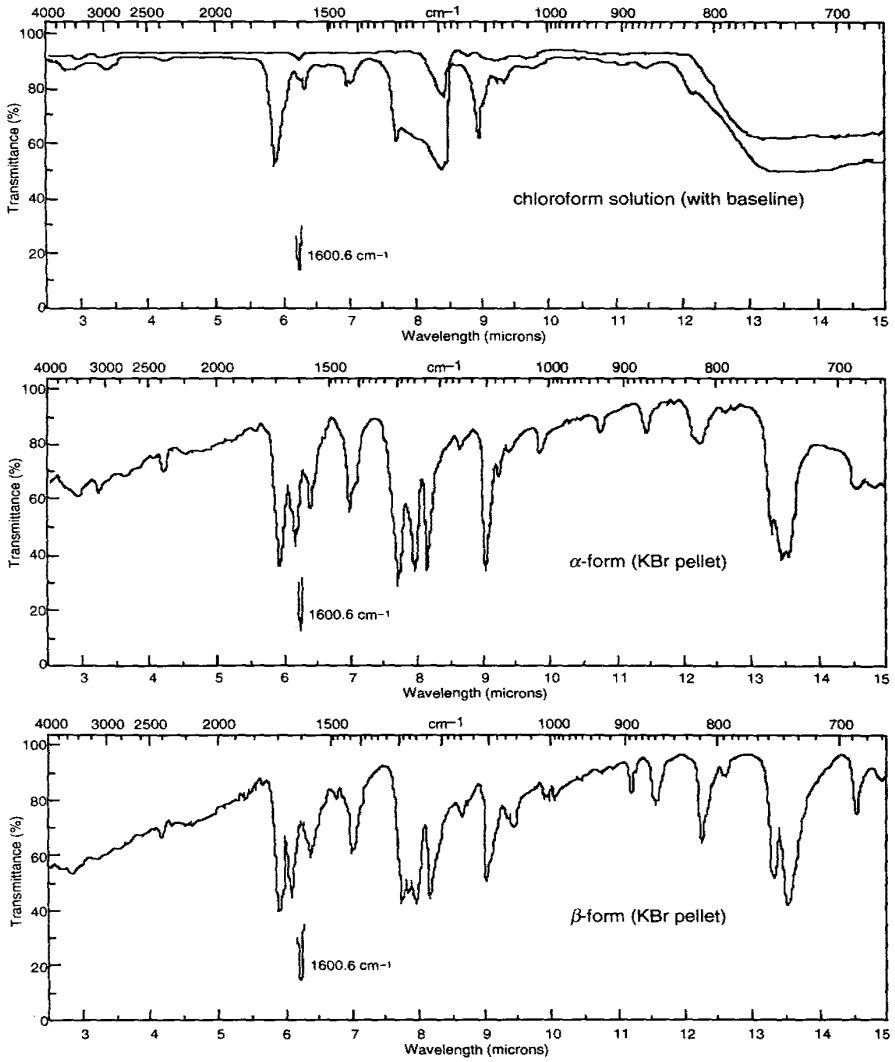
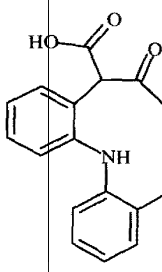


Figure 10.12 Infrared spectra of 3-oxo-3*H*-2,1-benzoxiodol-1-yl 3-chlorobenzoate (Gougoutas and Lessinger, 1974).

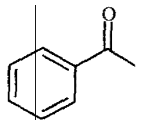
E. TAUTOMERIZATION



keto for
3-(4-chlorop
2-[2-(2-(methoxyca
amino)phenyl]-3-oxo

Schulenberg (1968) has
phenyl)amino)phenyl]-3
form has a melting point
consistent with the
phenyl)amino)phenyl]-3
110–122 °C and upon di
(4-chlorophenyl)-3-hydr
acid. Addition of triethy
ing 70% of the keto forn

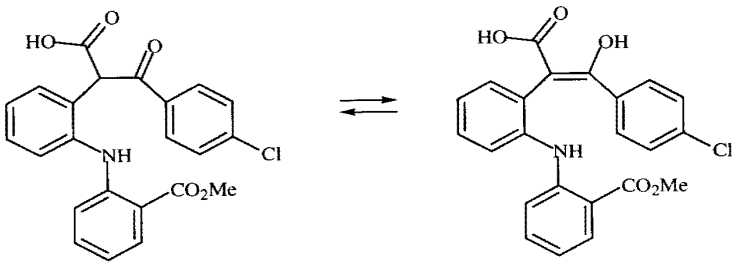
Although the crysta
mined, this study illustra
containing an individual
phism (*cf.* p. 143).



E-conformer of t
1,3-diphenylprop

Several other case
enol of 1,3-diphenylprc
the *E*-isomer and the ot
there are numerous exar
isomer or tautomer out
(1972).

E. Tautomerizational Polymorphism

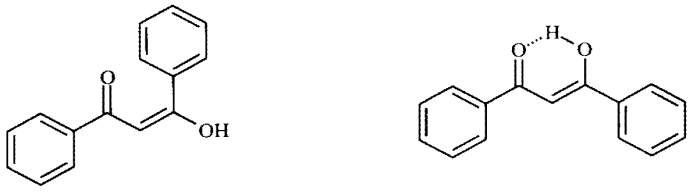


keto form
3-(4-chlorophenyl)-2-[2-(2-(methoxycarboxyphenyl)-amino)phenyl]-3-oxopropanoic acid

enol form
3-(4-chlorophenyl)-3-hydroxy-2-[2-(2-(methoxycarboxyphenyl)-amino)phenyl]propenoic acid

Schulenberg (1968) has reported that 3-(4-chlorophenyl)-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]-3-oxopropanoic acid crystallizes in two tautomeric forms. One form has a melting point of 93–99 °C that upon dissolution in $CDCl_3$ gave NMR spectra consistent with the keto form, 3-(4-chlorophenyl-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]-3-oxopropanoic acid. The other form had a melting point of 110–122 °C and upon dissolution gave NMR spectra consistent with the enol form, 3-(4-chlorophenyl)-3-hydroxy-2-[2-(2-(methoxycarboxyphenyl)amino)phenyl]propenoic acid. Addition of triethylamine to either solution gave an equilibrium mixture containing 70% of the keto form and 30% of the enol form.

Although the crystal structures of the keto and enol forms have not been determined, this study illustrates a case in which two different crystalline forms exist, each containing an individual tautomer. This situation is termed tautomerizational polymorphism (*cf.* p. 143).



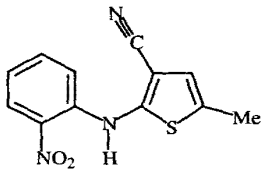
E-conformer of the enolate of
1,3-diphenylpropane-1,3-dione

Z-conformer of the enolate of
1,3-diphenylpropane-1,3-dione

Several other cases of tautomerizational polymorphism exist. For example, the enol of 1,3-diphenylpropane-1,3-dione crystallizes in two forms. One form contains the *E*-isomer and the other contains the *Z*-isomer (Eistert *et al.*, 1952). In addition, there are numerous examples of the crystallization process freezing one configurational isomer or tautomer out of solution. These cases are reviewed by Curtin and Engelmann (1972).

F. Polychromism

One of the most striking differences in physical properties among polymorphs is **polychromism** (*i.e.*, different colors). Polychromism has been reported for only a limited number of cases. Dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate, for example, crystallizes in yellow, light-yellow, and white polymorphs (Byrn *et al.*, 1972; Fletton *et al.*, 1986; Yang *et al.*, 1989; Richardson *et al.*, 1990). The colors of these three polymorphs are attributed to differences in orientation of the carboxylate group with respect to the aromatic ring (see also Sections 10.7E and 20.1A).



5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
(ROY)

5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile is a dramatic example of polychromism. Crystallization of this compound from ethanol yields a mixture of yellow and red prisms, whereas crystallization from methanol yields orange needles; hence the alias ROY for the red, orange, and yellow forms (Borchardt, 1997). Crystals of the red form also appear to be **pleochroic**, displaying both red and orange colors under polarized illumination.

The three polymorphs are free of solvent and stable at room temperature. The red, orange, and yellow forms are similar in energy with melting points of 106.2, 114.8, and 109.8 °C, respectively (Yu, 1998). The red and orange forms undergo solution-mediated transformation to the yellow form at room temperature, indicating the latter is the most stable at room temperature. The yellow and orange forms are related enantiotropically, with yellow being more stable at low temperature. Between room temperature and the melting point, the red form is always less stable than the yellow form. The heats of melting, as measured by DSC, confirmed these stability relationships. Solid-state phase transitions from red to yellow and from red to orange have been observed between 70—90 °C in a solvent free environment. The transition from red to yellow (at temperatures greater than 90 °C) results in a dramatic change in color but no apparent change in crystal morphology, whereas the transition from red to orange leads to the growth of orange needles from the initial red crystals.

The crystal structures of red, orange, and yellow forms have been determined by single-crystal X-ray diffraction and show that the molecule adopts a dramatically different conformation in each of the forms. Subsequent studies show that these different conformations are the reasons for the different colors. Hydrogen bonding in the polymorphs is exclusively intramolecular—between the adjacent amine and nitro substituents. The heteroatom-to-heteroatom distances of the hydrogen bond in red, orange, and yellow are 2.636(2), 2.607(3), and 2.625(3) Å, respectively. The conformations of the molecule in the three polymorphs are significantly different (Figure 10.13). In the yellow and orange forms, the nitro group is essentially co-planar with the phenyl ring, whereas in the red form it is twisted out-of-plane by 18°. The color of the polymorphs may be related to the degree of electron delocalization, which is related to the angle between the planes of the phenyl and the thiophene moieties (red 46°,

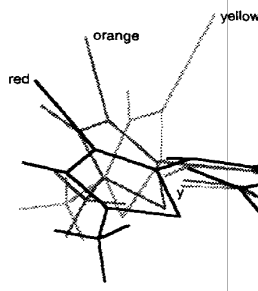


Figure 10.13 Conformations
crystalline form

orange 54°, and yellow 1(
order of the expected w
Section 8.1). Studies ha
direct result of the differe
1998; Yu, 1998). The ol
those calculated from the
^{13}C CP/MAS solid-st
tinguish the polymorphs.
reported for polymorphic
shifts of C3 (the carbon in
97.9, 105.2, and 109.3
covering a range of 11
104.41 ppm in solution.)
red form with respect to t
conjugation effect. Smitl
(total suppression of spir
shift anisotropy (CSA) o
increases in magnitude by
ric as the coplanar angle
electrons between the tw
site.

This parallels the re
quency are 2211, 2223,
tively (see Section 8.1).
the red form from a highe
vations confirm the signi
pronounced color change

A number of deriva
nitrile were synthesized
nitrophenylaminothiophe
Me) crystallized in three
the gold form were un
polymorph" class. How

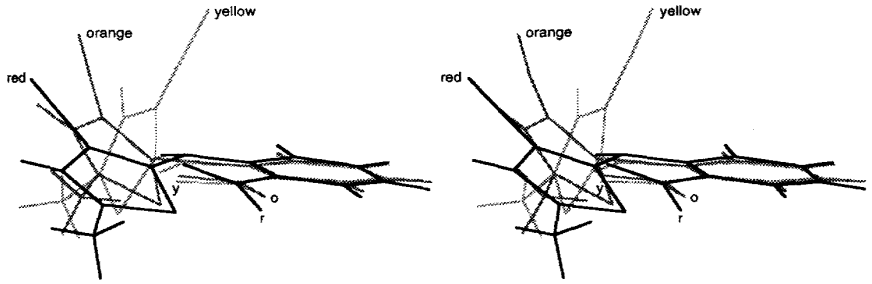


Figure 10.13 Conformations of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile in three crystalline forms.

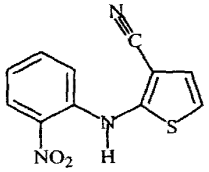
orange 54°, and yellow 106°). The order of these angles appears to correlate with the order of the expected wavelengths of absorption by the colored polymorphs (see Section 8.1). Studies have shown that the different colors of the polymorphs are a direct result of the difference in molecular conformation (Borchardt, 1997; Smith *et al.*, 1998; Yu, 1998). The observed XRPD patterns of the three polymorphs agree with those calculated from the single-crystal structures.

^{13}C CP/MAS solid-state NMR, solid-state FT-IR, and XRPD can be used to distinguish the polymorphs. The observed spectral differences are among the largest reported for polymorphic organic compounds. For example, the ^{13}C NMR chemical shifts of C3 (the carbon in the thiophene ring to which the nitrile group is attached) are 97.9, 105.2, and 109.3 ppm for the red, orange, and yellow forms, respectively, covering a range of 11.4 ppm. (For comparison, the chemical shift of C3 is 104.41 ppm in solution.) This indicates an increase in the electron density of C3 in the red form with respect to the yellow and orange forms, possibly a result of an increased conjugation effect. Smith and coworkers (1998) have used a two-dimensional TOSS (total suppression of spinning sidebands) pulse sequence to investigate the chemical-shift anisotropy (CSA) of C3. These studies show that the extent of the CSA for C3 increases in magnitude by 30 ppm and the line shape appears to become more asymmetric as the coplanar angle increases. This was taken to reflect a greater transfer of π electrons between the two ring systems and hence a greater electron density at the C3 site.

This parallels the results from IR spectroscopy in which the nitrile stretching frequency are 2211, 2223, and 2231 cm^{-1}, for the red, orange, and yellow forms, respectively (see Section 8.1). This shift is indicative of the decreased nitrile bond strength in the red form from a higher degree of conjugation with the aromatic ring. These observations confirm the significant changes in the electronic structure, as demonstrated by pronounced color changes among different polymorphs.

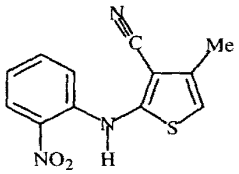
A number of derivatives of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile were synthesized in order to determine the extent of the color polymorphism of nitrophenylaminothiophenes. 2-[(2-Nitrophenyl)amino]-3-thiophenecarbonitrile (NorMe) crystallized in three forms: red, orange, and gold. Numerous attempts to obtain the gold form were unsuccessful thus placing the gold from in the "disappearing polymorph" class. However, crystallization of a newly synthesized lot of NorMe gave

the gold form once again only to disappear when the material was subjected to further crystallization and handling. As with other disappearing polymorphs, this behavior is due to the presence of impurities and the fact that the gold polymorph is unstable in the presence of seeds of the other forms (Dunitz and Bernstein, 1995).

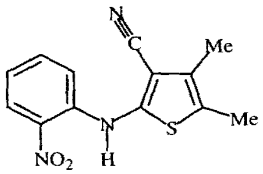


2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
(NorMe)

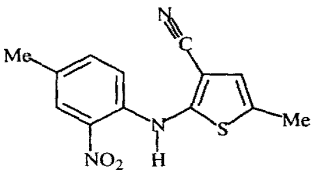
The XRPD patterns of the three forms of NorMe are different from the parent compound. The crystal structure of the red form NorMe was determined (Borchardt, 1997). The red form is nearly coplanar further substantiating the concept that the red color is associated with planarity. The IR spectra of the NorMe polymorphs are quite similar to ROY. The red form has a nitrile stretching absorption at 2210 cm^{-1}, the orange is a 2222 cm^{-1}, and the yellow at 2230 cm^{-1}.



4-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
(4-Me)



4,5-dimethyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile
(4,5-DiMe)



5-methyl-2-[(4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile
(4'-Me)

The conformation of the red form of 4-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4-Me) is the most coplanar of the structures determined (see Figure 10.14). 4,5-Dimethyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (4,5-DiMe) crystallized in two polymorphs: red and orange. As with the previous derivatives, the conformation of the red form as determined by single-crystal X-ray methods is rather coplanar (see Figure 10.14). 5-Methyl-2-[4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (4'-Me) was crystallized in red, dark red, light red, and orange forms. Only the red form gave crystals suitable for structure determination. As with the previous derivatives, this red form has a nearly coplanar conformation. Figure 10.14 compares the conformation of the various red forms in this nitrophenylaminothiophene series. In all cases, the red form has the most coplanar conformation of the polymorphs. This further supports the conclusion that the conformation of the nitrophenylaminothiophene determines the color of the polymorph.

Griesser and He (1998) have carried out a preliminary study of the solubilities and interconversions of the four forms of 4'-Me and found that all four forms are within 4 kJ/mol or less of each other in energy. These studies allowed the development of the energy–temperature diagram (see Section 5.2) shown in Figure 10.15. Such diagrams

are extremely usefu
polymorphs.

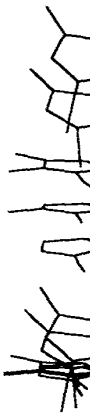


Figure 10.14 Stereovie
the thiop
Hydroger

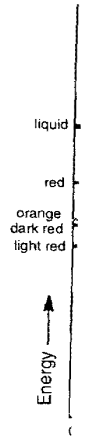


Figure 10.15 Energy–t
phenyl)a

are extremely useful in visualizing the energy–temperature relationships between polymorphs.

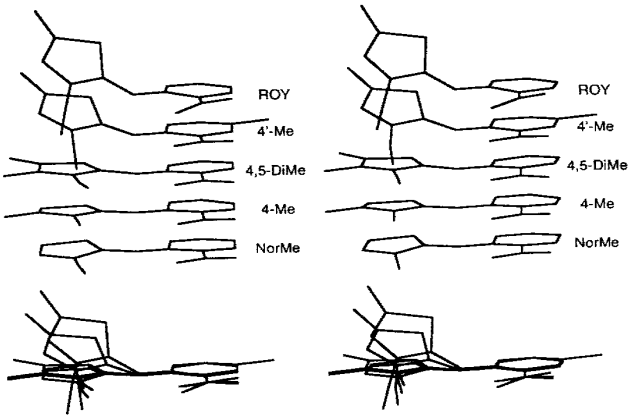


Figure 10.14 Stereoview showing a comparison (both stacked and overlayed) of the conformations of the thiophene and phenyl rings in the nitrophenylaminothiophene series red forms. Hydrogens were omitted for clarity.

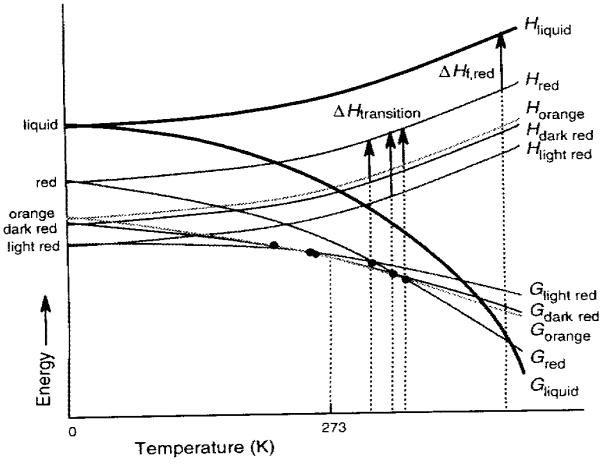


Figure 10.15 Energy–temperature diagram for the four forms of 5-methyl-2-[4-methyl-2-nitrophenyl)amino]-3-thiophenecarbonitrile (Griesser and He, 1998).

10.3 SULFONAMIDES

The polymorphism of sulfonamides has been investigated and reviewed by Kuhnert-Brandstätter (1971). These studies were carried out using microscopy on a Kohfler hot stage (see Section 4.4). Sulfonamides exhibited behavior expected of polymorphs, including successive melting points as the temperature is raised and changes in color under crossed Nicol gratings (crossed polarizers). Table 10.5 summarizes the results of Kuhnert-Brandstätter's (1971) studies on these compounds.

Although all of these studies have not been confirmed by crystallographic data, the crystal structures of several polymorphs of sulfonamides have been determined and will

Table 10.5 Polymorphism of Sulfonamides and Related Compounds[a]

Compound	Melting Point of Form (°C)						
	I	II	III	IV	V	VI	VII
Acetazolamide	258-260	248-250					
Acetyl Sulfisoxazole	190-195	176-177	173-174				
Chlorthalidone	212-224	188-189					
Clofenamide	210-215	203-207	183-185	168-170			
Diphenylmethane-4,4'-disulfonamide	185-187	172-174					
Mafenide HCl	250-260	235-240	220-225	210-212			
4'-(Methylsulfamoyl)-sulfanilanilide	148-151	144-146					
Phthalylsulfathiazole	260-274	230					
Sulfachlorpyridazine	196-197	178-181					
Sulfadicramide	176-180	174-176					
Sulfadimethoxine	194-198	176-177	156-158				
Sulfaethidole	188	181	149				
Sulfaguanidine	187-191	174-176	143-145				
Sulfameline	210-212	197-199	181-183	179-181	176-177	155	
Sulfamerazine	235-238	228					
Sulfamethazine	206-208	199	178	~175			
Sulfamethizole	209	193					
Sulfamethoxazole	169	168	166				
Sulfamethoxypyridazine	180-182	158-159	153-154				
Sulfamidochrysoidine	224-228	217-219	212				
Sulfamoxole	200-204	188-195	177-180				
Sulfanilamide	165	156	153				
N-Sulfanilyl-3,4-xylamide	215-218	208	203	196			
Sulfapyridine	192	185	179	176	174	167	149
Sulfathiazole	202	175	162	158			
Sulfathiourea	178-180	168-171					
Sulfatriazine	158-166	132-135					
Sulfazamet	182-185	176-178					
Sulfisoxazole	190-195	131-133					
Tolbutamide	127	117	106				

[a] Kuhnert-Brandstätter (1971).

be discussed next. In gen
polymorphs. Thus, in th
ble for polymorphism.

A. SULFANILAMIDE

NH

Sulfanilamide exists in th
ters shown in Table 10.6
(O'Conner and Maslen,
phenyl rings. In each sta
···amino···sulfonamide··
substituent in each stack.

The crystal packing
the α-form (Alleaume an
but the order of the s
···amino···sulfonamide··
stack.

The crystal packing
10.18 appears, in genera
sulfonamide amino grou
successive rings in a sta
which resembles that of t

The density of the
(see Table 10.6). The p
sulfanilamide have been
diagram constructed. It i
group is similar in all for
plane of the phenyl ring
relationships between th
depicted in Figures 10.1
10.19.

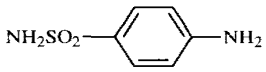
Table 10.6 Crystallographi

Parameter	
Space group	
a (Å)	
b (Å)	
c (Å)	
β	
Z	
ρ_{calc} (g cm^{-3})	
V (Å^3)	

O'Conner and Maslen, 1965

be discussed next. In general, the conformations of the drug are similar in the different polymorphs. Thus, in these cases, differences in crystal packing are mainly responsible for polymorphism.

A. Sulfanilamide



sulfanilamide

Sulfanilamide exists in three crystalline forms which have the crystallographic parameters shown in Table 10.6. The α-form has the crystal packing shown in Figure 10.16 (O'Conner and Maslen, 1965). The crystal packing of this form contains layers of phenyl rings. In each stack, the order of the substituent groups on successive rings is ···amino···sulfonamide···sulfonamide···amino···, etc., resulting in alternating pairs of substituent in each stack.

The crystal packing of the β-form shown in Figure 10.17 is quite different from the α-form (Alleaume and Decap, 1965). There are, again, columns of phenyl rings but the order of the substituent groups on successive rings is ···sulfonamide··· ···amino···sulfonamide···amino···, etc., resulting in alternating substituents in the stack.

The crystal packing of the γ-form (Alleaume and Decap, 1966) shown in Figure 10.18 appears, in general, to be similar to the α-form with layers of phenyl rings and sulfonamide amino groups. In these columns, the order of substituent groups on successive rings in a stack is ···amino···sulfonamide···amino···sulfonamide···, etc., which resembles that of the β-form.

The density of the β-form (the most thermodynamically stable form) is greatest (see Table 10.6). The polymorphic interconversions and thermodynamic properties of sulfanilamide have been investigated by Burger (1973a–b) and an energy-temperature diagram constructed. It is interesting to note that the conformation of the sulfanilamide group is similar in all forms, with the nitrogen atom being the atom furthest out of the plane of the phenyl ring. A comparison of the α-, β-, and γ-forms showing the relationships between the arrangement of the substituents in successive molecules depicted in Figures 10.16, 10.17, and 10.18 is illustrated in a stereoview in Figure 10.19.

Table 10.6 Crystallographic Data for the Polymorphs of Sulfanilamide

Parameter	Form α	Form β	Form γ
Space group	*Pbca*	$P2_1/c$	$P2_1/c$
a (Å)	5.65	8.98	7.95
b (Å)	18.51	9.01	12.95
c (Å)	14.79	10.04	7.79
β	90.00°	111.43°	106.50°
Z	8	4	4
ρ_{calc} (g cm^{-3})	1.47	1.51	1.49
V (Å^3)	1547.1	755.2	768.7

O'Conner and Maslen, 1965

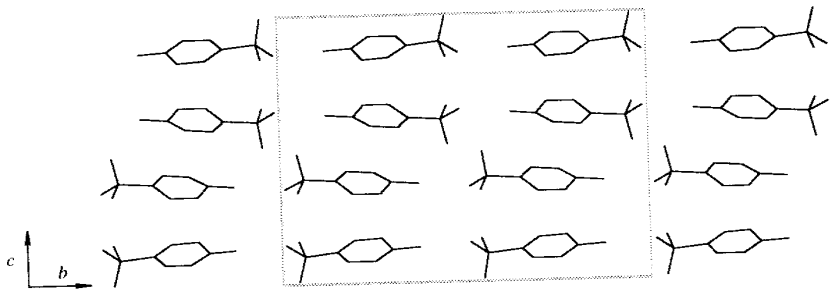


Figure 10.16 Molecular packing of the α-form of sulfanilamide (O'Conner and Maslen, 1965).

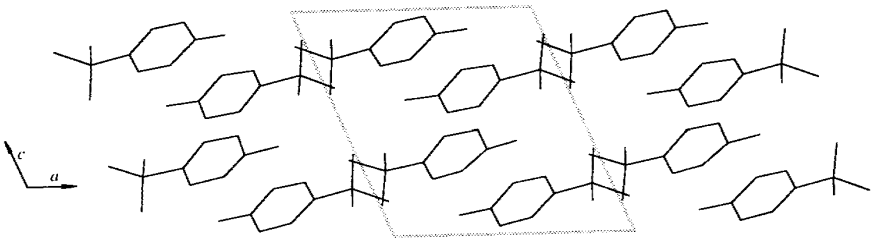


Figure 10.17 The crystal packing of the β-form of sulfanilamide (Alleaume and Decap, 1965).

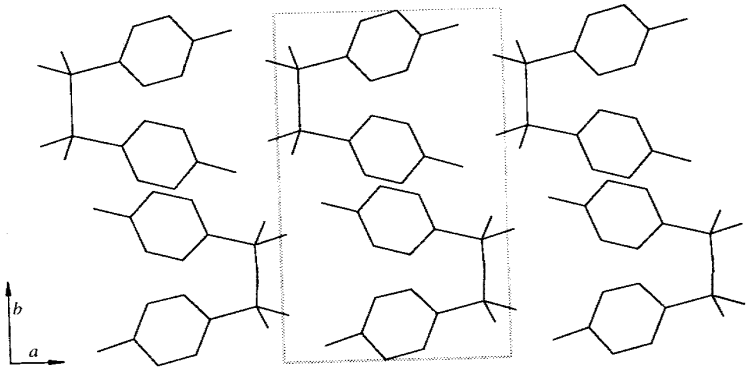


Figure 10.18 Crystal packing of the γ-form of sulfanilamide (Alleaume and Decap, 1966).

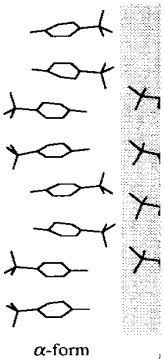


Figure 10.19 Stereovie
α-, β-, ar

B. SULFATHIAZOLE

NH_2

Table 10.7 indicates
(1983) have studied
the four polymorphs.
dynamically stable at
of all three polymorp
mide group is the at
This is in marked si
molecule in all three
between these forms

Table 10.7 Crystallogr

Parameter
Space Group
a (Å)
b (Å)
c (Å)
β
Z
ρ_{meas} (g cm^{-3})
V (Å^3)
Habit
Melting point
Transition point

a Kruger and Gafner, 19

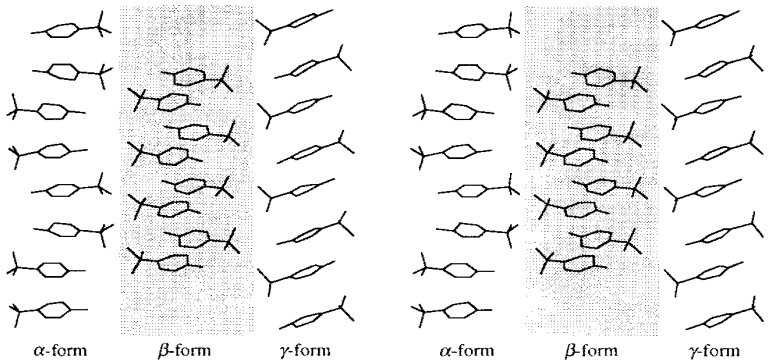
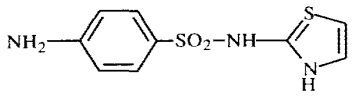


Figure 10.19 Stereoview showing the molecular arrangement of sulfanilamide columns in the α-, β-, and γ-forms.

B. Sulfathiazole



sulfathiazole

Table 10.7 indicates that sulfathiazole exists in four polymorphs. Burger and Dialer (1983) have studied this system and have produced an energy-temperature diagram of the four polymorphs. Form I is the least stable of the four forms; Form III is thermodynamically stable at room temperature. Figures 10.20–10.22 show packing drawings of all three polymorphs of sulfathiazole. It is obvious that the nitrogen of the sulfonamide group is the atom that is the greatest distance from the plane of the phenyl ring. This is in marked similarity to sulfanilamide. In addition, the conformation of the molecule in all three forms is very similar. The major crystallographic difference between these forms is the nature and type of hydrogen bonds.

Table 10.7 Crystallographic Parameters for the Polymorphs of Sulfathiazole

Parameter	Form I[a]	Form II[b]	Form III[a]
Space Group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a (Å)	10.554	8.235	17.570
b (Å)	13.220	8.550	8.574
c (Å)	17.050	15.558	15.583
β	108.06°	93.67°	112.93°
Z	8	4	8
ρ_{meas} (g cm^{-3})	1.50	1.55	1.57
V (Å^3)	2261.7	1093.2	2162.0
Habit	Rods	Hexagonal prisms	Hexagonal plates
Melting point	200-202	200-202	173-175 (or 200-202)
Transition point	...	173-175	173-175

a Kruger and Gafner, 1971a. *b* Kruger and Gafner, 1971b.

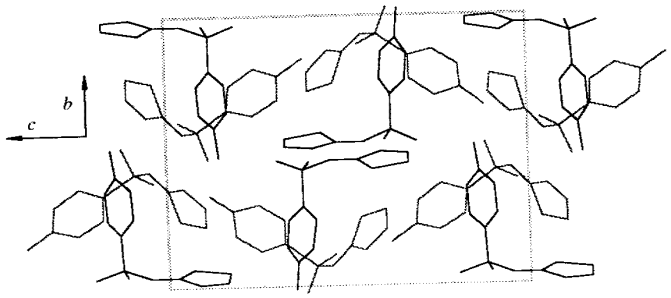


Figure 10.20 Crystal packing of sulfathiazole Form I (Kruger and Gafner, 1971a).

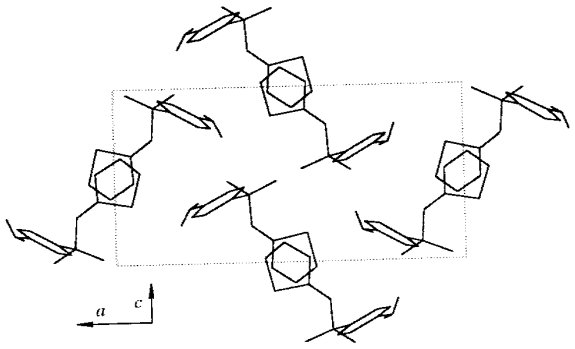


Figure 10.21 Crystal packing of sulfathiazole Form II (Kruger and Gafner, 1971b).

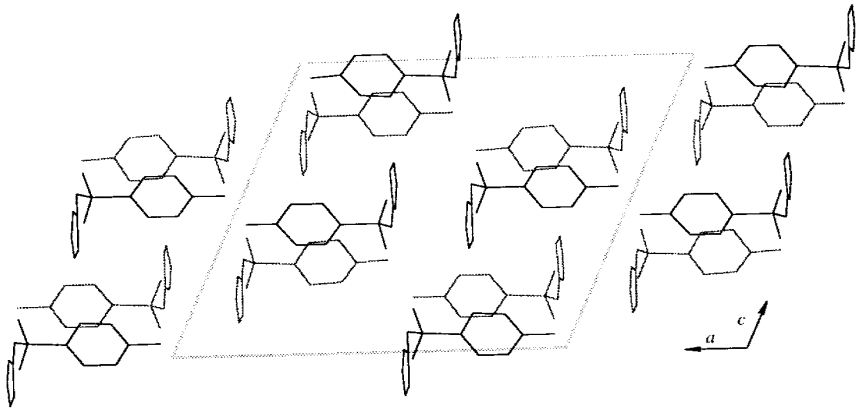


Figure 10.22 Crystal packing of sulfathiazole Form III (Kruger and Gafner, 1971a).

Table 10.8 Dissolution Rate

Temperature (°C)	Form (mg cm^{-2}
59.1	0.18
48.8	0.10
39.4	0.05
29.6	0.03
24.1	0.02
20.4	0.02

Milosovich, 1964.

The crystallographic
morphs of sulfathiazole; I
polymorphism of this dru
Kuhnert-Brandstätter rep
stage microscopy. In the
lory (1967), and Higuchi
Shenouda (1970) also in
Mesley (1971) using IR,
of three polymorphs. He
with mixtures of the three
these findings and charac
microscopy, solubility, a

To avoid prolonged
involve separation of hal
each habit. X-ray powd
crystal X-ray data and
approach would make su

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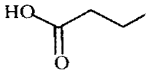
solubility than Form I. T
II should have a slower d

C. Succinylsulfathi



In early studies of succi
and Higuchi, 1963) a lar

Table 10.8 Dissolution Rate and Solubility of Forms I and II of Sulfathiazole

Temperature (°C)	Dissolution Rate		Solubility	
	Form I (mg cm^{-2} sec^{-1})	Form II (mg cm^{-2} sec^{-1})	Form I (g/1000 gm)	Form II (g/1000 gm)
59.1	0.185	0.239	31.5	40.7
48.8	0.102	0.145	19.8	28.1
39.4	0.0598	0.0913	14.0	21.4
29.6	0.0355	0.0597	9.93	16.7
24.1	0.0237	0.0413	8.15	14.2
20.4	0.0201	0.0371	7.10	13.1

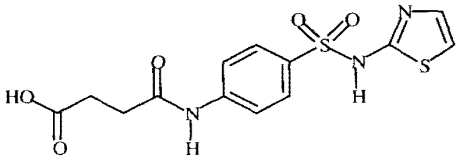
Milosovich, 1964.

The crystallographic data clearly established the existence of at least four polymorphs of sulfathiazole; however, at this point, it is worthwhile to review studies of the polymorphism of this drug using other techniques. As reported earlier in this section, Kuhnert-Brandstätter reported that sulfathiazole has four polymorphs based on hot stage microscopy. In the 1960's, three groups of workers [Milosovich (1964), Guillory (1967), and Higuchi *et al.* (1967)] reported only two polymorphs. DSC work by Shenouda (1970) also indicated the existence of only two polymorphs. Studies by Mesley (1971) using IR, DSC, and X-ray powder diffractometry showed the existance of three polymorphs. He suggested that most of the earlier workers had been dealing with mixtures of the three polymorphic forms. Burger and Dialer (1983) reinvestigated these findings and characterized four polymorphs by IR-spectroscopy, DSC, thermomicroscopy, solubility, and density.

To avoid prolonged confusion of this sort, studies of unfamiliar systems should involve separation of habits under a microscope and then crystallographic studies of each habit. X-ray powder diffraction patterns should be calculated from the single crystal X-ray data and compared with the experimentally observed XRPDs. This approach would make sure that mixtures of polymorphs are not involved.

The physical properties of sulfathiazole Forms I and II have been studied (Sunwoo and Eisen, 1971; Milosovich, 1964). These studies, which used a flow cell, measured the dissolution rate under conditions where Form II did not transform to Form I. The results in Table 10.8 show that Form II has a significantly higher dissolution rate and solubility than Form I. This is not consistent with the densities which predict that Form II should have a slower dissolution rate and be less soluble than Form I.

C. Succinylsulfathiazole



succinylsulfathiazole

In early studies of succinylsulfathiazole (Armour Research Foundation, 1949; Shefter and Higuchi, 1963) a large number of different crystal forms were found. The studies

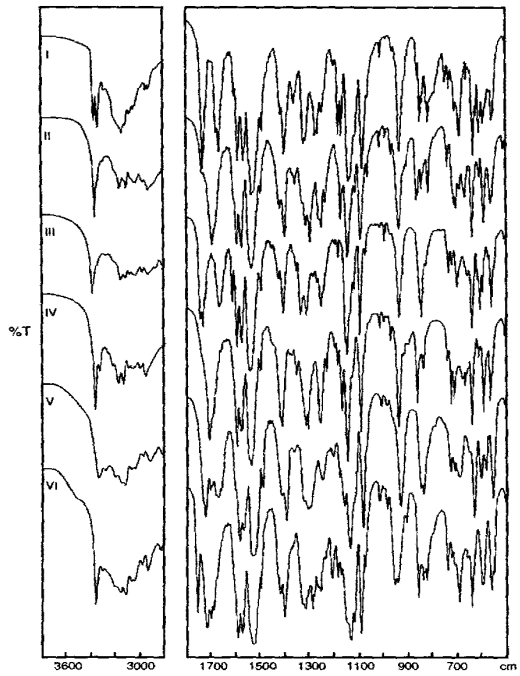


Figure 10.23 IR spectra (KBr pellets) of the unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

by Burger and Griesser (1989; 1991) provide the most complete summary of the solid-state behavior of this compound. As summarized in Table 10.9, they found that succinylsulfathiazole crystallized in six anhydrous crystal forms, three polymorphic monohydrates, as well as an acetone solvate and an *n*-butanol solvate. These different crystal forms were prepared by a variety of methods involving crystallization from different solvents and by drying the different solvates. For example, Form IV was prepared by drying the acetone solvate at 150 °C. Form VI was prepared by dehydration of one of the monohydrates in vacuum at 100 °C. The three monohydrates are termed "polymorphic" because they contain the same chemical composition (compound and solvent) but exist in different crystal structures. The IR spectra of all eleven crystal forms were measured in KBr pellets. The polymorphs and solvates were also characterized by thermal microscopy and DSC. Figure 10.23 shows the IR spectra of the six unsolvated crystal forms and Figure 10.24 shows the DSC thermograms of these polymorphs. The IR spectra of the different crystal forms are different and indicate that these are different polymorphs. The DSC thermograms of Forms I through V show destinctive differences in melting points. The DSC thermogram of Form VI shows an incongruent melting process. However, IR appears to be better than DSC for distinguishing these forms. Figure 10.25 shows the X-ray powder diffraction patterns of the six crystal forms which are all different and confirm the IR results.

Table 10.9 Comparison of Succinyls

Form	Stability (20 °C)	
I	Stable[a]	Suspens solv
II	< I	Evapora EtO
III	< II	Dehydra °C
IV	< III	Suspens EtO
V	< IV	Anneali 160
VI	< V	Dehydra
H_I	Stable	Suspens water
H_{II}	< H_I	Crystalli
H_{III}	< H_{II}	Suspensi for 1

a in the absence of water. water at 20 °C. (Burger a

Figure 10.24 DSC therm Griesser, 1

Table 10.9 Comparison of the Physical Properties of the Polymorphic Anhydrates and Monohydrates of Succinylsulfathiazole

Form	Stability (20 °C)	Preparation	MP[b] (°C)	MP[c] (°C)	1st Peak in IR (cm^{-1})	Density ($g\ cm^{-3}$)	Solubility[d] Ratio to H_I
I	Stable[a]	Suspension of acetone solvate in EtOAC	204	205	3361	1.592	3.24
II	< I	Evaporation of absolute EtOH solution	195-199	195	3360	1.535	5.69
III	< II	Dehydration of H_I at 100 °C	189-194	188-191	3372	1.571	6.15
IV	< III	Suspension of V or VI in EtOAC	187-191	189	3338	1.518	9.26
V	< IV	Annealing of I at 160 °C	182-185	182-187	3330	1.488	~12.7
VI	< V	Dehydration of H_{II}	139-143	135-138	3350	1.463	—
H_I	Stable	Suspension of any form in water	123-125		3480 (OH) 3320 (NH)	1.527	1.00
H_{II}	< H_I	Crystallization from water	~110		3500 (OH) 3350 (NH)	1.520	1.81
H_{III}	< H_{II}	Suspension of III in water for 15 min	105		3450 (OH) 3335 (NH)		

a in the absence of water. *b* by thermomicroscopy. *c* by differential scanning calorimetry (DSC). *d* in water at 20 °C. (Burger and Griesser, 1991)

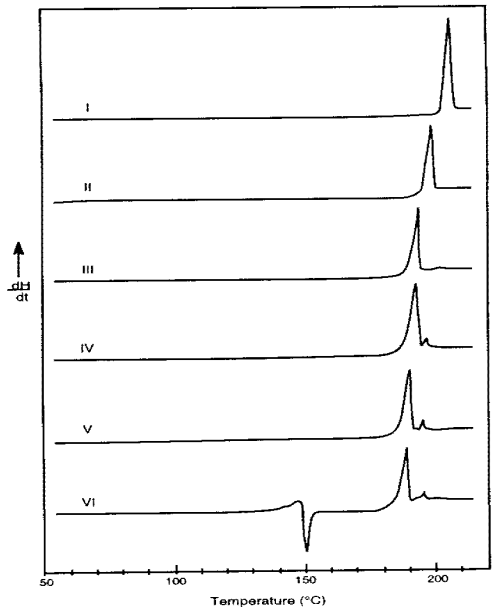


Figure 10.24 DSC thermograms of the unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

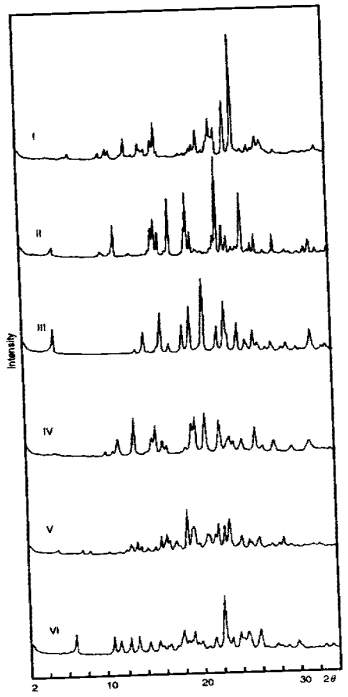


Figure 10.25 X-ray powder diffraction patterns of the six unsolvated crystal forms of succinylsulfathiazole (Burger and Griesser, 1989).

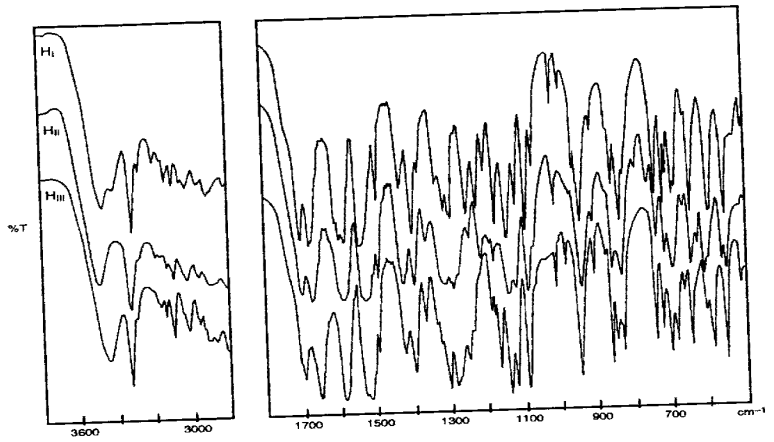


Figure 10.26 IR spectra of the polymorphic monohydrates of succinylsulfathiazole (Burger and Griesser, 1989).

Figure 10.26 shows
sulfathiazole. The IR sp
are different polymorph
tion patterns shown in F

The physical stabili
of succinylsulfathiazole
Figure 10.28. The mo
variety of methods used
crystal forms have diff
high humidity. The solu

Figure 10.27 X-ray powde
(Burger and

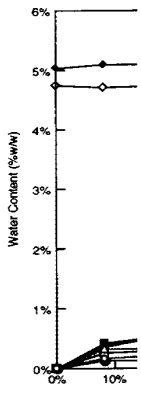


Figure 10.28 Water vapor
(Burger and

Figure 10.26 shows the IR spectra of the polymorphic monohydrates of succinylsulfathiazole. The IR spectra of these materials are also different establishing that these are different polymorphs. This conclusion is confirmed by the X-ray powder diffraction patterns shown in Figure 10.27.

The physical stability, water sorption, and solubility of the different crystal forms of succinylsulfathiazole have also been studied and are summarized in Table 10.9 and Figure 10.28. The most stable forms are Form I and hydrate H_I. In addition, the variety of methods used to prepare the different crystal forms are noted. The different crystal forms have differences in hygroscopicity and interconvert in the presence of high humidity. The solubilities of the different forms are also different. Most notable

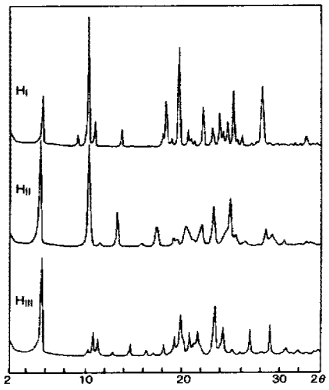


Figure 10.27 X-ray powder diffraction patterns of the three monohydrates of succinylsulfathiazole (Burger and Griesser, 1989).

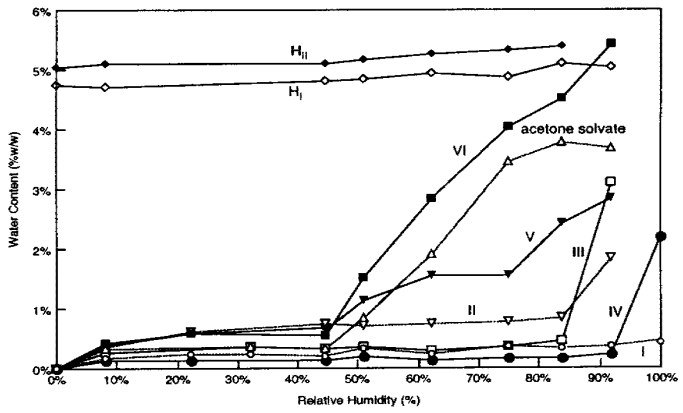


Figure 10.28 Water vapor sorption isotherms of the different crystal forms of succinylsulfathiazole (Burger and Griesser, 1991).

is that the differences in solubility among the anhydrate crystal forms is as large as a factor of 4 and that differences in solubility between anhydrate and hydrate crystal forms are as large as a factor of 12. This is one of many cases where anhydrate crystal forms have significantly higher solubilities than the hydrate.

Figure 10.28 shows the water vapor sorption isotherms for the different succinylsulfathiazole crystal forms. It is clear that some of the anhydrate forms absorb water relatively easily; furthermore, this data shows that the metastable forms are more hygroscopic.

Figure 10.29 shows the dissolution behavior of the different crystal forms of succinylsulfathiazole in buffer solution at pH 1.20 at 20 °C. It is clear that at equilibrium many of the anhydrates recrystallize and approach the solubility of the hydrates as might be expected. Figure 10.30 shows a van't Hoff plot for four of the crystal forms of succinylsulfathiazole. These curves do not cross in the temperature ranges studied and this indicates, in connection with the thermodynamic data, that all of the forms are monotropically related. Recall that monotropic forms retain the order of stability at all temperatures (see Section 5.2).

Figure 10.31 shows a scheme which illustrates the interconversion of the different crystal forms and methods to prepare each form. This figure illustrates how complicated interconversion of the different crystal forms can be. The van't Hoff plot clearly shows that the transformation of the more soluble form into the less soluble hydrate will occur at room temperature. This indicates the complications that can arise by relying on just one study and shows that several different approaches should be used to try to understand the interconversion of different crystal forms.

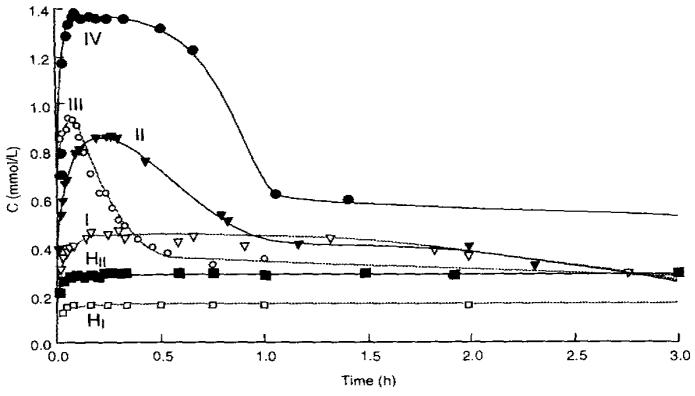


Figure 10.29 Dissolution behavior of the different crystal forms of succinylsulfathiazole in buffer solution, pH 1.3 at 20 °C (Burger and Griesser, 1991).

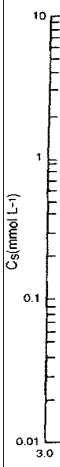


Figure 10.30 Van't Hoff pl
pH 1.3 (Burge

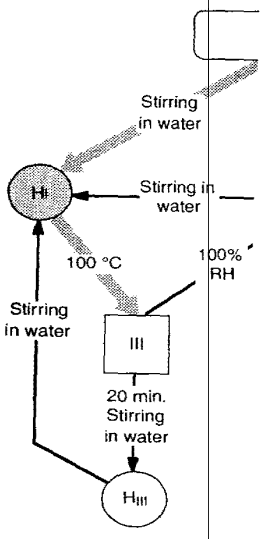


Figure 10.31 Diagram illu
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mark paths w
most stable f

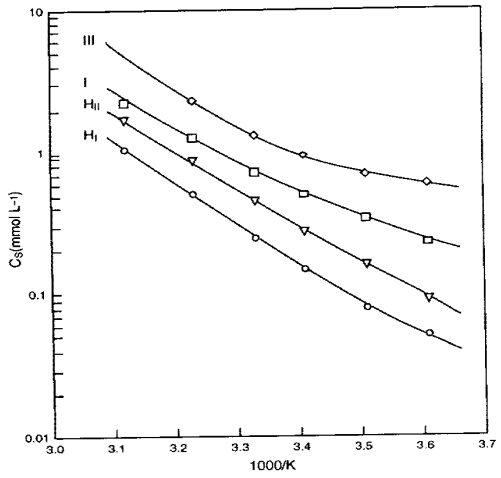


Figure 10.30 Van't Hoff plot of the solubility of four of the crystal forms of succinylsulfathiazole at pH 1.3 (Burger and Griesser, 1991).

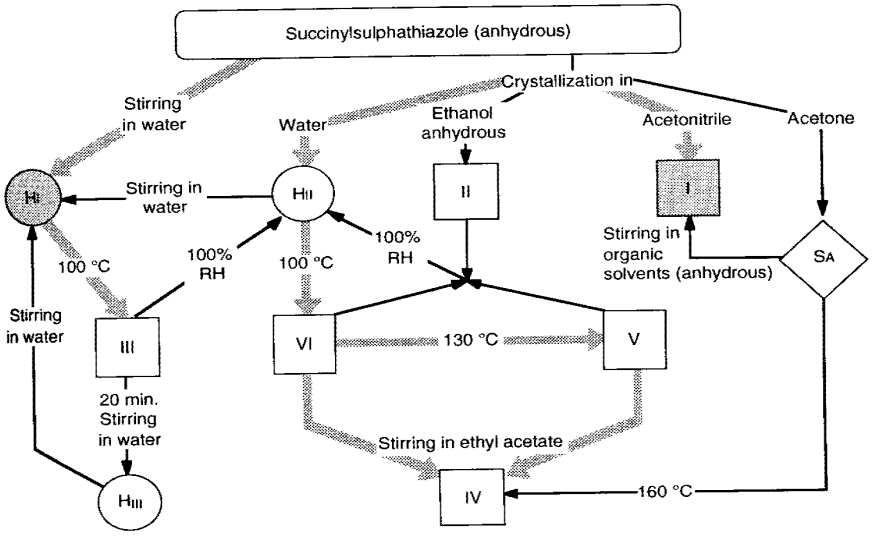
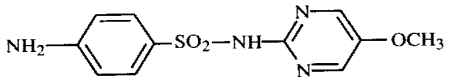


Figure 10.31 Diagram illustrating the most important transformation paths and production ways to produce the different crystal forms of succinylsulfathiazole. The thick, gray arrows mark paths whereby the different crystal forms can be produced in gram quantities. The most stable forms, Forms I and H_I, are shaded (Burger and Griesser, 1991).

D. SULFAMETER



sulfameter

Sulfameter (sulfamethoxydiazine) exists in at least six different forms (Moustafa *et al.*, 1971). Form I (see Figure 10.32 and Table 10.10) is obtained by crystallization from boiling water or by heating any other form to 150 °C. Form II is prepared by rapid cooling of a saturated ethanol solution. Form III (see Figure 10.33 and Table 10.10) is obtained from a number of solvents including methanol, isopropanol, and ethanol. Forms IV and V are probably solvates and are obtained from dioxane and chloroform, respectively. An amorphous form is also known.

These forms were characterized by their infrared spectra, which are all slightly different, particularly in the 800-875, 900-970, 1550-1600, and 3000-3500 cm^{-1} regions of the spectrum. The powder diffraction patterns of these forms are also significantly different.

The forms can be interconverted by heating or grinding. Heating converts all forms to Form I, while grinding or suspension in water converts all forms to Form III. This behavior is discussed in more detail in the interconversion section (see Section 13.2B).

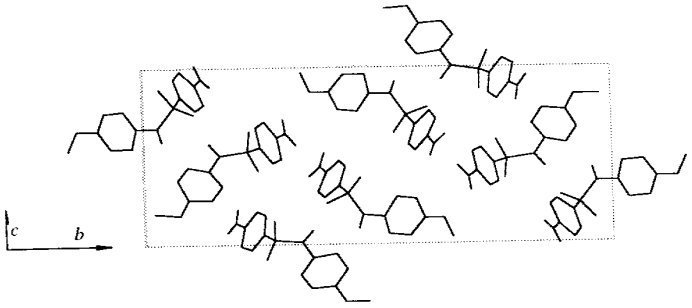


Figure 10.32 Crystal packing of sulfameter Form I (Giuseppetti *et al.*, 1977).

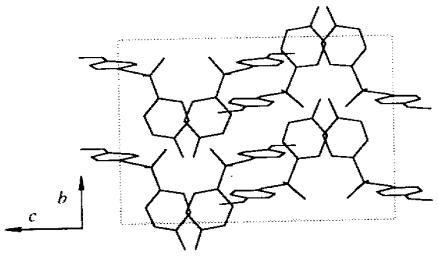


Figure 10.33 Crystal packing of sulfameter Form III (Giuseppetti *et al.*, 1977).

Table 10.10 Crystallographi

Parameter	
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	1
Z	
ρ_{calc} (gm cm^{-3})	
V (Å^3)	

Giuseppetti *et al.*, 1977.

The dissolution rates
their relative bioavailabilit
ments are shown in Figu
dissolve most rapidly. F
Form II. It is also interest
amorphous form, sugges
surface area of Form II ma

Commercial preparati
mixtures of Forms I and I
ing. The significance of a
to be determined in separa

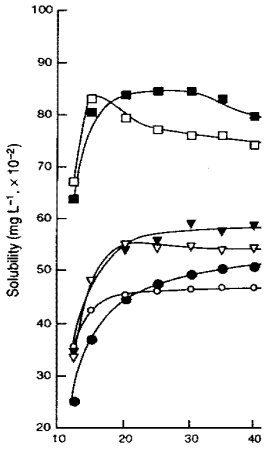


Figure 10.34 Dissolution rate

Table 10.10 Crystallographic Parameters for Sulfameter Forms I and III

Parameter	Form I	Form III
Space Group	$P2_1/c$	$C2/c$
a (Å)	8.358	13.370
b (Å)	26.833	11.735
c (Å)	11.964	15.928
β	111.36°	97.90°
Z	8	8
ρ_{calc} (gm cm^{-3})	1.490	1.504
V (Å^3)	2499	2475

Giuseppetti *et al.*, 1977.

The dissolution rates of these forms have been measured as a means of estimating their relative bioavailabilities (Moustafa *et al.*, 1971). The results of these measurements are shown in Figure 10.34. Obviously, Form II and the amorphous form dissolve most rapidly. Form III has the slowest dissolution rate, about half that of Form II. It is also interesting to note that Form II has a faster dissolution rate than the amorphous form, suggesting that the amorphous form may crystallize or that the surface area of Form II maybe much larger than that of the amorphous form.

Commercial preparations were also studied and, in general, contained Form I or mixtures of Forms I and III. These forms are the most stable and the slowest dissolving. The significance of any such differences with respect to bioavailability would have to be determined in separate experiments.

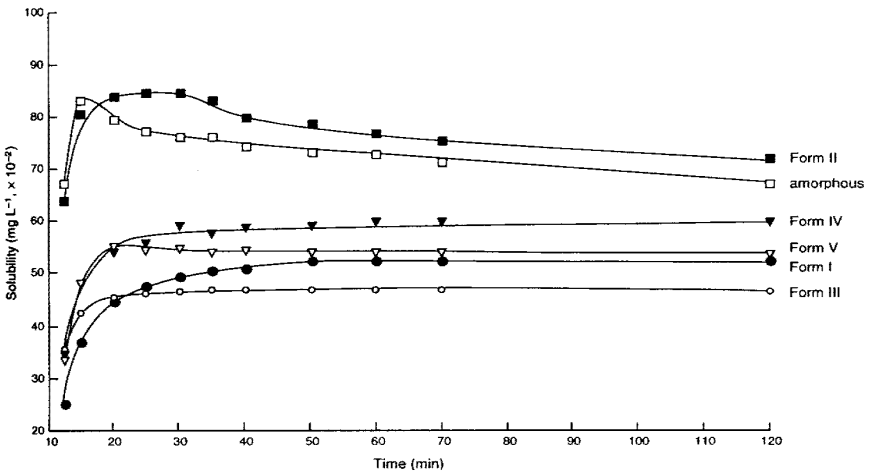
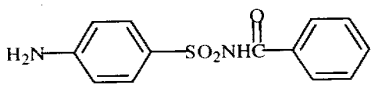


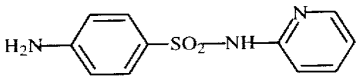
Figure 10.34 Dissolution rates of the different forms of sulfameter (Moustafa *et al.*, 1971).

E. Other Sulfonamides



sulfabenzamide

Sulfabenzamide. Sulfabenzamide exists in four polymorphs and three solvates (Yang and Guillory, 1972). Form III can be transformed to Form I by **trituration**, and Form IV can be transformed to Form III and then Form I by heating. Desolvation of two of the solvates yielded Form II (see Figure 10.35).



sulfapyridine

Sulfapyridine. Sulfapyridine (see Figures 10.35–10.39) exists in at least four polymorphs and one amorphous form (Yang and Guillory, 1972). The infrared spectra of two of these forms are identical, but their X-ray diffraction patterns are completely different. In addition, hot-stage experiments indicated that sulfapyridine crystallized in at least seven forms (Kuhnert-Brandstätter, 1971).

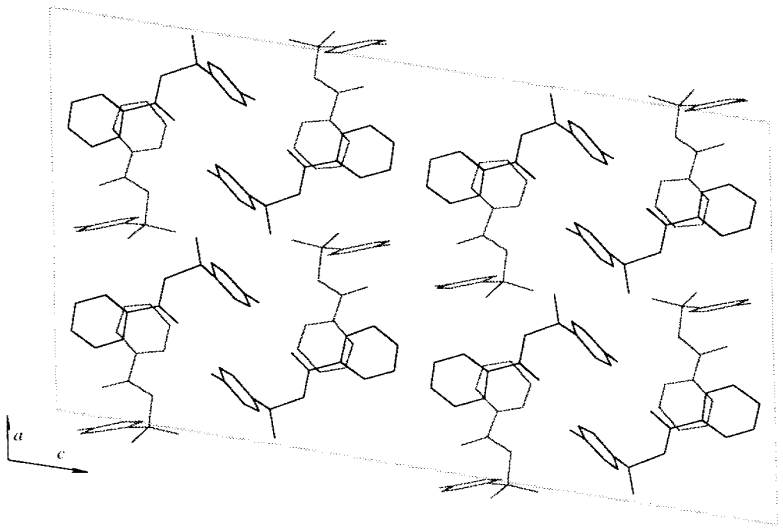


Figure 10.35 Crystal packing of sulfabenzamide Form II (Rambaud *et al.*, 1980).

Figure 10.36 Cryst

Figure 10.37 Cryst

Figure 10.38 Cryst

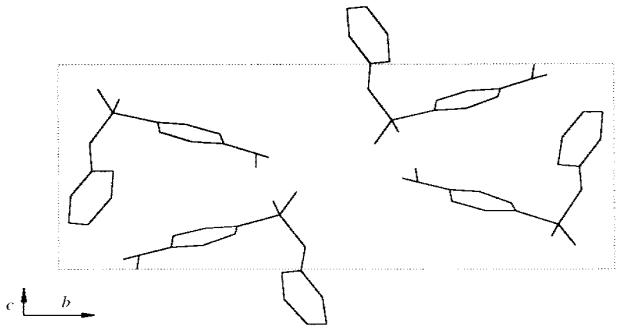


Figure 10.36 Crystal packing of sulfapyridine Form II (Bar and Bernstein, 1985).

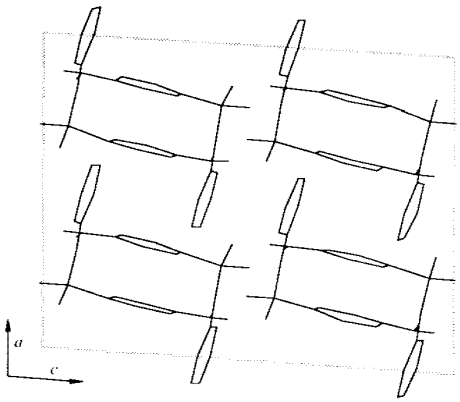


Figure 10.37 Crystal packing of sulfapyridine Form III (Basak *et al.*, 1984).

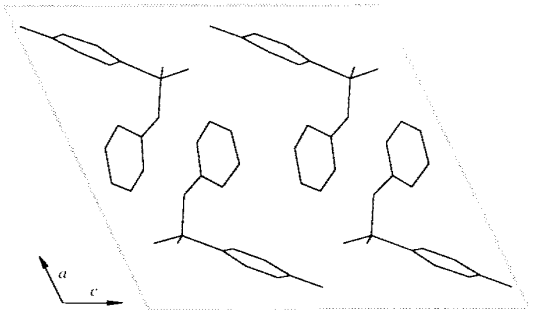


Figure 10.38 Crystal packing of sulfapyridine Form IV (Bernstein, 1988).

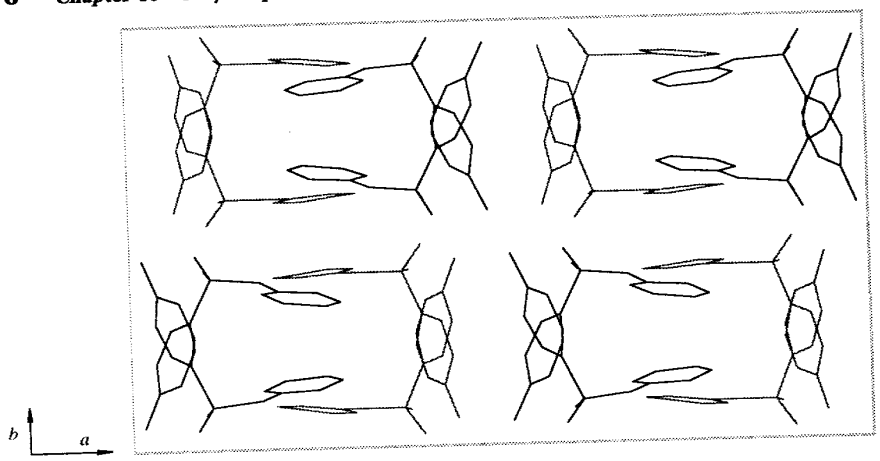


Figure 10.39 Crystal packing of sulfapyridine Form V (Bar and Bernstein, 1985).

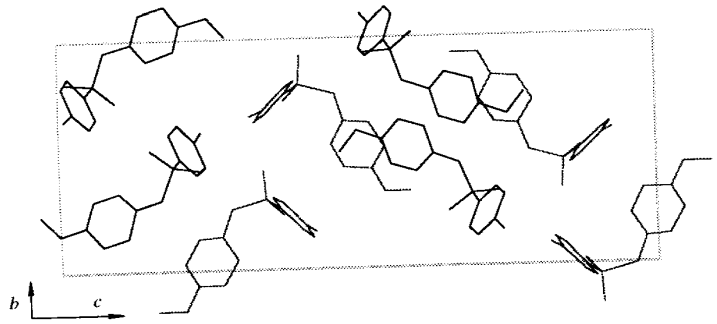
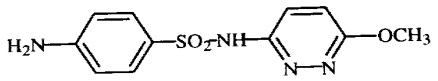
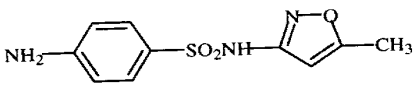


Figure 10.40 Crystal packing of sulfamethoxypyridiazine Form I (Basak *et al.*, 1987).



sulfamethoxypyridazine

Sulfamethoxypyridiazine. Sulfamethoxypyridiazine (see Figure 10.40) exists in at least three crystalline forms (Yang and Guillory, 1972). Form II can be transformed to Form I at 154 °C.



sulfamethoxazole

Sulfamethoxazole. Sulfamethoxazole (see Figures 10.41–10.42) exists in three polymorphs, and Form II can be converted to Form I at 164 °C (Yang and Guillory, 1972). These studies are in agreement with Kuhnert-Brandstätter (1971) who also

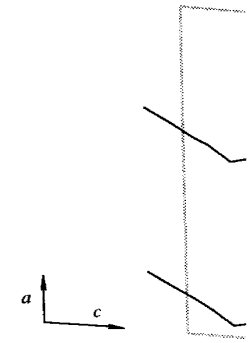


Figure 10.41 Crystal packing

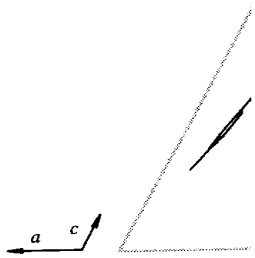


Figure 10.42 Crystal packing

showed there were three p
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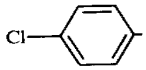


Chlorpropamide. Ch
morphs that have differe
obtained from aqueous et
or II at 110 °C. The infi

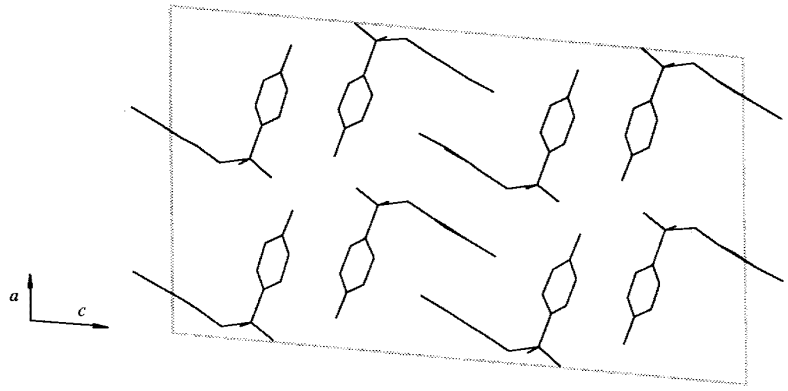


Figure 10.41 Crystal packing of sulfamethoxazole Form I (Bettinetti *et al.*, 1982).

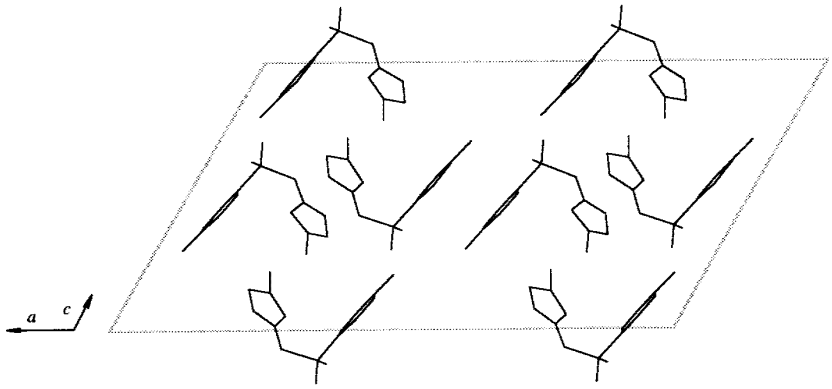
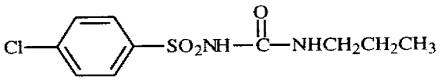


Figure 10.42 Crystal packing of sulfamethoxazole Form II (Bettinetti *et al.*, 1982).

showed there were three polymorphs of sulfamethoxazole. The crystal structures of the two forms of sulfamethoxazole were determined by Bettinetti *et al.* (1982). Figures 10.41 and 10.42 show the crystal packing in these two different forms. It appears that the conformations of the molecule in the two crystal forms are similar.



chlorpropamide

Chlorpropamide. Chlorpropamide (see Figure 10.43) exists in at least three polymorphs that have different diffraction patterns (Simmons *et al.*, 1973). Form I is obtained from aqueous ethanol, Form II from benzene, and Form III by heating Form I or II at 110 °C. The infrared spectra of all three forms are slightly different and the

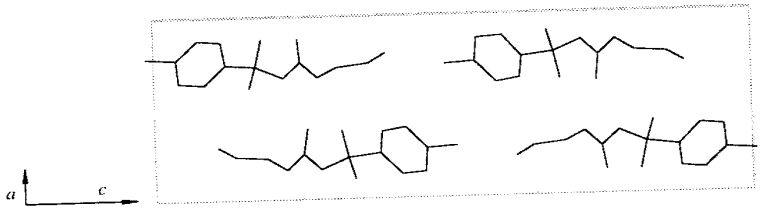
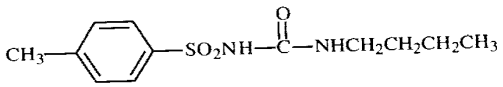


Figure 10.43 Crystal packing of chlorpropamide Form I (Koo *et al.*, 1980).

X-ray powder patterns of all three forms are significantly different, whereas the DSC thermograms obtained for the three forms are very similar.

The three forms of chlorpropamide have different dissolution rates. The dissolution rates of Forms I and III in water are identical, while Form II dissolves about half as fast. However, in beagle dogs, the serum levels following oral administration are identical for all three forms (Simmons *et al.*, 1973). Further single-crystal studies are necessary to completely characterize these forms and explain these results.



tolbutamide

Tolbutamide. Early studies (Simmons *et al.*, 1972) showed that tolbutamide crystallizes in two forms. Form I (see Figure 10.44) is obtained from benzene-hexane, and the crystals are prismatic with mp 127–128 °C. Form II is obtained from aqueous ethanol and the crystals are plates with mp 126–128 °C. Both the infrared spectra and the DTA thermograms of Forms I and II are slightly different. The DTA of Form II shows an endotherm at 113 °C that is not present in Form I. This endotherm apparently corresponds to the conversion of Form II to Form I. The dissolution rates of Forms I and II are the same in water at pH 5.5 and 7.3. The serum levels of these two forms are also identical. One explanation of this data is that, upon exposure to liquid, Form II is converted to Form I by a solution-mediated phase transformation.

More recent studies showed that tolbutamide exists in four crystal forms (Burger, 1975). In addition, aqueous suspensions of tolbutamide were found to thicken to an unpourable state upon occasional agitation. Analysis of the IR spectra and X-ray diffraction patterns confirmed that Form III had crystallized (Rowe and Anderson,

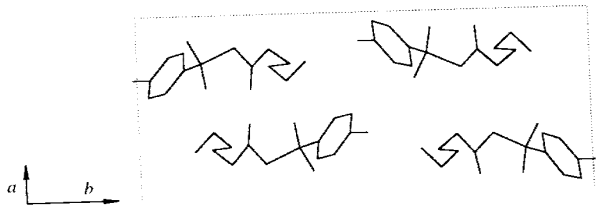


Figure 10.44 Crystal packing of tolbutamide Form I (Donaldson *et al.*, 1981; Nirmala and Gowda, 1981).

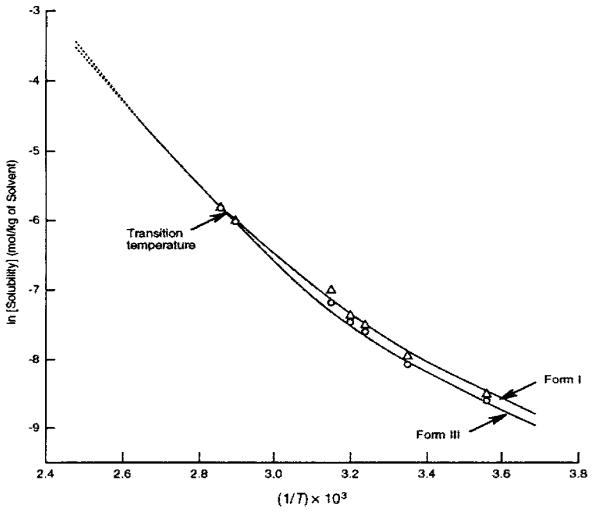


Figure 10.45 Van't Hoff plot of the solubilities of Forms I and III of tolbutamide showing the transition temperature (Rowe and Anderson, 1984).

1984). This is surprising since the suspensions were prepared with Form I which was thought to be the most stable polymorph. Solubility studies gave the van't Hoff plot shown in Figure 10.45. The aqueous solubilities of Form I and Form III are very close. Because of this, Form I may appear to be quite stable at low temperatures in suspensions; however, given sufficient time, Form I will transform to the Form III, the lower energy form. This interconversion was observed at room temperature in ten other solvents.

These data suggests that Form III is more stable than Form I at room temperature and that Form I is more stable than Form III at higher temperatures. This observation was verified by microscopy (Rowe and Anderson, 1984) in which Form III crystals were placed in mineral oil on a microscope hot stage. The sample was heated at 100 °C for several hours with periodic agitation by pressing and rotating the cover slip. When the temperature was reduced to 95 °C, prismatic crystals, typical of Form I, began to grow throughout the oil mixture and the Form III crystals dissolved. Upon cooling to room temperature, fine needles, typical of Form III, grew and the Form I crystals dissolved. These observations experimentally verify the result of the van't Hoff plot shown in Figure 10.45. These studies show the power of van't Hoff plots and also thermal microscopy in studying the interconversion of polymorphs.

F. Conclusion

This section shows the extent of polymorphism in the sulfonamides. The fact that polymorphism of these drugs is widespread yet unpredictable is probably due to (a) the availability of a variety of hydrogen-bonding schemes and (b) the occurrence of a number of ring-ring stacking modes. Further study of the polymorphism of these

compounds using single-crystal X-ray techniques should, no doubt, lead to a better general understanding of polymorphism.

10.5 STEROIDS

Steroids exhibit widespread polymorphism that may affect their bioavailability. A few examples of the polymorphism of steroids have been discussed in preceding sections.

Kuhnert-Brandstätter (1971) has studied the polymorphism of steroids using a Kofler hot stage, and the results of her studies are summarized in Table 10.11. This table clearly shows the extent of polymorphism in this important class of compounds. It should be noted that these studies are based mainly on hot-stage results. Other methods would be useful to verify the existence of these polymorphs and clarify the possible involvement of solvates.

Table 10.11 Melting Points of Polymorphic Steroids[a]

Compound	Forms I	II	III	IV	V
Allopregnane-3β,20α-diol	215–219	162–168			
Allopregnane-3,20-dione	202–206	198–203			
Androstane-3β,17β-diol	168–169	163–164	158–161	146–147	
Androstane-3,17-dione	132–134	128–130			
Androstanolone	182	168			
Δ^5-Androstene-3β,17α-diol	202–205	180–195			
Δ^5-Androstene-3β,17β-diol	181–185	177–180	155–158		
Δ^4-Androstene-3,17-dione	170–174	142–145			
Corticosterone	180–186	175–179	162–168	155–160	
Cortisone enanthate	138–140	135–137	129–132		
Dehydroepiandrosterone	149–153	139–141	137–140	130–136	
Dehydroepiandrosterone acetate	170–172	132–135	94–96	65–69	
Epiandrosterone	174–176	167–169			
α–Estradiol	225	223			
β–Estradiol	178	169			
Estradiol benzoate	188–195	177.5	176		
Estradiol dipropionate	107	97	82		
Estradiol 17-propionate	198–200	154–156			
Estrone	260–263	256	254		
Estrone methyl ether	172–174	123–126	88–92		
Etiocholane-3α-ol-17-one	150–152	141–143	133		
Etiocholane-17β-ol-3-one	141–143	103			
Fluorocortisone trimethylacetate	192–198	184–190			
9α-Fluorohydrocortisone acetate	225–233	208–212	205–208		
Hydrocortisone hemisuccinate	198–205	182–188	168–172		
Methandriol	205–208	202–205	196–198		
Methandriol dipropionate	83–86	74–75			
17α-Methandrostane-3β,17β-diol	213	205			

a Data from Kuhnert-Brandstätter (1971)

Table 10.11 (continued) Me

Compound
1-Methylandrostenolone acet
17α-Methylestradiol
6α-Methylprednisolone aceta
17-Norethisterone
Prednisolone
Prednisolone acetate
Progesterone
Testosterone
Testosterone isobutyrate
Testosterone nicotinate
Testosterone propionate

a Data from Kuhnert-Brandstät

A. ESTRONE

HO

As indicated in Table 10.1 of all three polymorphs ha of the estrone molecule is three forms is shown in molecules, but not obviou and stacks of estrone mol molecules. The crystal pa of 2.26 and 2.47 Å; the c

Table 10.12 Crystallographic

	Form I
Space group	$P2_12_12_1$
a (Å)	12.188
b (Å)	16.301
c (Å)	7.463
β	90.00°
Z	4
V (Å^3)	1481
Source	Sublimati

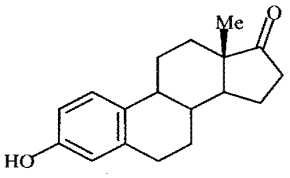
Busetta *et al.*, 1973

Table 10.11 (continued) Melting Points of Polymorphic Steroids[a]

Compound	Forms I	II	III	IV	V
1-Methylandrostenolone acetate	143	106			
17α-Methylestradiol	190–194	188			
6α-Methylprednisolone acetate	225–229	208–212	205–210		
17-Norethisterone	200–207	199			
Prednisolone	218–234	215			
Prednisolone acetate	232–241	225–228	217–220		
Progesterone	131	123	111	106	100
Testosterone	155	148	144	143	
Testosterone isobutyrate	131–133	88–90			
Testosterone nicotinate	194–196	185–188			
Testosterone propionate	122	74			

a Data from Kuhnert-Brandstätter (1971)

A. Estrone



estrone

As indicated in Table 10.12 estrone exists in three polymorphs. The crystal structures of all three polymorphs have been determined (Busetta *et al.*, 1973). The conformation of the estrone molecule is similar in all three polymorphs. The crystal packing of these three forms is shown in Figures 10.46–10.48. Form I contains layers of estrone molecules, but not obvious stacks of estrone molecules. Form III contains both layers and stacks of estrone molecules. Form II has a herringbone arrangement of estrone molecules. The crystal packing of Form I appears to be controlled by H···H contacts of 2.26 and 2.47 Å; the crystal packing of Form II appears to be controlled by C···C

Table 10.12 Crystallographic Parameters of Three Estrone Polymorphs

	Form I	Form II	Form III
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$
a (Å)	12.188	10.043	9.271
b (Å)	16.301	18.424	22.285
c (Å)	7.463	7.787	7.610
β	90.00°	90.00°	111.45°
Z	4	4	4
V (Å^3)	1481	1440	1461
Source	Sublimation	Acetone	Sublimation

Busetta *et al.*, 1973

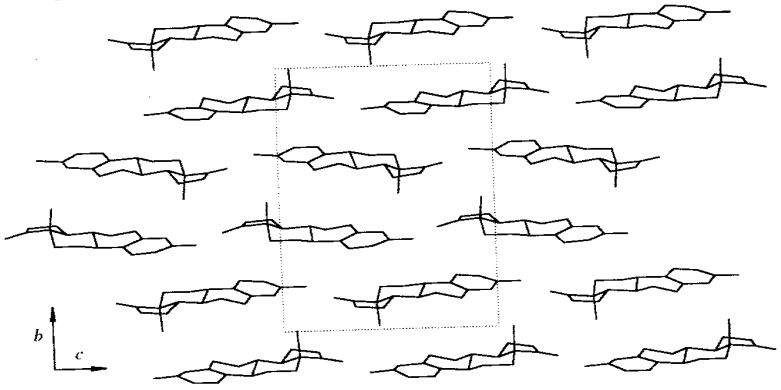


Figure 10.46 Crystal packing of estrone Form I (Busetta *et al.*, 1973).

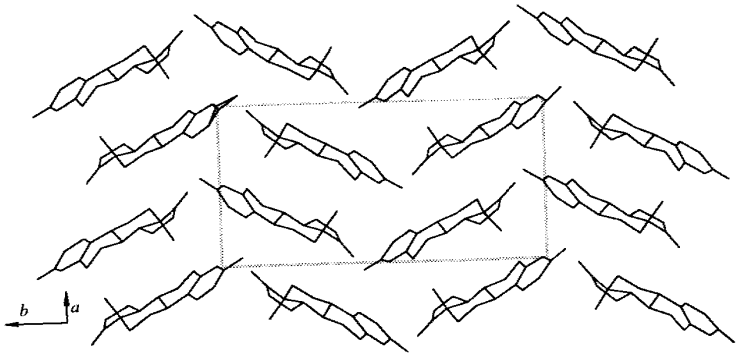


Figure 10.47 Crystal packing of estrone Form II (Busetta *et al.*, 1973).

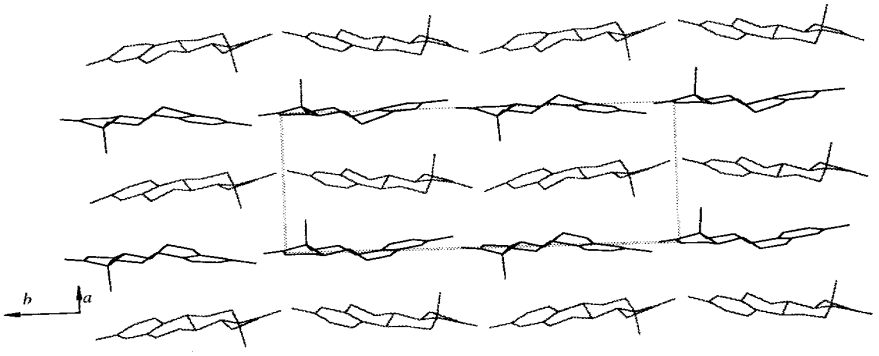


Figure 10.48 Crystal packing of estrone Form III (Busetta *et al.*, 1973).

contacts of 3.35
reported; howeve

B. PREDNISOLO

In our laboratory
Three crystal for
parameters and c
10.13. The cryst
ture of Form III
prednisolone in t

Table 10.13 Cryst

Space Group
a (Å)
b(Å)
c (Å)
β
Z
ρ_{calc} (g cm^{-3})
V (Å^3)
R

Sutton, 1984

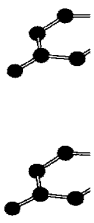
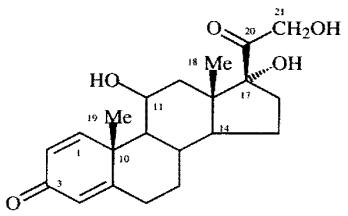


Figure 10.49 Stereo
(Sutto

contacts of 3.35 Å. No transformations or interconversions of these forms have been reported; however, it is likely that the densest form, Form II, is the most stable.

B. Prednisolone



prednisolone

In our laboratory we have investigated the polymorphs of prednisolone (Sutton, 1984). Three crystal forms were obtained by crystallization from various solvents. The cell parameters and other crystallographic data for these three forms are shown in Table 10.13. The crystal structures of Forms I and II were determined but the crystal structure of Form III could not be refined to an acceptable R value. The conformation of prednisolone in the two crystal forms (Forms I and II) is shown in Figure 10.49 and

Table 10.13 Crystallographic Data for the Polymorphs of Prednisolone

	Form I	Form II	Form III
Space Group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	6.350 (3)	11.808 (7)	24.56 (2)
b (Å)	12.985 (8)	6.009 (2)	24.77 (4)
c (Å)	10.971 (9)	25.643 (12)	6.415 (3)
β	91.24°	90.00°	90.00°
Z	2	4	8
ρ_{calc} (g cm^{-3})	1.32	1.32	1.29
V (Å^3)	904.4	1819.5	3903.5
R	0.672	0.672	> 0.10

Sutton, 1984

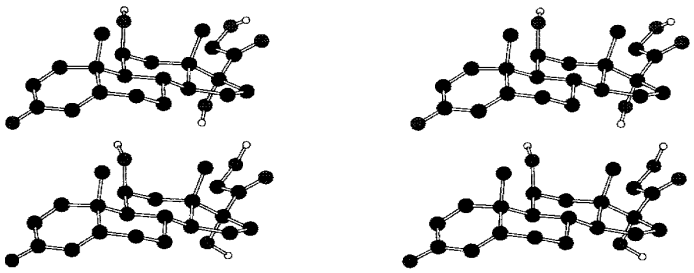


Figure 10.49 Stereoview of prednisolone Forms I (upper) and II (lower) conformations in the crystal (Sutton, 1984).

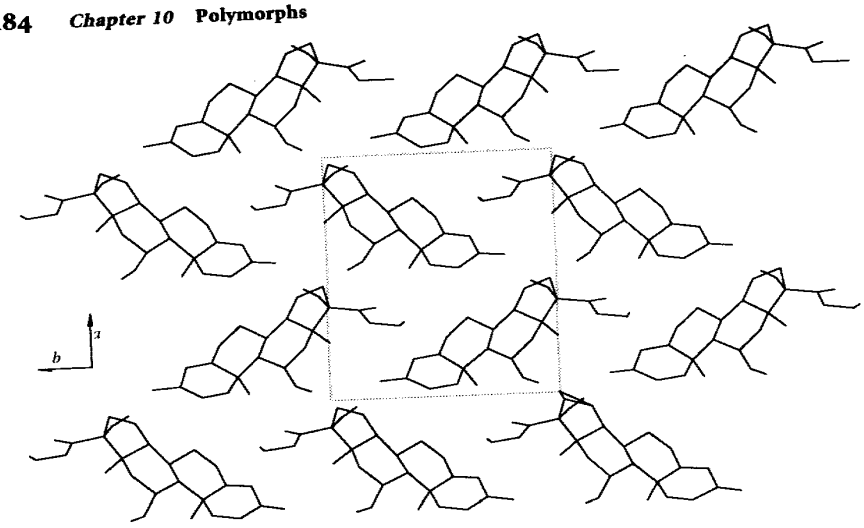


Figure 10.50 Crystal packing stereoview of prednisolone Form I (Sutton, 1984).

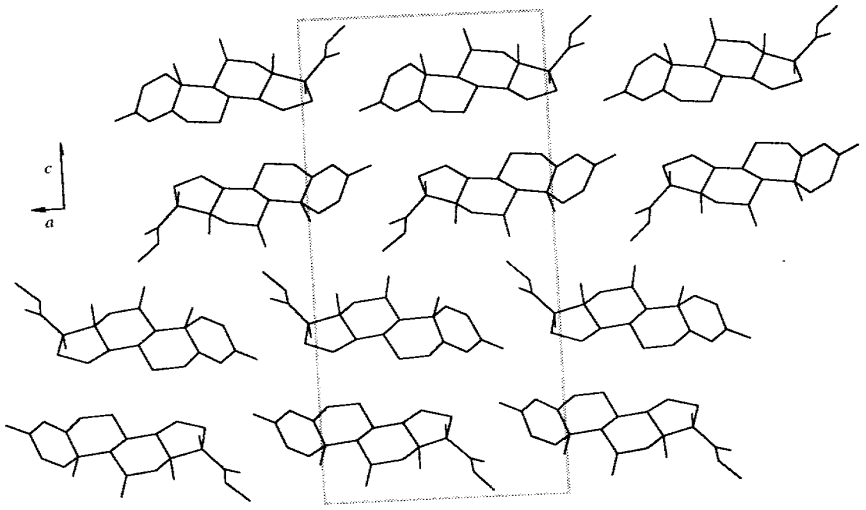


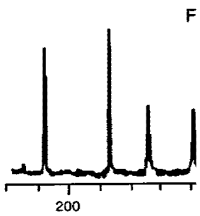
Figure 10.51 Crystal packing stereoview of prednisolone Form II (Sutton, 1984).

the crystal packing is shown in Figures 10.50–10.51.

The crystal packing shows that the arrangements of the prednisolone molecules in the unit cells of Forms I and II are similar but not identical. However, the solid-state NMR spectra of Forms I and II of prednisolone are different as illustrated by the spectra and the chemical shifts in Figure 10.52 and Table 10.14 (Saindon *et al.*, 1993).

Especially important for pu
the resonances assigned to
respectively.

The solid-state CP/MA
(labeled amount of 5 mg)
10.53 and required long a
comprises only about 5%
spectra shows that product
Further analysis showed th



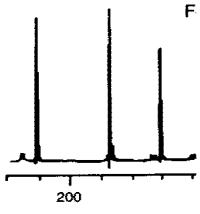


Figure 10.52 Solid-state CP/
(Saindon *et al.*,

Table 10.14 ^{13}C NMR Chem

Atom	Form I	Form II
C20	209.5	211.8
C3	188.1	187.g
C5	175.1	171.0
C13	159.8	157.3
C2	125.9	130.2
C4	121.8	123.8
C17	91.4	90.2
C11	69.9	70.4
C21	67.1	67.7
C9	55.4	54.8
C14	52.2	52.8

[d] The assignment of this peak

Especially important for purposes of identification is the difference in chemical shifts of the resonances assigned to carbons C2 and C4 which occur between 120 and 140 ppm, respectively.

The solid-state CP/MAS ^{13}C NMR spectra of three generic prednisolone products (labeled amount of 5 mg) were also determined. These spectra are shown in Figure 10.53 and required long acquisition times since the active ingredient (prednisolone) comprises only about 5% of the approximately 100 mg tablets. Inspection of these spectra shows that products A and B contain Form I while product C contains Form II. Further analysis showed that all three products passed the USP dissolution test. Thus,

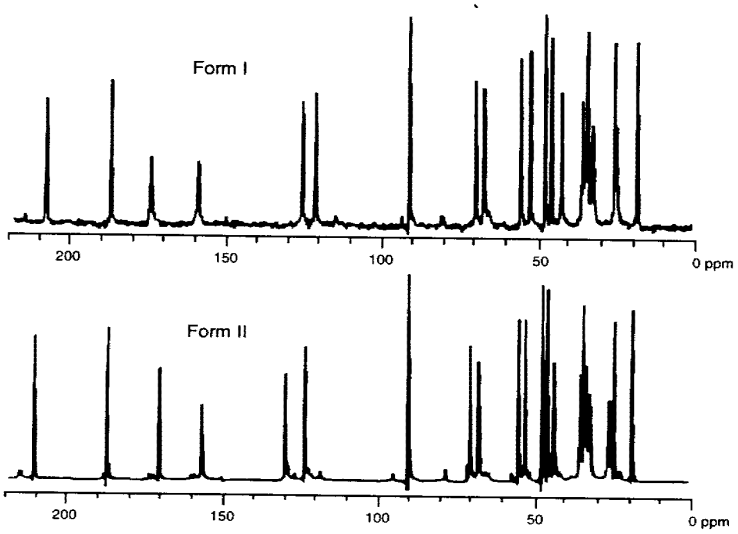


Figure 10.52 Solid-state CP/MAS ^{13}C NMR spectra of prednisolone Forms I (top) and II (bottom) (Saindon *et al.*, 1993).

Table 10.14 ^{13}C NMR Chemical Shifts of Prednisolone in the Solid-State and Solution

Atom	Form I	Form II	Solution	Atom	Form I	Form II	Solution
C20	209.5	211.8	211.5	C13	47.5	47.1	46.7
C3	188.1	187.g	185.1	C10	45.3	45.1	43.9
C5	175.1	171.0	170.5	C12	42.1	43.1	39.0
C13	159.8	157.3	156.8	C8[a]	35.3	34.7	34.1
C2	125.9	130.2	127.2	C16[a]	34.3	33.5	33.0
C4	121.8	123.8	121.7	C15[a]	33.5	32.7	32.7
C17	91.4	90.2	88.5	C6[a]	31.8	31.5	31.6
C11	69.9	70.4	68.6	C7[a]	24.6	25.4	31.2
C21	67.1	67.7	66.1	C18[a]	23.9	23.7	21.0
C9	55.4	54.8	55.5	C19[a]	17.3	18.1	17.0
C14	52.2	52.8	51.2				

a The assignment of this peak should be considered tentative (Saindon *et al.*, 1993)

molecules in
the solid-state
trated by the
et al., 1993).

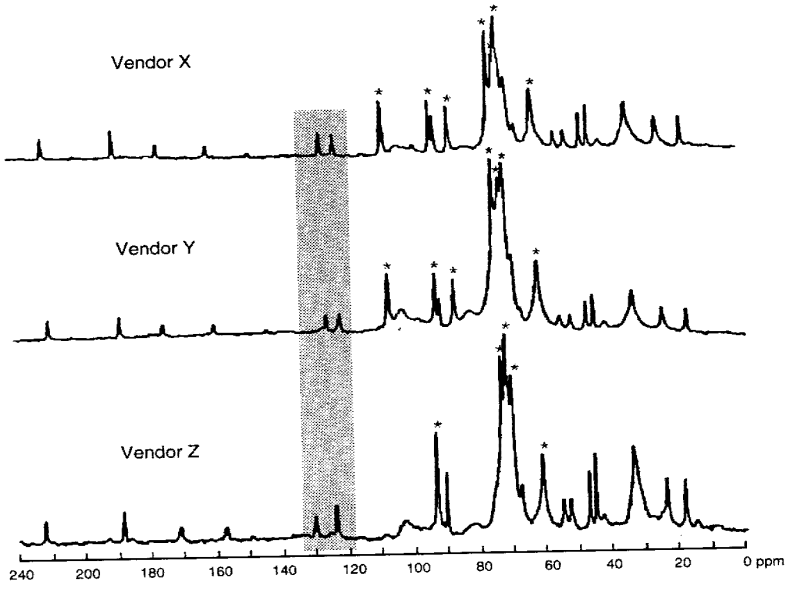
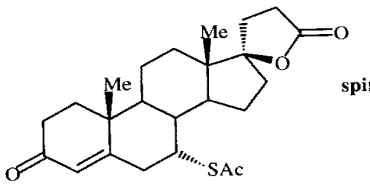


Figure 10.53 Solid-state CP/MAS ^{13}C NMR spectra of prednisolone tablets from three different vendors. The most evident differences are noted within the shaded region and the excipient signals are labeled with a star. (Byrn *et al.*, 1988).

these tablets represent a control problem because they contain different crystal forms but hopefully do not represent a serious clinical problem since they all meet the USP dissolution test.

C. Spironolactone



spironolactone

The polymorphism of spironolactone has been carefully studied using X-ray crystallography (Agafonov *et al.*, 1991). The data for the different forms are described in Table 10.15.

Spironolactone is of interest because it shows variable solubility and dissolution rate as well as pharmaceutical performance as an oral drug. Recently, a number of crystal forms of this compound have been discovered (see Table 10.15). As is the case for many steroids, both solvated and unsolvated crystal forms have been obtained. Figure 10.54 shows the TGA curves of the different crystal forms, clearly Forms III

Table 10.15 Spironolacto

Solvent	Method[a]
Acetone	1
Acetone	2
Dioxane	1
Dioxane	2
Chloroform	1
Chloroform	2
Acetonitrile	—[b]
Ethanol	—[b]
Ethyl acetate	—[b]
Methanol	—[b]

a Method 1—the sample is
0° C within a few hours; m
ture and the solvent allowe
the two methods of prepar
fraction pattern. (Agafono

through VI are solvate
crystal forms confirmin

Table 10.16 lists t
spironolactone, clearly
10.17 tabulates the pow
that Forms I through I
(Agafonov *et al.*, 1991
crystal forms of spiron
(Form I) is shown in Fi
Figure 10.57. The conf
it is clear that the crystal

Mass (mg)

Figure 10.54 TGA curves

Table 10.15 Spironolactone Single-Crystal Preparation Methods and Thermodynamic Data

Solvent	Method[a]	Form Obtained	T_{dec} (°C)	ΔH_{dec} (J/g)	T_f (°C)	ΔH_f (J/g)
Acetone	1	I	...	...	205 ± 1	48 ± 3
Acetone	2	II	...	...	210 ± 1	53 ± 4
Dioxane	1	Glass[c]	...	...	...	...
Dioxane	2	II	...	...	210 ± 1	53 ± 4
Chloroform	1	Glass[c]	...	...	...	...
Chloroform	2	II	...	...	210 ± 1	53 ± 4
Acetonitrile	—[b]	Solvate (2:1) (III)	137 ± 2	38 ± 2	210 ± 1	52 ± 4
Ethanol	—[b]	Solvate (2:1) (IV)	100 ± 2	28 ± 2	210 ± 1	54 ± 4
Ethyl acetate	—[b]	Solvate (4:1) (V)	102 ± 6	28 ± 1	210 ± 1	54 ± 4
Methanol	—[b]	Solvate (1:2) (VI)	25-126	50 ± 2	210 ± 1	52 ± 3

a Method 1—the sample is dissolved in the solvent at close to its boiling point and cooled to 0° C within a few hours; method 2—the sample is dissolved in the solvent at room temperature and the solvent allowed to evaporate slowly during several weeks. *b* For these solvents, the two methods of preparation give the same results. *c* Glass-like solid without X-ray diffraction pattern. (Agafonov *et al.*, 1991)

through VI are solvates. Figure 10.55 shows the DSC thermograms of the different crystal forms confirming that Forms III through VI contain solvent of crystallization.

Table 10.16 lists the crystallographic parameters of the different crystal forms of spironolactone, clearly showing that the different forms have distinct structures. Table 10.17 tabulates the powder patterns for Forms I through III. It is clear from this table that Forms I through III have different powder diffraction patterns. These workers (Agafonov *et al.*, 1991) were able to determine the crystal structures of three of the crystal forms of spironolactone and the contents of the unit cell for the needle form (Form I) is shown in Figure 10.56, the contents of the unit cell for Form II is shown in Figure 10.57. The conformation of the steroid is the same in all three crystal forms but it is clear that the crystal packing is different.

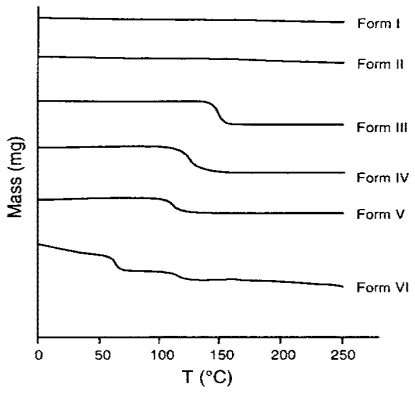


Figure 10.54 TGA curves of spironolactone crystal forms (Agafonov *et al.*, 1991).

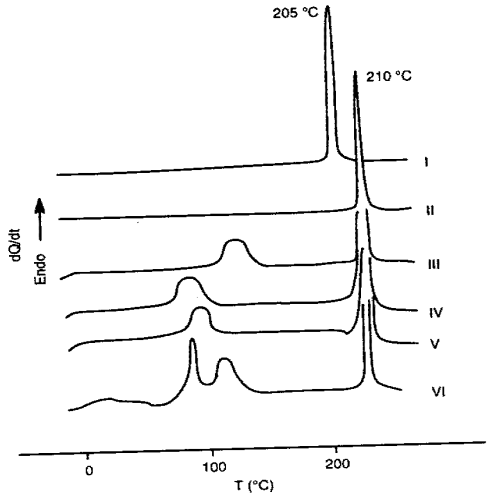


Figure 10.55 DSC thermograms of spironolactone crystal forms (Agafonov *et al.*, 1991).

Table 10.16 Crystallographic Data for the Crystal Forms of Spironolactone

Parameter	Form I	Form II	Form III	Form IV	Form V
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a (Å)	9.979	10.584	11.857	10.14	10.15
b (Å)	35.573	18.996	19.655	36.21	36.22
c (Å)	6.225	11.005	11.346	6.28	6.29
β	90.00	90.00	118.13	90.00	90.00
Z	4	4	2	4	4
V (Å^3)	2209.8	2212.6	2318.7	2306	2315
Crystal System	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Morphology	Needle-like	Prisms	Trigonal prisms	Needle-like	Needle-like
Solvate	...	...	½ acetonitrile	½ ethanol	¼ ethyl acetate

Agafonov *et al.*, 1991.

Table 10.17 X-ray Powder Diffraction Data for the Different Crystal Forms of Spironolactone

Form I			Form II			Form III		
d_{hkl} (Å)	I^a	$h\ k\ l$	d_{hkl} (Å)	I^a	$h\ k\ l$	d_{hkl} (Å)	I^a	$h\ k\ l$
17.8	w	0 2 0	9.5	s	0 2 0	9.8	s	0 2 0
8.9	m	0 4 0	7.63	w	1 0 1	8.9	w	0 1 1
8.7	vs	1 2 0	7.00	m	1 2 0	8.8	w	1 1 1
7.63	s	1 3 0	5.43	s	1 3 0	6.99	w	1 2 1
6.64	m	1 4 0	5.29	s	0 1 2	5.55	s	1 3 0

a vs–very strong intensity, s–strong intensity, m–medium intensity, w–weak intensity, vw–very weak intensity (Agafonov *et al.*, 1991).

Table 10.17 (continued)

Form I		
d_{hkl} (Å)	I^a	$h\ k\ l$
6.13	w	0 1 1
5.93	vw	0 6 0
5.10	w	1 6 0
4.94	m	2 1 0
4.68	vs	0 5 1
4.599	s	2 3 0
4.528	s	1 7 0
4.351	m	2 4 0
3.870	m	2 0 1
3.699	m	1 9 0

a vs–very strong intensit
intensity (Agafonov *et a*

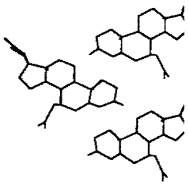


Figure 10.56 Contents o

Figure 10.57 Contents of

Table 10.17 (continued) X-ray Powder Diffraction Data for the Different Crystal Forms of Spironolactone

Form I			Form II			Form III		
d_{hkl} (Å)	I^a	*h k l*	d_{hkl} (Å)	I^a	*h k l*	d_{hkl} (Å)	I^a	*h k l*
6.13	w	0 1 1	5.10	m	2 1 0	5.48	s	0 3 1
5.93	vw	0 6 0	4.87	w	1 0 2	5.46	s	1 3 1
5.10	w	1 6 0	4.73	w	1 1 2	5.09	s	1 2 1
4.94	m	2 1 0	4.333	m	1 4 0	5.05	w	2 1 0
4.68	vs	0 5 1	4.263	w	2 1 2	4.97	m	2 0 –2
4.599	s	2 3 0	4.032	m	1 4 1	4.91	s	0 4 0, 1 2 2
4.528	s	1 7 0	3.815	w	2 0 2	4.456	m	0 2 2, 1 4 0
4.351	m	2 4 0	3.741	w	2 1 2	4.287	m	1 3 2
3.870	m	2 0 1	3.576	w	1 5 0	3.931	w	2 0 1
3.699	m	1 9 0	3.540	w	2 2 2	3.837	w	3 1 1, 3 0 2

a vs–very strong intensity, s–strong intensity, m–medium intensity, w–weak intensity, vw–very weak intensity (Agafonov *et al.*, 1991).

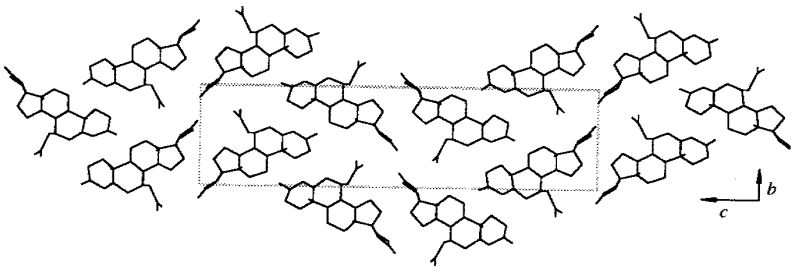


Figure 10.56 Contents of the unit cell of Form I of spironolactone (Dideberg *et al.*, 1972).

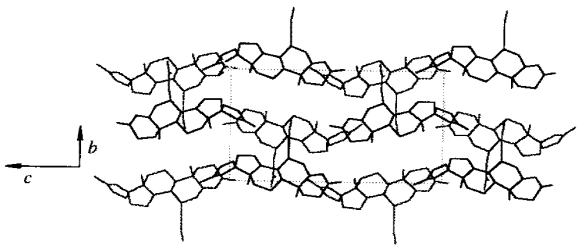
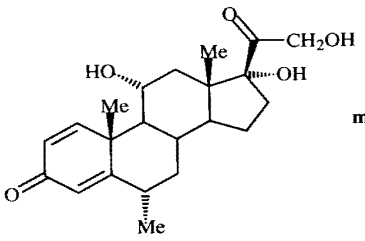


Figure 10.57 Contents of the unit cell of Form II of spironolactone (Agafonov *et al.*, 1989).

D. Methylprednisolone



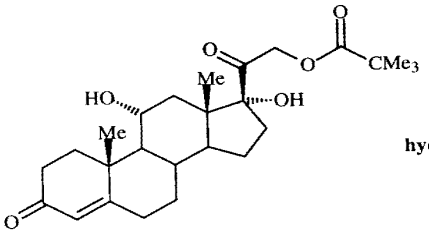
methylprednisolone

Methylprednisolone exists in two polymorphs. Form I can be prepared by recrystallization from acetone, and Form II by sublimation at 190 °C (Hamlin *et al.*, 1962). Dissolution rates of pellets of these two forms were studied under varying conditions of agitation. Under all conditions, except the most rapid agitation, Form II has a faster dissolution rate than Form I. *In vivo* tests of the rate of dissolution of Forms I and II using pellet implants in rats showed that Form II has a faster dissolution rate than Form I.

Studies of the intrinsic dissolution rates (see Chapter 6) of Forms I and II also showed that Form II has a faster dissolution rate than Form I. At increased stirring rates, Forms I and II had more similar dissolution rates. These studies also indicated that low agitation rates give data that correlate with the pellet-implant *in vivo* data, while higher agitation rates are required to give results that correlate with data from trials involving tablets dissolving in the stomach (Levy and Procknal, 1964).

Infrared spectroscopy showed that the surfaces of pellets of Form II revert to Form I in water, even after only a 2-minute exposure. This appears to be a water-mediated phase transformation of the type discussed by Haleblian and McCrone (1969). This observation explains some of the conflicting data obtained in measuring the dissolution rates of Form II in water (Higuchi *et al.*, 1969).

E. Hydrocortisone 21-*tert*-Butylacetate



hydrocortisone 21-*tert*-butylacetate

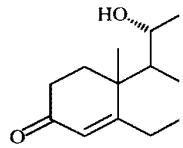
Biles (1963) reported that hydrocortisone 21-*tert*-butylacetate crystallizes in three forms. X-ray diffraction studies in our laboratory indicate that there are actually at least four different forms, and elemental analysis shows that two of these forms contain different amounts of ethanol. The results of these studies are shown in Table 10.18. Several other forms (from other solvents or from desolvation of a solvate by heating) are also known and have a melting point of 234–238 °C (Lin *et al.*, 1982).

Table 10.18 Crysta

Crystal Form
I
II
III
IV

a The exact melting
at this temperature
melt resolidified as

During recrys
III, often formed
new form, design
120 °C. Forms I
while Form III ch



hydrocortiso

All crystal fo
light. Form I
ultraviolet light i
°C. The formatio
NMR chemical sh
by gas chromato
21-*tert*-butylaceta

Table 10.19 Desol
Butyl

Days
1
2
3
6
10
14
21

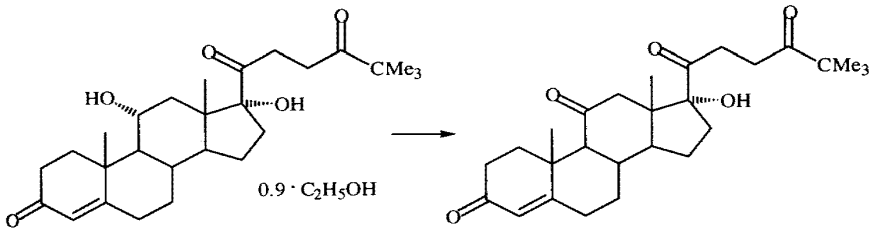
Lin *et al.*, 1982.

Table 10.18 Crystal Forms of Hydrocortisone 21-*tert*-Butylacetate

Crystal Form	Ethanol Content (mole ratio)	Oxidation in UV Light	Mp[a] (°C)
I	0.9 (variable)	Reaction	170-180
II	1.0	No Reaction	110-120[b]
III	0	No Reaction	123-126[c]
IV	0	No Reaction	234-238

a The exact melting temperature may vary from one crystal to another. *b* Opaque at this temperature range with final melting at 234–238 °C. *c* After melting, the melt resolidified as the temperature was increasing. (Lin *et al.*, 1982)

During recrystallization from ethanol, a mixture of crystal forms, Forms I, II, and III, often formed but a pure single form could be obtained under certain conditions. A new form, designated Form IV, was produced when Forms I, II, and III were heated at 120 °C. Forms I and II underwent desolvation and phase transformation to Form IV, while Form III changed from one phase to another.



hydrocortisone 21-*tert*-butylacetate **cortisone 21-*tert*-butylacetate**

All crystal forms, except for Form I, were stable upon irradiation with ultraviolet light. Form I was oxidized to cortisone 21-*tert*-butylacetate upon irradiation with ultraviolet light in air. A known weight of crystals was put in vials and irradiated at 30 °C. The formation of cortisone 21-*tert*-butylacetate was determined by the change in the NMR chemical shift of the C18 methyl signal, and the content of ethanol was measured by gas chromatography. The percent of desolvation and oxidation of hydrocortisone 21-*tert*-butylacetate to cortisone 21-*tert*-butylacetate is shown in Table 10.19. The loss

Table 10.19 Desolvation and Oxidation of Crystalline Hydrocortisone 21-*tert*-Butylacetate Form I (0.9 Ethanolate) upon Exposure to UV Light

Days	% Oxidation	Ethanol Lost
1	20.0	43.3%
2	38.9	75.6%
3	50.0	83.3%
6	52.9	88.9%
10	56.3	93.3%
14	66.7	95.6%
21	71.4	96.7%

Lin *et al.*, 1982.

of ethanol is faster than oxidation but does not completely precede oxidation. In addition, ethanol loss does not occur from crystals stored in the dark, indicating that oxidation is required for ethanol loss to begin. Further studies of this interesting reaction are in order. This behavior is different from that of dihydrophenylalanine hydrate, in which water loss almost completely preceded oxidation (Byrn and Lin, 1976).

F. Conclusion

The steroids exhibit a wide range of polymorphic and solvate behavior which appears to affect both the bioavailability and stability of these compounds. Of particular interest are the cases where one form is chemically reactive in the solid state while the others are stable.

10.6 Barbiturates

Barbiturates are another class of drugs which generally exhibit polymorphism. As in the discussions of the polymorphism of sulfonamides and steroids just presented, this section begins with Table 10.20 describing the results of hot-stage experiments on barbiturates (Kuhnert-Brandstätter, 1971).

Table 10.20 Melting Points of Polymorphs of Barbiturates[a]

Compound	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
Allobarbital	173	~122									
5-Allyl-5-(2-Cyclopentenyl-1-yl)barbituric acid	148	126	124	115	—						
5-Allyl-5-phenyl-barbituric acid	159	133	130	129	128	126					
Amobarbital	157	151									
Aprobarbital	141	139	133	130	~116	~95					
Barbital	190	184	183	181	176	159					
Butallylonal	131	128	104								
Buthalitone	149	117	~95								
5-Crotyl-5-ethyl-barbituric acid	117	90									
Cyclobarbital	173	161									
Dipropylbarbital	148	146	126	120	~110	105	85				
Dormovit	171	146									
Ethallobarbital	160	149	137	129	117	108					
5-Ethyl-5-(1-piperidyl)-barbituric acid	217	210	204								
Heptabarbital	174	150	145	143	141	137	127	100			
Hexobarbital	146										

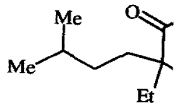
a Kuhnert-Brandstätter (1971).

Table 10.20 (continued) Melting Points

Compound	I
5-Methyl-5-phenyl-barbituric acid	226
Pentobarbital	129
Phenobarbital	176
Propallylonal	184
Secobutabarbital	166
Thialbarbital	146
Thiothyr	176
Vinbarbital	166

a Kuhnert-Brandstätter (1971).

A. Amobarbital



ven and Vizzini (1969) have det
phs of amobarbital (5-ethyl-5-iso
parameters shown in Table 10.21
The conformation of amobarbita
rystal packing is different (see F
double-ribbon arrangement; ho
ets, while in Form II an interl
density.

.21 Crystallographic Parameters fo

eter	Form I
oup	*C2/c*
	21.480
	11.590
	10.370
	97.07°
	8
	2562.0
³)	1.171
t	Plates developed on
	154–156

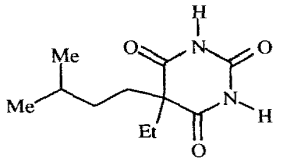
zini, 1969.

Table 10.20 (continued) Melting Points of Polymorphs of Barbiturates[a]

Compound	I	II	III	IV	V	VI	VII	VIII	IX	X	XI
5-Methyl-5-phenyl-barbituric acid	226	226	200								
Pentobarbital	129	114	108								
Phenobarbital	176	174	167	163	160	157	153	141	133	126	112
Propallylonal	184	180	~179	~127	~123						
Secobutabarbital	166	—									
Thialbarbital	146	125									
Thiothyr	176	172									
Vinbarbital	166	129	106								

a Kuhnert-Brandstätter (1971).

A. Amobarbital



amobarbital

Craven and Vizzini (1969) have determined the crystal structures of the two polymorphs of amobarbital (5-ethyl-5-isopentylbarbituric acid). The two forms have the cell parameters shown in Table 10.21.

The conformation of amobarbital is virtually identical in the two polymorphs but the crystal packing is different (see Figures 10.58–10.59). Both forms show the so-called double-ribbon arrangement; however, in Form I there is no interaction between the sheets, while in Form II an interlocking structure is present resulting in a slightly higher density.

Table 10.21 Crystallographic Parameters for the Two Forms of Amobarbital

Parameter	Form I	Form II
Space group	$C2/c$	$P2_1/c$
a (Å)	21.480	10.281
b (Å)	11.590	22.061
c (Å)	10.370	11.679
β	97.07°	109.10°
Z	8	8
V (Å^3)	2562.0	2503.1
ρ_{calc} (g cm^{-3})	1.171	1.178
Crystal habit	Plates developed on 1 0 0	Needles elongated along b-axis
Mp (°C)	154–156	160–162

Craven and Vizzini, 1969.

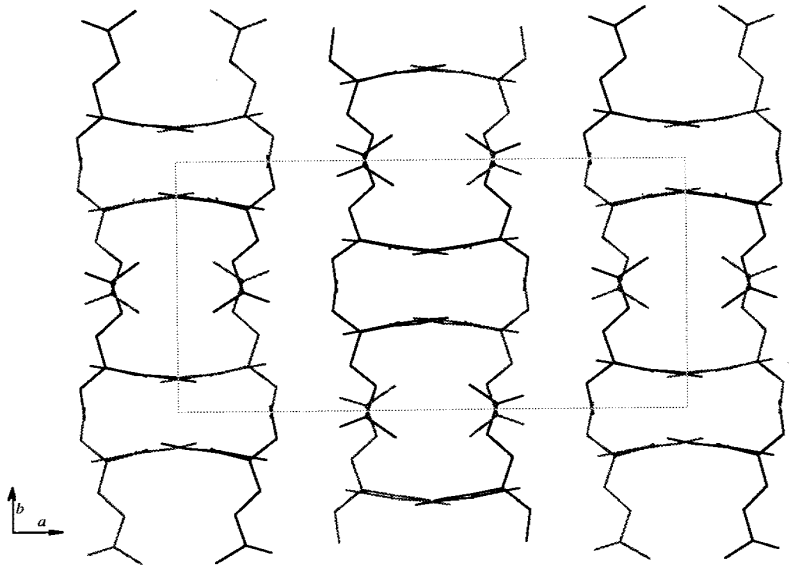


Figure 10.58 The crystal structure of Form I of amobarbital viewed down the *c* axis (Craven and Vizzini, 1969).

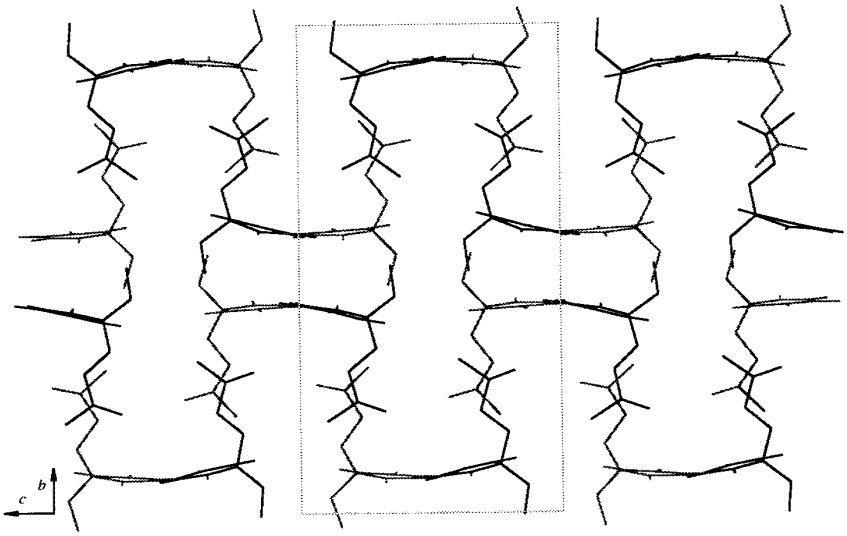


Figure 10.59 The crystal structure of Form II of amobarbital viewed down the *a* axis (Craven and Vizzini, 1969).

B PHENOBARBITAL

Phenobarbital (5-ethyl-5-ph
many as thirteen modificati
least four distinct anhydrou

The crystal structures
have been determined (W
phenobarbital, including the
two forms. The crystal pac
somewhat different; howev
hydrogen-bonded pyrimidi

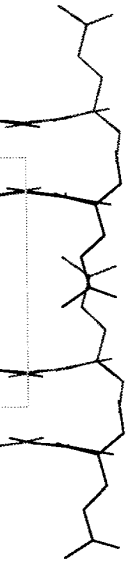
Kopp *et al.* (1988) repo
of polymorphic phenobarbi
can easily lead to misunder
to identify the different cry
obtained if different heating
also influenced the DSC re
DSC methodology outlined

A study by Szabó-Révé
ers Avicel® PH 101 or Hew
(obtained by heating a comr
two commercial sources lab
phenobarbital. The dissolut
were different as shown in
and other similar observat
dissolution rates.

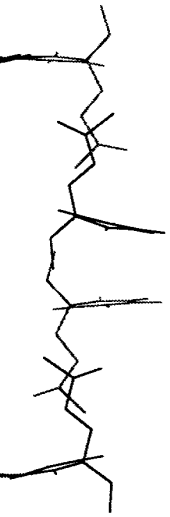
Table 10.22 Crystallographic

Parameter	Form I[a]
Space group	$P2_1/n$
a (Å)	6.800
b (Å)	47.174
c (Å)	10.695
α	90.00°
β	94.18°
γ	90.00°
Z	12
V (Å^3)	3421.7
ρ_{calc} (gm cm^{-3})	1.352

a Williams, 1973. *b* Williams,

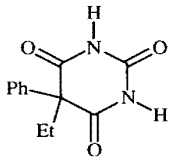


c axis (Craven and



e *a* axis (Craven and

B PHENOBARBITAL



phenobarbital

Phenobarbital (5-ethyl-5-phenylbarbituric acid) has been reported to crystallize in as many as thirteen modifications. Single-crystal studies of these polymorphs revealed at least four distinct anhydrous forms and one hydrate (see Table 10.22).

The crystal structures of the hydrate (Form XIII) and of Forms I, II, III, and V have been determined (Williams, 1973; Williams, 1974). The conformations of phenobarbital, including the angle between the two rings, are slightly different in these two forms. The crystal packing of these two forms, shown in Figures 10.60–10.61, is somewhat different; however, both forms contain layers of phenyl rings and layers of hydrogen-bonded pyrimidine rings.

Kopp *et al.* (1988) reported a study of DSC and X-ray powder diffraction patterns of polymorphic phenobarbital. Their work demonstrates that using one technique alone can easily lead to misunderstandings. It was not possible to use the DSC thermograms to identify the different crystal forms of phenobarbital because different results were obtained if different heating rates were used. In addition, they found that particle size also influenced the DSC results. These results are consistent with the discussion of DSC methodology outlined in Chapter 5.

A study by Szabó-Révesz *et al.* (1987) used direct compression with the dry binders Avicel® PH 101 or Heweten® 40 to evaluate manufactured tablets containing Form I (obtained by heating a commercial product near 160 °C for 3 h), Form II (obtained from two commercial sources labeled II_1 and II_2), or Form III (obtained by spray drying) of phenobarbital. The dissolution rates of the tablets containing the various crystal forms were different as shown in Figure 10.62 but by only a few percent. This observation and other similar observations suggest that different polymorphs may give similar dissolution rates.

Table 10.22 Crystallographic Parameters for the Crystal Forms of Phenobarbital.

Parameter	Form I[a]	Form II[a]	Form III[b]	Form V[a]	Form XIII (hydrate)[a]
Space group	$P2_1/n$	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$Pbca$
a (Å)	6.800	6.784	9.534	12.66	7.157
b (Å)	47.174	23.537	11.855	6.75	30.879
c (Å)	10.695	10.741	10.794	27.69	10.87
α	90.00°	91.89°	90.00°	90.00°	90.00°
β	94.18°	94.43°	111.56°	106.9°	90.00°
γ	90.00°	89.03°	90.00°	90.00°	90.00°
Z	12	6	4	8	8
V (Å^3)	3421.7	1708.8	1134.6	2264.1	2402.3
ρ_{calc} (gm cm^{-3})	1.352	1.354	1.360	1.362	1.384

a Williams, 1973. *b* Williams, 1974.

The effect of additives on the crystallization of phenobarbital has also been investigated (Kato *et al.*, 1984). Kato and co-workers prepared two forms of phenobarbital by adding barbital or cyclobarbital to the crystallization. In these studies rather large quantities of additive (7.5% for barbital and 7% cyclobarbital) were required to achieve the effect.

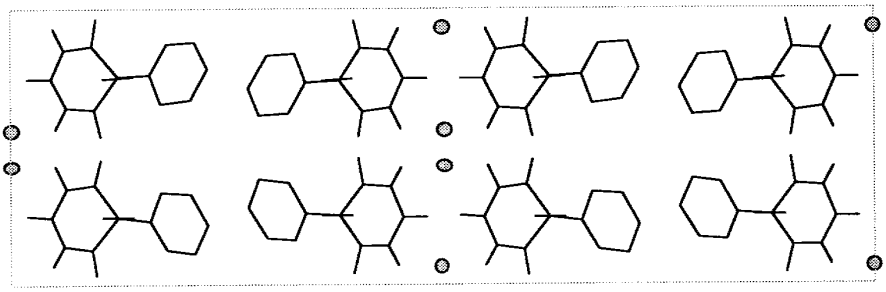


Figure 10.60 Crystal packing of phenobarbital Form XIII hydrate (◎ water molecule) viewed down the *z* axis. (Williams, 1973).

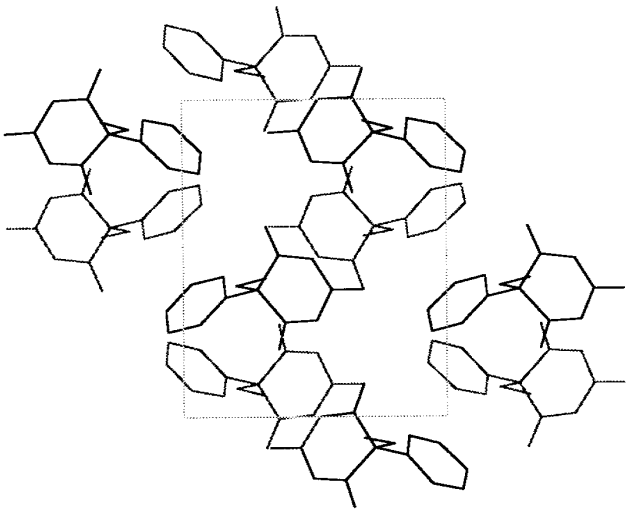


Figure 10.61 Crystal packing of phenobarbital Form III viewed down the *b* axis (Williams, 1974).

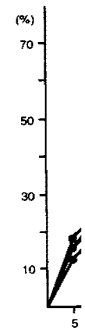
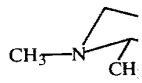


Figure 10.62 Dissolution rate of
pressure of 20 kN,
cial sources), and II

10.7 OTHER DRUGS

In this section the polymorph
this review is not exhaustive,
pharmaceuticals.

A. PROMEDOL ALCOHOL



DeCamp and Ahmed (1972
monoclinic and rhombohedr
methyl-4*e*-phenylpiperidin-4
alcohol is the same in bot

Table 10.23 Crystallographic Pa

Parameter	Mono
Space Group	
a (Å)	
b (Å)	
c (Å)	
β	
Z	
V (Å^3)	1
ρ_{calc} (gm·cm^{-3})	

a DeCamp and Ahmed, 1972a. *b*

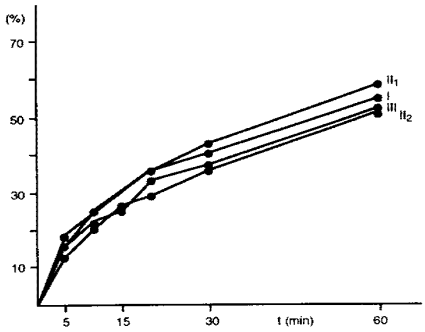
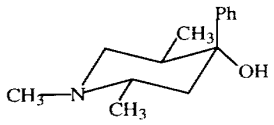


Figure 10.62 Dissolution rate of phenobarbital tablets prepared using the binder Heweten® 40, a pressure of 20 kN, and the four different crystal forms, Forms I, II (from two commercial sources), and III (Szabó-Réveśz *et al.*, 1987).

10.7 Other Drugs

In this section the polymorphic properties of several other drugs are reviewed. While this review is not exhaustive, it illustrates several important studies of polymorphism in pharmaceuticals.

A. Promedol Alcohol



(±)-β-promedol alcohol

DeCamp and Ahmed (1972a–b) have determined the crystal structure of both the monoclinic and rhombohedral forms of (±)-β-promedol alcohol, (±)-α-1,2*a*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, (see Table 10.23). The conformation of β-promedol alcohol is the same in both forms, but the crystal packing differs (see Figures

Table 10.23 Crystallographic Parameters for the Two Forms of (±)-β-Promedol Alcohol

Parameter	Monoclinic Form[a]	Rhombohederal Form[b]
Space Group	$P2_1/n$	$R\bar{3}$
a (Å)	13.298	29.754
b (Å)	7.721	29.754
c (Å)	12.776	7.713
β	90.09°	60.0°
Z	4	18
V (Å^3)	1311.8	5913.5
ρ_{calc} (gm·cm^{-3})	1.109	1.110

a DeCamp and Ahmed, 1972a. *b* DeCamp and Ahmed, 1972b

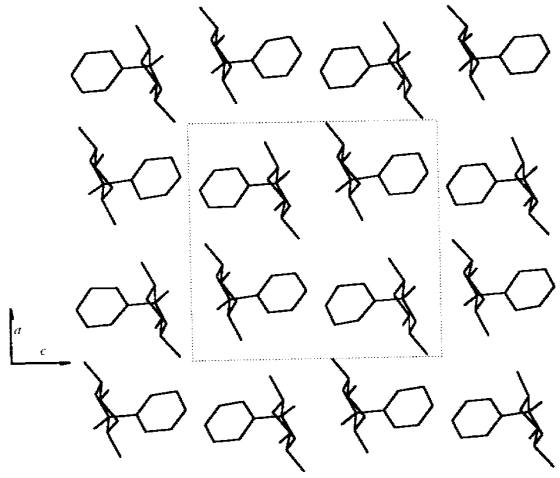


Figure 10.63 Crystal packing of (±)-β-promedol alcohol monoclinic form (DeCamp and Ahmed, 1972a).

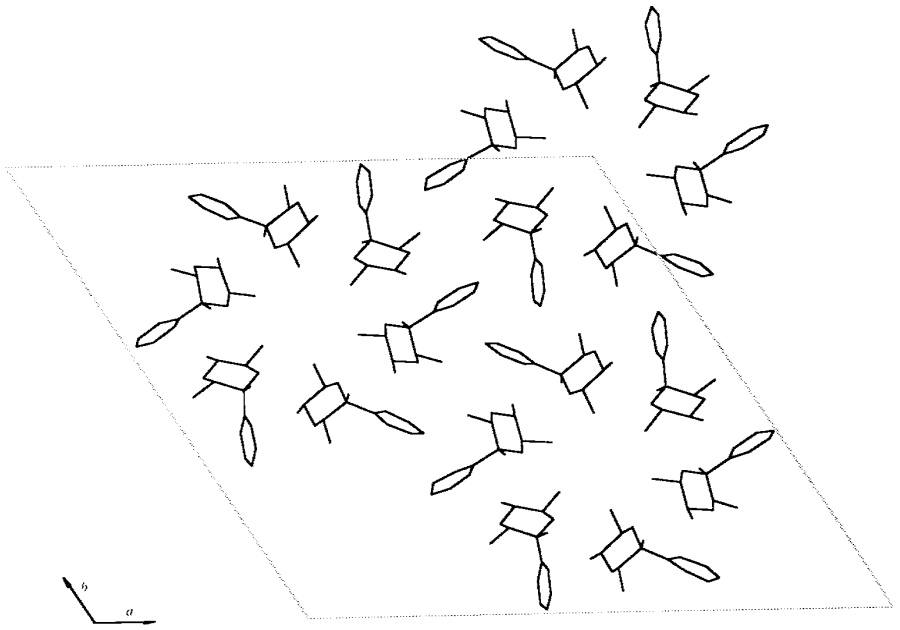
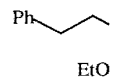


Figure 10.64 Crystal packing of (±)-β-promedol alcohol rhombohedral form (DeCamp and Ahmed, 1972b).

10.63–10.64). In the
same chirality to form
gen bonds; however,
Despite the differenc
have almost the sam
104.5–105 °C, where
difference in melting
since the OH···N dis
the densities indicate
DeCamp and Ahmed
rings of molecules of
molecules of the sam
ordering results in a
monoclinic form. S
(1971).

B. Enalapril Ma



This example illustra
morphs. Enalapril
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respectively. The
forms as shown in F
of the two crystal fo
the DSC analysis, th
solution data, as sho
dissolution for the

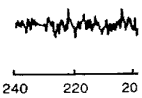
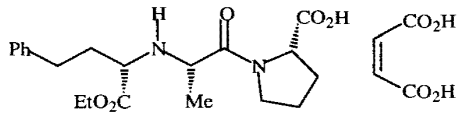


Figure 10.65 Solid-st

10.63–10.64). In the monoclinic form, OH···N hydrogen bonds link molecules of the same chirality to form chains. In the rhombohedral form, there are also OH···N hydrogen bonds; however, these link molecules of alternating chirality into hexameric rings. Despite the differences in crystal packing, the monoclinic and rhombohedral crystals have almost the same density. The melting point of the rhombohedral form is 104.5–105 °C, whereas the melting point of the monoclinic form is 90.5–91 °C. This difference in melting point is probably not related to differences in hydrogen bonding since the OH···N distances are approximately the same in the two forms. In addition, the densities indicate that the two forms have nearly equal packing energies. Thus, DeCamp and Ahmed (1972a) suggested that, since the rhombohedral form contains rings of molecules of alternating chirality while the monoclinic form contains stacks of molecules of the same chirality, the monoclinic form is more ordered. This increased ordering results in an entropy difference that results in a lower melting point for the monoclinic form. Similar arguments were also advanced by Krigbaum and Wildman (1971).

B. Enalapril Maleate



enalapril maleate

This example illustrates the need for using more than one method in looking for polymorphs. Enalapril maleate (Ip *et al.*, 1986) exists in two crystal forms which give different solid-state ^{13}C NMR spectra. (Figures 10.65 and 10.66). The signals of the ethyl ester methyl and maleate carbon signals are at 11–13 ppm and 137–138 ppm, respectively. The XRPD patterns also display a difference between the two crystal forms as shown in Figures 10.67 and 10.68. However, the FT-IR and Raman spectra of the two crystal forms are very similar. Under the experimental conditions used in the DSC analysis, the thermograms of both forms cannot be distinguished. Heat of solution data, as shown in Table 10.24, indicate that there are differences in the heats of dissolution for the two forms, although both crystal forms have virtually identical

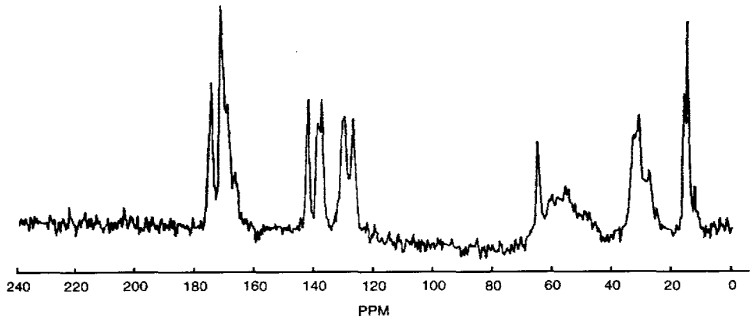


Figure 10.65 Solid-state ^{13}C NMR of enalapril maleate Form I (Ip *et al.*, 1986).

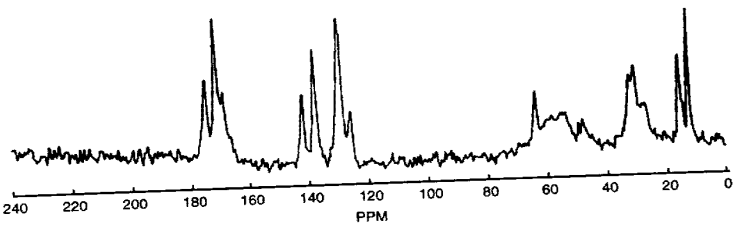


Figure 10.66 Solid-state ^{13}C NMR of enalapril maleate Form II (Ip *et al.*, 1986).

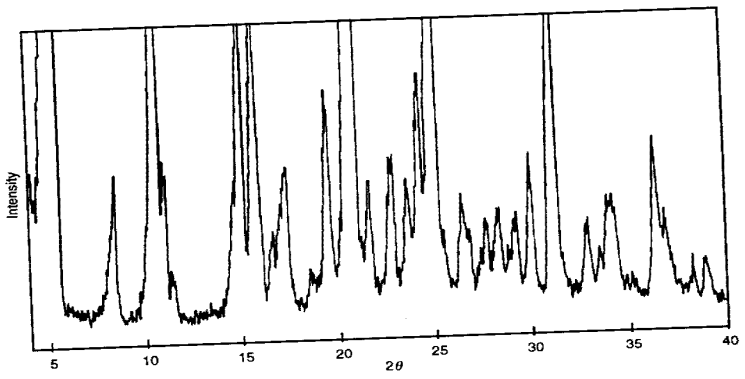


Figure 10.67 Powder X-ray diffraction pattern of enalapril maleate Form I (Ip *et al.*, 1986).

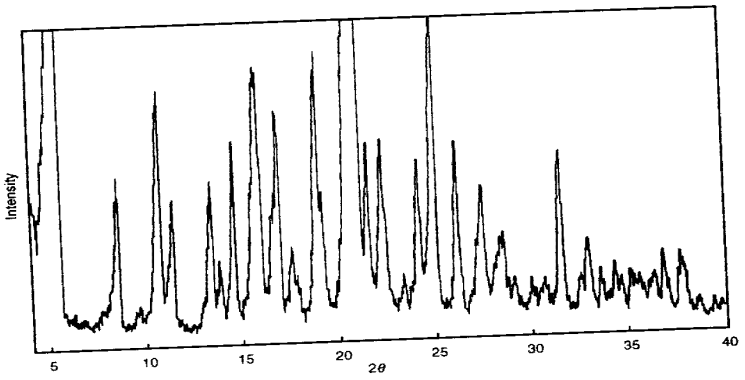


Figure 10.68 Powder X-ray diffraction pattern of enalapril maleate Form II (Ip *et al.*, 1986).

in vitro dissolution rates (s
number of methods on two
two crystal forms are very
properties.

Table 10.24 Heats of Solution

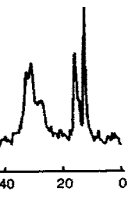
Solvent	**Form I Δ** (kJ/mo
Methanol	36.5(
	35.6
	35.9
	36.2(
	36.4
Mean ± S.D.	36.33 ±
Acetone	59.4
	59.7
	59.1
	59.7
Mean ± S.D.	59.52 ±

Ip *et al.*, 1986.

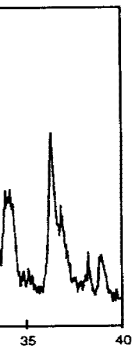
Table 10.25 Dissolution Dat

Enalapril Maleate Formulation	**Crys**
Capsules	
	I
	I
Tablets	

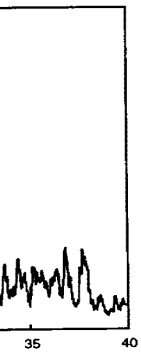
Ip *et al.*, 1986.



86).



p *et al.*, 1986).



(Ip *et al.*, 1986).

in vitro dissolution rates (see Table 10.25). In summary, this represents a study by a number of methods on two crystal forms of an important compound. It is clear that the two crystal forms are very similar in structure and have very similar pharmaceutical properties.

Table 10.24 Heats of Solution and Transition of Enalapril Maleate Polymorphs

Solvent	Form I ΔH_{soln} (kJ/mol)	Form II ΔH_{soln} (kJ/mol)	ΔH_{Trans} (kJ/mol)
Methanol	36.50	38.47	
	35.64	38.21	
	35.95	38.54	
	36.20	38.62	
	36.46		
Mean ± S.D.	36.33 ± 0.25	38.46 ± 0.11	2.05
Acetone	59.44	62.71	
	59.73	61.99	
	59.19	62.66	
	59.73	62.54	
Mean ± S.D.	59.52 ± 0.25	62.41 ± 0.29	2.89

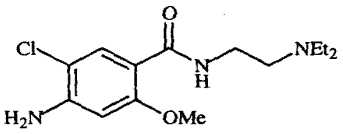
Ip *et al.*, 1986.

Table 10.25 Dissolution Data for Enalapril Maleate Capsules and Tablets

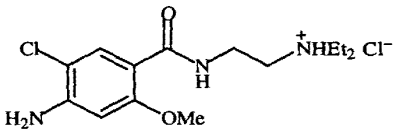
Enalapril Maleate Formulation	Crystal Form	Potency (mg)	Average Percent Dissolved at 30 min
Capsules	II	2.5	89
	I	2.5	100
	I and II	2.5	101
	I	2.5	96
	I and II	20	82
	I	20	99
	II	20	95
	I	20	92
Tablets	I	10	100
	II	10	99
	I	10	99
	I and II	10	98
	I	40	103
	I and II	40	102
	II	40	96

Ip *et al.*, 1986.

C. Metoclopramide and Metoclopramide Monohydrochloride



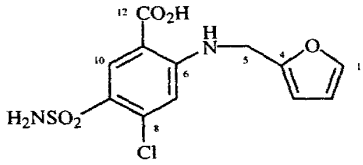
metoclopramide



metoclopramide monohydrochloride

Mitchell (1985) has studied the polymorphism of both metoclopramide and metoclopramide monohydrochloride. Each exists in two crystal forms and metoclopramide monohydrochloride also forms a monohydrate. Metoclopramide exists in two enantiotropic polymorphs with a transition temperature of 125 °C from Form I (stable at low temperature) to Form II (stable at high temperature) having a melting point of 147 °C. This process can also be reversed. Dehydration of metoclopramide monohydrochloride monohydrate, depending on the conditions, give rise to one of two anhydrous polymorphs; Form I (mp 187 °C) is formed from the melt under slow crystallization conditions, whereas, Form II (mp 155 °C) is formed from the melt under fast crystallization conditions. All of these crystal forms were detected by DSC, thermal microscopy, X-ray diffraction, and infrared spectroscopy.

D. Furosemide



furosemide

Doherty and York (1988) described the two crystal forms of furosemide readily detected by X-ray powder diffraction. In a more recent study, Matsuda and Tatsumi (1990) discovered three additional polymorphs as well as two solvates and an amorphous form. Interestingly, it was found that the forms produced could be related to the boiling point of the solvent. Thus, Form I was obtained from the lower boiling solvents used [acetone (bp 57 °C), methanol (bp 65 °C), ethanol (bp 79 °C), and methyl ethyl ketone (bp 80 °C)], Form II was obtained from the higher boiling solvents used [isobutyl alcohol (bp 108 °C), butanol (bp 118 °C), and pentanol (bp 138 °C)], and mixtures of both forms were obtained from solvents with intermediate boiling points used [isopropyl alcohol (bp 83 °C) and propanol (bp 97 °C)] by slow crystallization from a hot solution. To our knowledge this is the first such relationship which has been reported. In addition, they reported that the rate of solvent evaporation affected the crystal form obtained. Figure 10.69 shows the XRPDs of furosemide and Figure 10.70 shows the IR spectra of the different crystal forms.

Doherty and York (1988) also showed that Forms I and II had different solid-state NMR spectra as shown in Figure 10.71. Figure 10.72 shows the DSC and TG

thermograms of the six dif
all forms are unique and w

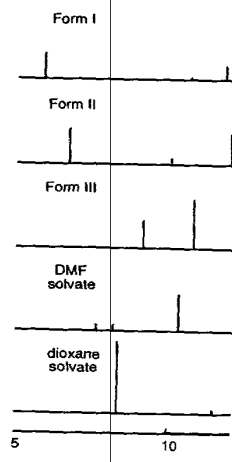


Figure 10.69 X-ray powder di
and Tatsumi, 19

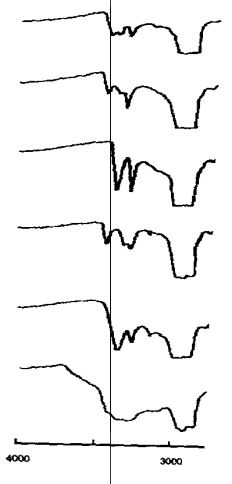


Figure 10.70 Infrared spectra
1990).

thermograms of the six different forms of furosemide. It is clear from these studies that all forms are unique and well characterized.

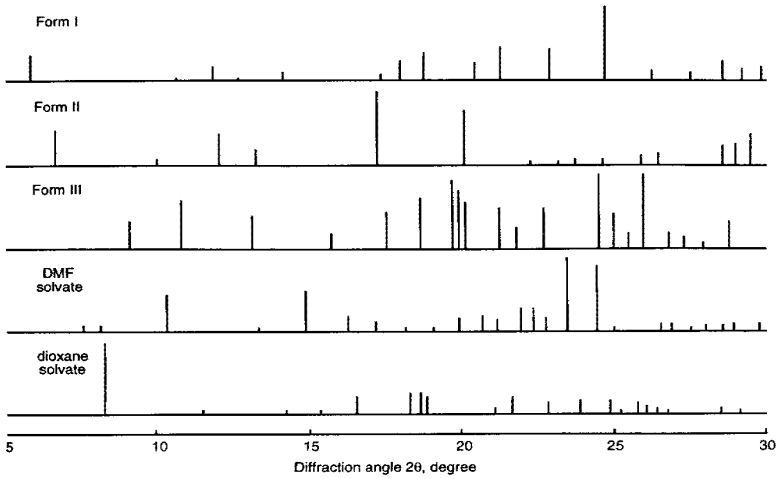


Figure 10.69 X-ray powder diffraction patterns of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

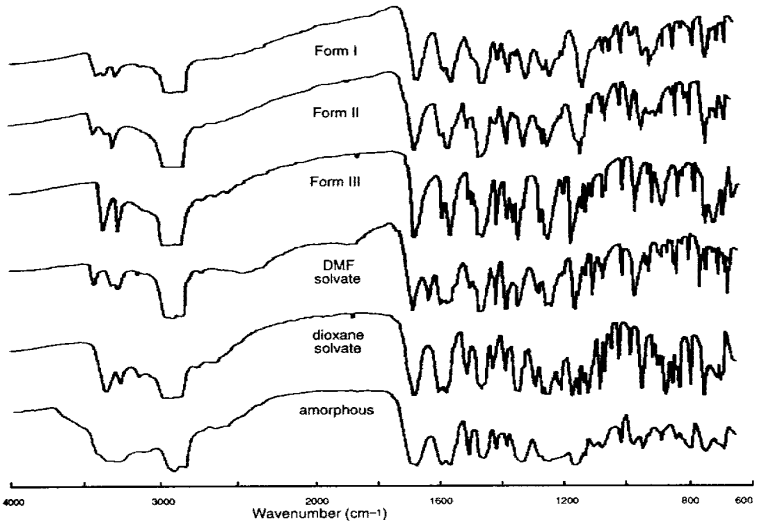


Figure 10.70 Infrared spectra of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

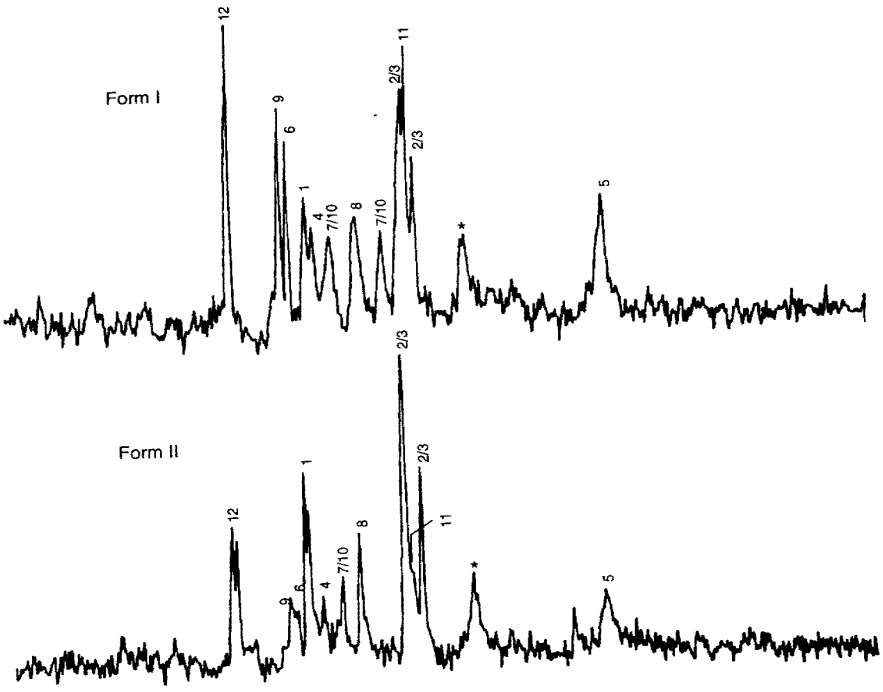


Figure 10.71 Solid-state ^{13}C CP/MAS NMR spectra for two furosemide forms at ambient temperature with peak assignments. The peaks marked with a star are due to the Delrin® rotor (Doherty and York, 1988).

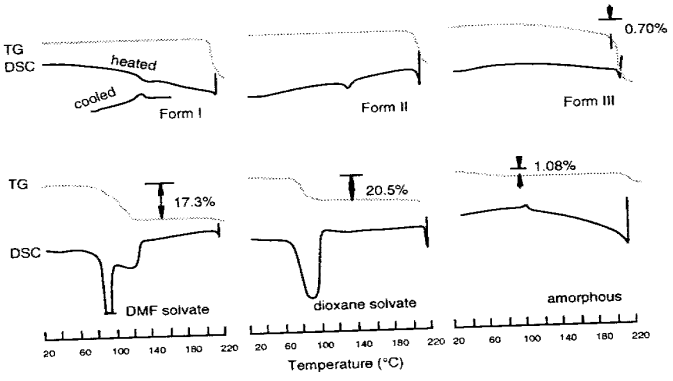


Figure 10.72 DSC and TG thermograms of the different crystal forms of furosemide (Matsuda and Tatsumi, 1990).

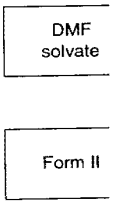


Figure 10.73 Interconvers
and Tatsum

Matsuda and Tats
which could be obtaine
studied the interconvers
rized in Figure 10.73.
most stable form, Form
Form I upon heating (s
Matsuda and Tats

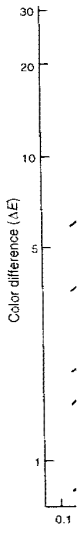


Figure 10.74 Double-log
forms unde

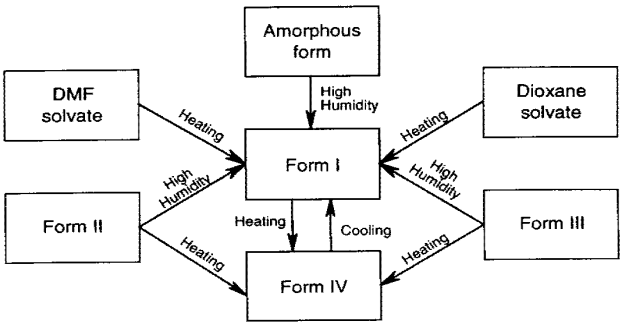


Figure 10.73 Interconversion scheme of furosemide crystal forms under various conditions. (Matsuda and Tatsumi, 1990).

Matsuda and Tatsumi (1990) found a high temperature crystal form (Form IV) which could be obtained by heating Forms I, II, or III to 180 °C. In addition, they studied the interconversion of the crystal forms and these interconversions are summarized in Figure 10.73. It is clear that all of the crystal forms can be converted into the most stable form, Form I, at room temperature. The solvated forms also converted to Form I upon heating (see Figure 10.73).

Matsuda and Tatsumi also studied the physical and chemical properties of the

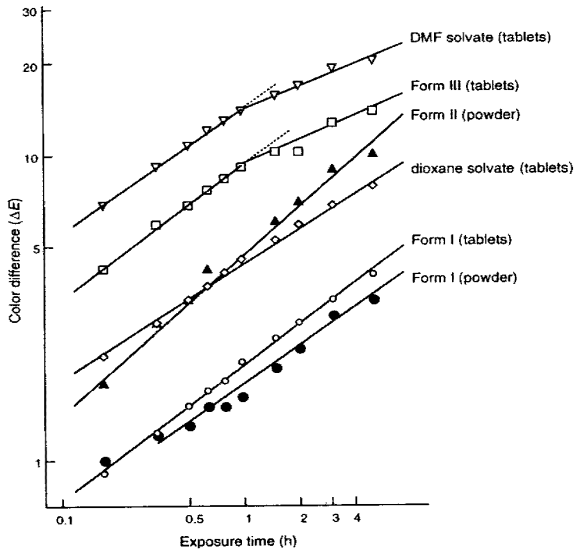


Figure 10.74 Double-logarithmic plots for the coloration process of different furosemide crystal forms under irradiation by a mercury vapor lamp (Matsuda and Tatsumi, 1990).

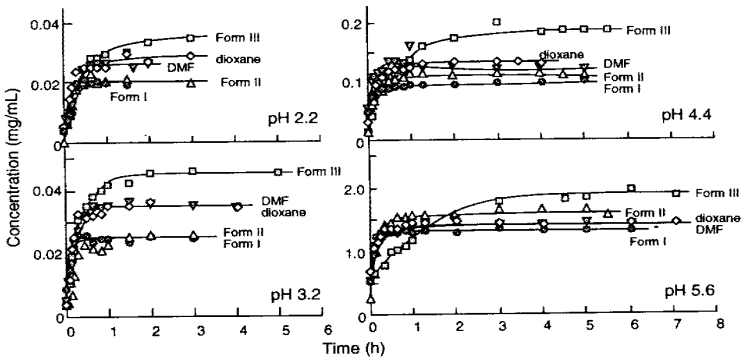
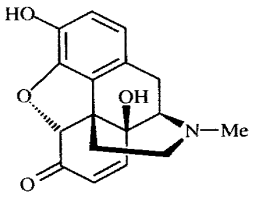


Figure 10.75 Dissolution profiles of the different crystal forms of furosemide in buffer solution at various pH values at 37° C (Matsuda and Tatsumi, 1990).

different crystal forms of furosemide. Figure 10.74 shows the studies on the photostability of the different crystal forms. It is apparent that the different crystal forms have a different amount of coloration initially but that the rate of change in coloration is about the same for all crystal forms. However, the relationship between coloration and degradation remains unknown.

Figure 10.75 shows the dissolution profiles of furosemide at different pH (2.2, 3.2, 4.4, and 5.6). It is apparent that Form II reaches the highest solubility at all pH's and that Form II and the DMF solvate are the least soluble. Judging by these profiles, some of the forms appear to interconvert in these experiments.

E. 14-Hydroxymorphinone—Color Dimorphism



14-hydroxymorphinone

The phenolic α,β-unsaturated ketone 14-hydroxymorphinone exists in two crystalline modifications (see Table 10.26), which are interconvertible by dissolution and recrystallization (Chiang *et al.*, 1978). Recrystallization from polar solvents (ethanol) yields yellow crystals, while crystallization from benzene gives colorless (white) crystals. Both forms are stable indefinitely in the solid state.

Infrared spectra show that the yellow form has a carbonyl absorption at 1685 cm^{-1}, while the colorless form has a carbonyl absorption at 1660 cm^{-1}. Since both forms have a carbonyl absorption, neither form contains an enol tautomer.

Crystallographic studies show that the conformation of 14-hydroxymorphinone in the two forms is similar; however, the yellow form contains an intermolecular OH···O

Table 10.26 Crystallogr

Parameter
Space group
a (Å)
b (Å)
c (Å)
Z
ρcalc (g cm^{-3})
V (Å^3)

Chiang *et al.*, 1978.

hydrogen bond, while bond.

The color of the y hydrogen bond, since dihydroxyterephthalate is that there is a weak adjacent phenyl ring in tion between these two

Numerous other re that are not drugs. The *et al.*, 1978; Byrn *et a* important compound I thebaine gave metathe sodium bicarbonate and NaOH or NH_3 and recry melting point, and both solution in benzene. U color and no investigati been reported.

M

F

F. Miscellaneous St

Kuhnert-Brandstätter an polymorphs of pharmac spectroscopy, and in so shown in Table 10.27. I of the different polymo

Table 10.26 Crystallographic Parameters for the Two Forms of 14-Hydroxymorphinone

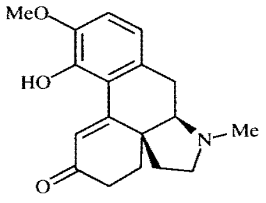
Parameter	Colorless Form	Yellow Form
Space group	$P2_12_12_1$	$P2_12_12_1$
a (Å)	12.918	13.150
b (Å)	14.074	13.508
c (Å)	8.035	7.837
Z	4	4
ρ_{calc} (g cm^{-3})	1.36	1.428
V (Å^3)	1460.8	1392.1

Chiang *et al.*, 1978.

hydrogen bond, while the white form contains an intramolecular OH···O hydrogen bond.

The color of the yellow form may, in part, result from the intermolecular OH···O hydrogen bond, since a similar effect was found for dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate (Byrn *et al.*, 1972; see Section 8.1). An alternative explanation is that there is a weak charge-transfer interaction between the C=O group and an adjacent phenyl ring in the yellow form, but not in the colorless form. A clear distinction between these two explanations is not possible.

Numerous other reports of color dimorphism have been published for compounds that are not drugs. These reports are briefly reviewed by (Desiraju *et al.*, 1977; Chiang *et al.*, 1978; Byrn *et al.*, 1972). Color dimorphism of at least one other biologically important compound has been reported (Small and Meitzner, 1933); reduction of thebaine gave metathebainone. Neutralization of a metathebainone solution with sodium bicarbonate and recrystallization gave yellow crystals, while neutralization with NaOH or NH_3 and recrystallization gave colorless crystals. Both crystals had the same melting point, and both gave a yellow solution in ethanol or water and a colorless solution in benzene. Unfortunately, no structural explanations of these differences in color and no investigation of differences in polymorphism of these compounds have been reported.



metathebainone

F. Miscellaneous Studies by Kuhnert-Brandstätter and Co-workers

Kuhnert-Brandstätter and co-workers have carried out an extensive study on the polymorphs of pharmaceuticals. Their studies generally use thermal microscopy, IR spectroscopy, and in some cases powder diffraction. The results of these studies are shown in Table 10.27. In many cases they were able to determine the relative stability of the different polymorphs and whether they were monotropic (one forms is most

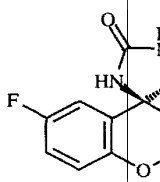
Table 10.27 Studies of Polymorphic Pharmaceuticals by Kuhnert-Brandstätter's Group

Pharmaceutical	No. of Forms	Thermodynamics*	Reference
Amiperone	2	II → I	Kuhnert-Brandstätter and Porsche, 1989b
Anilamate	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Benactyzine HCl	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Bentiromide	3 + hydrates	II → I, ···	Kuhnert-Brandstätter and Porsche, 1989b
Bromopride	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Brotizolam	4	IV → III, III → I, ···	Kuhnert-Brandstätter and Porsche, 1989b
Bumetanide	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Bupicomide	3	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Buspirone HCl	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Clenbuterol HCl	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dimethoxanate HCl	2	II → I	Kuhnert-Brandstätter *et al.*, 1982c
Diphenadione	2	II → I	Kuhnert-Brandstätter *et al.*, 1982c
Diphenidol HCl	3	III → II, III → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dipyridamole	2	II → I	Kuhnert-Brandstätter. and Wurian, 1982a
Dobutamine HCl	4	···	Kuhnert-Brandstätter and Porsche, 1989b
Famotidine	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Fenbufen	3	III → II, III → I	Kuhnert-Brandstätter and Porsche, 1989b
Flucabril	2	II → I	Kuhnert-Brandstätter *et al.*, 1982b
Flupirtine Maleate	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Gallic Acid Ethyl Ester	3	III → II, III → I	Kuhnert-Brandstätter. and Wurian, 1982a
Halofenate	3	Monotropic	Kuhnert-Brandstätter and Völlenklee, 1986
Heptolamide	3	···	Kuhnert-Brandstätter and Porsche, 1989a
Iprindol HCl	3	III → II, ···	Kuhnert-Brandstätter *et al.*, 1982b
Levobunolol HCl	5		Kuhnert-Brandstätter and Porsche, 1989a
Lorcainide HCl	2	II → I	Kuhnert-Brandstätter and Völlenklee, 1986
Maprotiline HCl	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Mexiletine HCl	3	III → I, II → I	Kuhnert-Brandstätter and Völlenklee, 1987
Minoxidil	3	III → II, II → I	Kuhnert-Brandstätter and Völlenklee, 1986
Mopidamol	4	IV → I, II → I, ···	Kuhnert-Brandstätter and Völlenklee, 1986
Nafoxidine HCl	3	III → I, II → I	Kuhnert-Brandstätter *et al.*, 1982c
Naftifine HCl	3	Monotropic	Kuhnert-Brandstätter and Porsche, 1989a
Oxypendyl 2HCl	4	III → I, II → I, ···	Kuhnert-Brandstätter and Völlenklee, 1987
Paxamate	2	II → I	Kuhnert-Brandstätter and Porsche, 1990
Penbutolol Sulfate	4	IV → III, III → II, ···	Kuhnert-Brandstätter and Völlenklee, 1987
Piretanide	4	II → I, ···	Kuhnert-Brandstätter and Porsche, 1989a
Pirprofene	2	Monotropic	Kuhnert-Brandstätter and Völlenklee, 1987
Propentofylline	4	Monotropic	Kuhnert-Brandstätter and Porsche, 1990
Renytoline HCl	3	III → II, II → I	Kuhnert-Brandstätter *et al.*, 1982b
Terconazole	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1989b
Triclabendazole	2	Monotropic	Kuhnert-Brandstätter and Porsche, 1990

* Some forms undergo inhomogeneous melting rather than transformation.

stable at all temperatures) o
peratures). Specifically, Ku
this table as cases where the
the highest melting point.

G. (2*R*,4*S*)-6-FLUORO-2-M

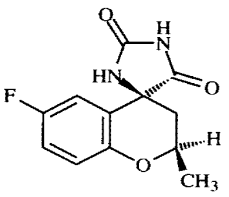


This aldose reductase inhil
studied by DSC, X-ray pow
1988). Figure 10.76 show
indicates that the β–form is
tent with the X-ray powder
sion of the β–form to the α
the α– and β–forms as wel
heating the β–form, indicati
α–form to the β–form appe

Figure 10.76 The DSC curv
dione (Ashizawa

stable at all temperatures) or enantiotropic (different forms are stable at different temperatures). Specifically, Kuhnert-Brandstätter defined enantiotropy for the purposes of this table as cases where the most stable form at room temperature is not the form with the highest melting point.

G. (2*R*,4*S*)-6-Fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione



(2*R*,4*S*)-6-fluoro-2-methylspiro-[chroman-4,4′-imidazoline]-2′,5-dione

This aldose reductase inhibitor exists in two crystal forms, α and β, which were studied by DSC, X-ray powder diffraction, and infrared spectroscopy (Ashizawa *et al.*, 1988). Figure 10.76 shows the DSC behavior of the β–form. This thermogram indicates that the β–form is converted to the α–form at high temperature and is consistent with the X-ray powder diffraction and infrared spectra which showed interconversion of the β–form to the α-form. Figure 10.77 shows the X-ray powder patterns of the α– and β–forms as well as that of a 1:1 mixture and the product obtained upon heating the β–form, indicating it is being transformed into the α–form. Addition of the α–form to the β–form appears to provide nuclei which allow the conversion to occur

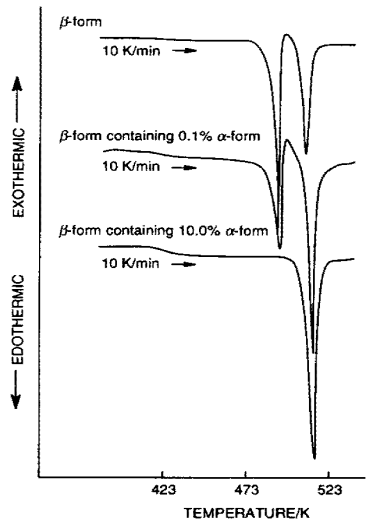


Figure 10.76 The DSC curve for (2*R*,4*S*)-6-fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione (Ashizawa *et al.*, 1988).

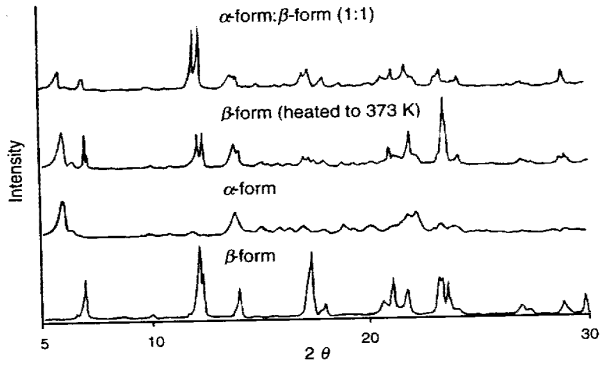
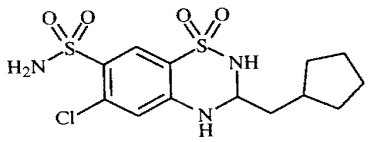


Figure 10.77 X-ray diffraction patterns of (2*R*,4*S*)-6-fluoro-2-methylspiro[chroman-4,4′-imidazoline]-2′,5-dione (Ashizawa *et al.*, 1988).

before melting of the β–form. This indicates the importance of nucleation in polymorphic interconversions.

The crystal structure of the β–form has been determined by single crystal X-ray methods (Ashizawa, 1989). They suggested that the crystal structure of the α–form is disordered and thus the structure could not be determined.

H. Cyclopenthiazide



cyclopenthiazide

The diuretic cyclopenthiazide exists in three polymorphic forms which are obtained by crystallization from ethanol:heptane:methanol (Form I), ethanol (Form II), and ethanol:water (Form III) (Gerber *et al.*, 1991).

These forms were characterized by DSC, thermomicroscopy, X-ray powder diffraction, scanning electron micrographs, IR, solid-state NMR, solution calorimetry, dissolution rates, and solubility determinations.

Figure 10.78 shows the DSC thermograms, Figure 10.79 shows the X-ray powder diffraction patterns, and Figure 10.80 shows the solid-state CP/MAS spectra. The DSC thermograms gave the following heats of fusion for the different polymorphs: Form I, 105.5 kJ/mol; Form II, 98.4 kJ/mol and Form III, 62.5 kJ/mol. The value for Form III is too low to be the ΔH_f and most likely represents a transformation process This was confirmed by thermomicroscopy in which Form III melted at 181 °C and recrystallized to Form I.

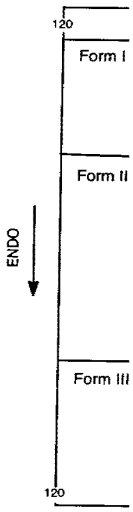


Figure 10.78 DSC the
238 °C;

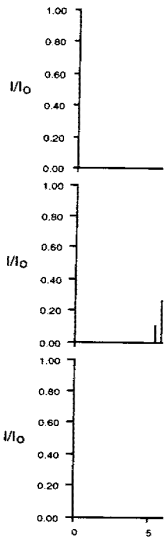


Figure 10.79 X-ray pov
1991).

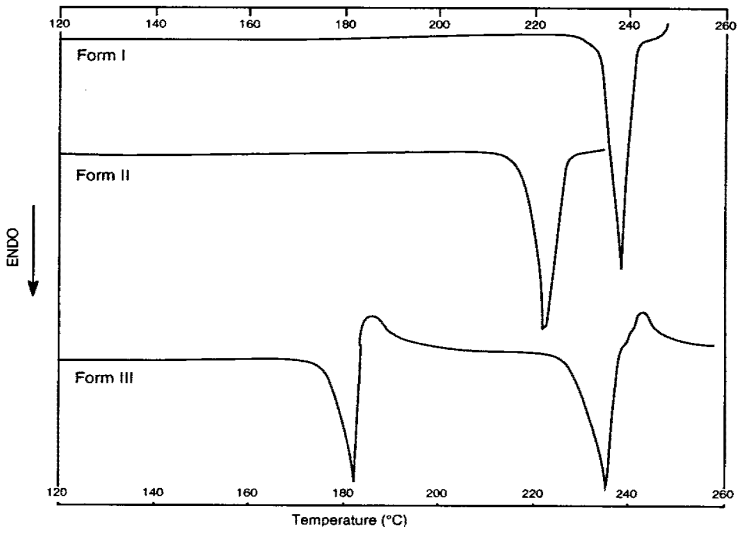


Figure 10.78 DSC thermograms of cyclopentathiazide polymorphs with melting points: Form I, 238 °C; Form II, 225 °C; and Form III, 181° and 235 °C (Gerber *et al.*, 1991).

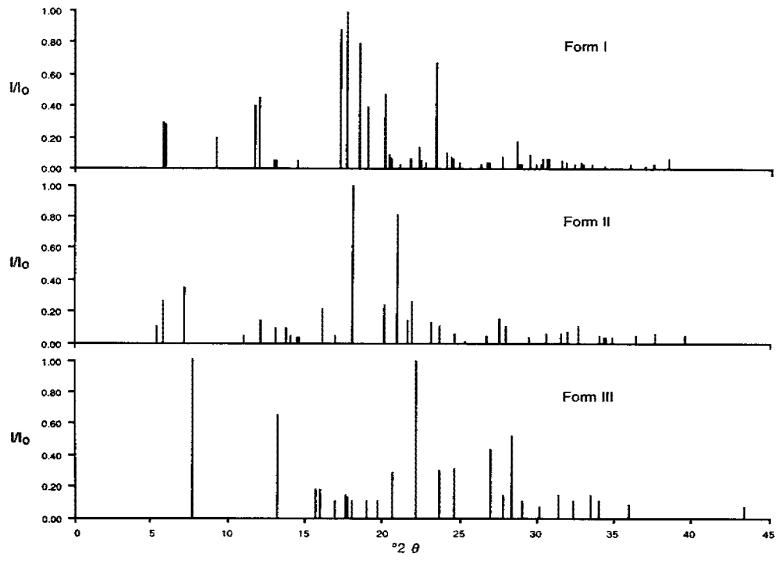


Figure 10.79 X-ray powder diffraction patterns of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

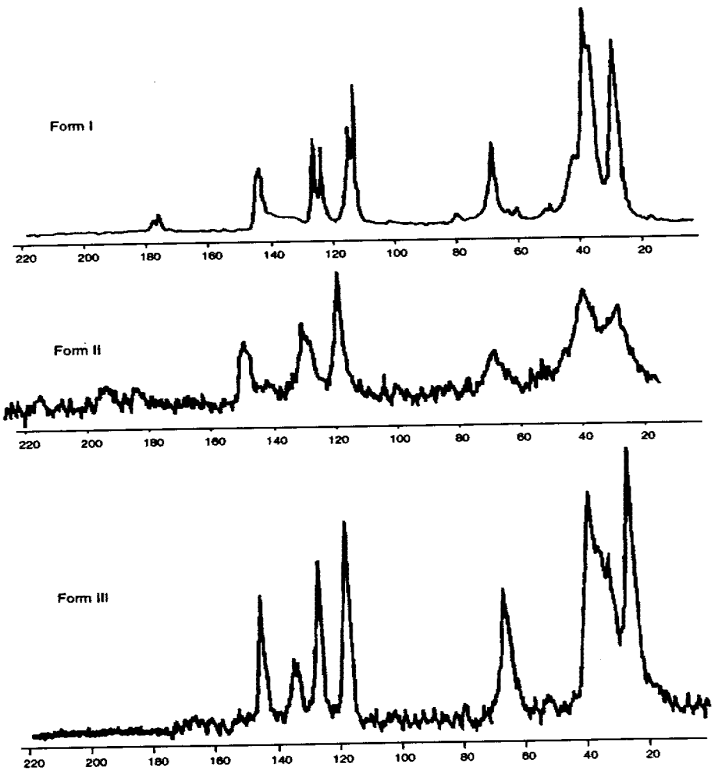


Figure 10.80 Solid-state ^{13}C NMR spectra of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

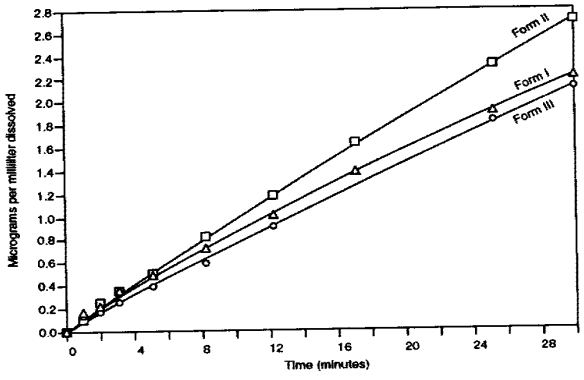
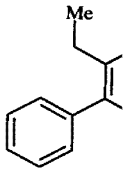


Figure 10.81 Intrinsic dissolution rates of cyclopentathiazide polymorphs (Gerber *et al.*, 1991).

It is evident from
of solution of the diff
Form I, 0.34 kJ/mol;
these measurements ra
solution within experi
were measured and are
tion rates but Form II h
three forms were also
solubility was Form II
most stable polymorph

I. TAMOXIFEN CITR



Tamoxifen citrate is w
(1987) have reported th
Form B. Figure 10.82
morph of tamoxifen citr
of Form A; however, t
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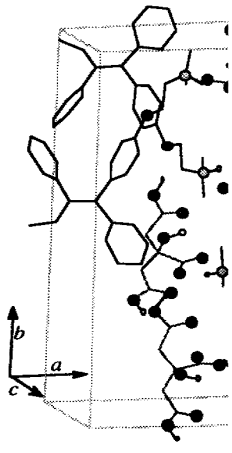
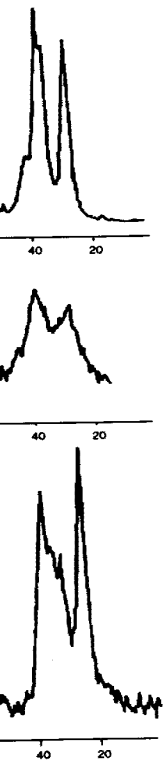


Figure 10.82 Stereoview o
Becker, 1987)

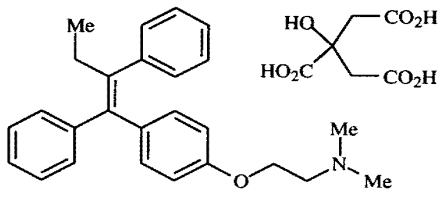


orphs (Gerber *et al.*, 1991).

phs (Gerber *et al.*, 1991).

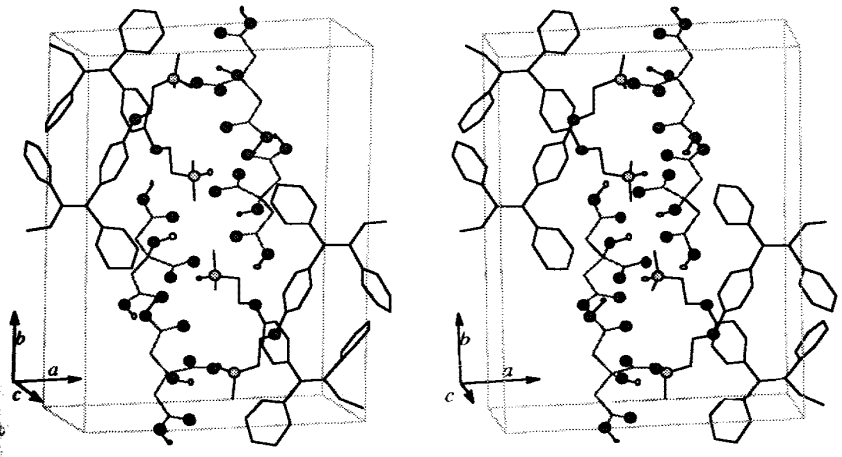
It is evident from all these data that these are truly different polymorphs. The heats of solution of the different polymorphs in 95% ethanol were also determined and are: Form I, 0.34 kJ/mol; Form II, 0.35 kJ/mol; and Form III, 0.86 kJ/mol. The errors in these measurements range 0.03–0.06 kJ/mol; thus Forms I and II have the same heat of solution within experimental error. The intrinsic dissolution rates of the three forms were measured and are shown in Figure 10.81. Forms I and III have similar dissolution rates but Form II has a significantly higher dissolution rate. The solubilities of the three forms were also determined in several solvents and in all cases the order of solubility was Form II > Form I > Form III. These data suggest that Form III is the most stable polymorph.

I. Tamoxifen Citrate



tamoxifen citrate

Tamoxifen citrate is well known as an antiestrogenic agent. Goldberg and Becker (1987) have reported the crystal structure of the more stable of two polymorphic forms, Form B. Figure 10.82 shows a stereoview of the crystal packing of the stable polymorph of tamoxifen citrate. Unfortunately they were not able to determine the structure of Form A; however, they point out that there are several indications that it is a less organized and less stable structure. For instance, they observed that at room



re 10.82 Stereoview of the crystal structure of Form B of tamoxifen citrate (Goldberg and Becker, 1987).

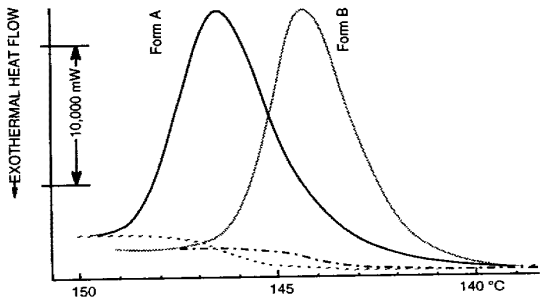


Figure 10.83 DSC thermograms of the two crystal forms of tamoxifen citrate (Goldberg and Becker, 1987).

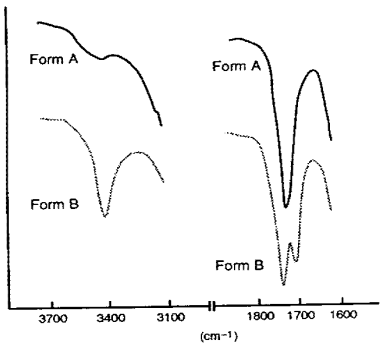


Figure 10.84 Infrared spectra of the two crystal forms of tamoxifen citrate: Form A, solid lines; Form B, dashed lines (Goldberg and Becker, 1987).

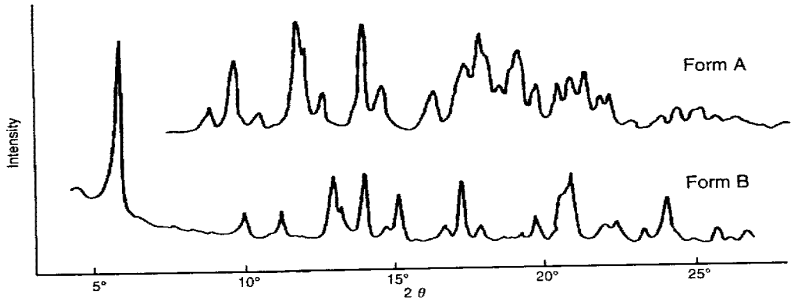


Figure 10.85 X-ray powder diffraction patterns of the two crystal forms of tamoxifen citrate (Goldberg and Becker, 1987).

temperature in an eth
They also reported
10.84), and the XRP

J. ANTIULCER AGE

HC≡C

Miyamae and co-work
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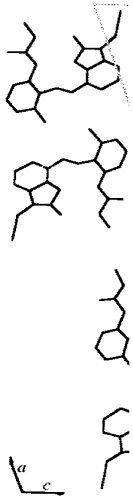
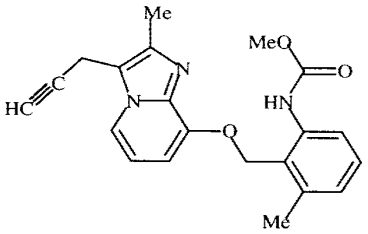


Figure 10.86 Stereoview of

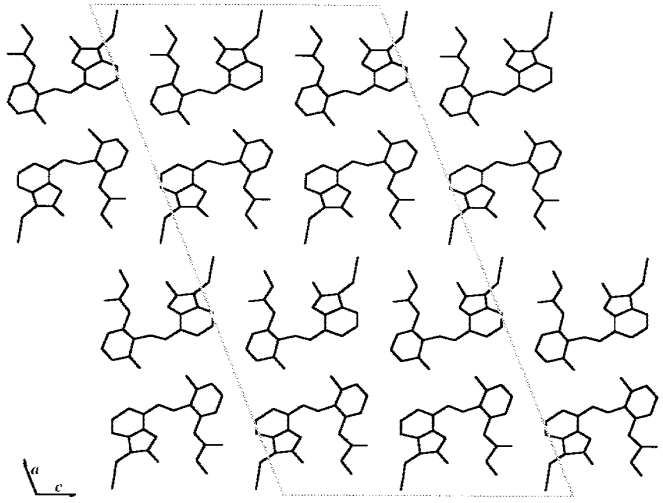
temperature in an ethanol suspension, Form A rearranges spontaneously to Form B. They also reported the DSC thermograms (Figure 10.83), the IR spectra (Figure 10.84), and the XRPDs (Figure 10.85) of the two polymorphs.

J. Antiulcer Agent FR101853



8-(2-methoxycarbonyl-amino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)-imidazo[1,2-*a*]pyridine (FR101853)

Miyamae and co-workers (1990) have carried out an extensive study of the polymorphism of an orally-active antiulcer compound 8-(2-methoxycarbonylamino-6-methylbenzyloxy)-2-methyl-3-(2-propynyl)imidazo[1,2-*a*]pyridine (FR101853) which exists in two crystal Forms A and B. Table 10.28 shows the crystallographic data for the two crystal forms which exhibit significantly different crystal packing (see Figures 10.86–10.87). In addition, the different crystal forms have different X-ray powder diffraction patterns and different DSC thermograms (Figure 10.88). Interestingly, the IR spectra of the two crystal forms are very similar (Figure 10.89) perhaps because the complicated absorptions of the molecule obscure any differences in infrared spectra that might be caused by different crystal packing.



re 10.86 Stereoview of the crystal packing of FR101853, Form A (Miyamae *et al.*, 1990).

Table 10.28 Crystal Data for the Two Crystal Forms of FR101853

Parameter	Form A	Form B
Space Group	$C2/c$	$P2_1/c$
a (Å)	42.936(14)	4.367(1)
b (Å)	4.356(1)	38.214(3)
c (Å)	21.536(6)	11.253(1)
β	109.92(4)°	95.47(2)°
Z	8	4
ρcalc (g cm^{-3})	1.275	1.292
V (Å^3)	3786.7(20)	1869.4(3)

Miyamae *et al.*, 1990.

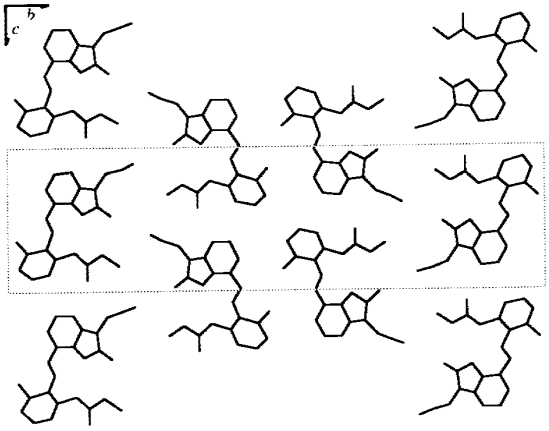


Figure 10.87 Stereoview of the crystal packing of FR101853, Form B (Miyamae *et al.*, 1990).

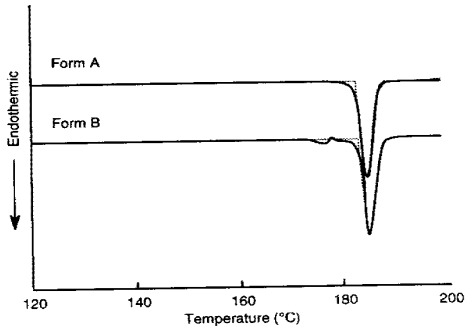


Figure 10.88 DSC thermograms of the different crystal forms of FR101853 (Miyamae *et al.*, 1990).

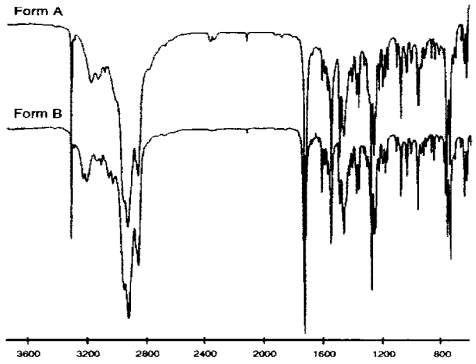


Figure 10.89 Infrared spectra of the different crystal forms of FR101853 (Miyamae *et al.*, 1990).

10.8 CARBOHYDRATES

In this section, polymorphism of carbohydrates is briefly discussed. This area is of substantial interest since carbohydrates are often used as excipients. Although numerous carbohydrates exhibit polymorphism, relatively few studies of these compounds have been reported.

Mannitol exists in four forms (Debord *et al.*, 1987). The α- and β-form have been isolated in the pure state, the δ-form has been isolated containing the α-form as an impurity. In addition, a fourth form was found but could not be characterized further. The different compressibilities and particle shapes of these forms could have important implications for their use as excipients. Figure 10.90 shows the X-ray powder diffraction patterns of the α- and β-forms as well as the "unknown" form. Figure 10.91 shows the X-ray powder patterns of different commercial products of mannitol. It is apparent that material from supplier 4 (S_4) contains a crystal form different from the other preparations. The water contents of the crystal forms and the different commercial products were determined after two months storage. Compression studies were also carried out and it was found that compression of the different samples produced tablets of different hardness. The different products and crystal forms took up small but different amounts of water, but the amount of water uptake did not seem to be related to the crystal form. The amounts of water uptake are so small that these measurements may be subject to variations from the amount of amorphous material present in the different crystal forms. Such studies have important implications for tablet preparation and demonstrate that it may be important to control the polymorphic form of excipients used in tablets.

Several other carbohydrates also exist in polymorphs. For example, the carbohydrate 4-methoxyphenyl-β-D-glucopyranoside exists in two forms (Forms I and II). Each form has a distinct powder pattern, and Form II can be converted to Form I at 161 °C (Shafizadeh and Susott, 1973). Phenyl-2-acetamidotri-*O*-acetyl-β-D-glucopyranoside also exists in two polymorphs that have different powder patterns. Form II can be converted to Form I at 185 °C (Shafizadeh and Susott, 1973). 4-Methoxy-2-acetamidotri-*O*-acetyl-β-D-glucopyranoside exists in four forms which have different

powder patterns (Shafizadeh and Susott, 1973). Form IV is converted to Form III at 158 °C, Form III can be converted to Form II at 177 °C, and Form II can be converted to the least stable form, Form I, at 183 °C. Form I melts at 192 °C.

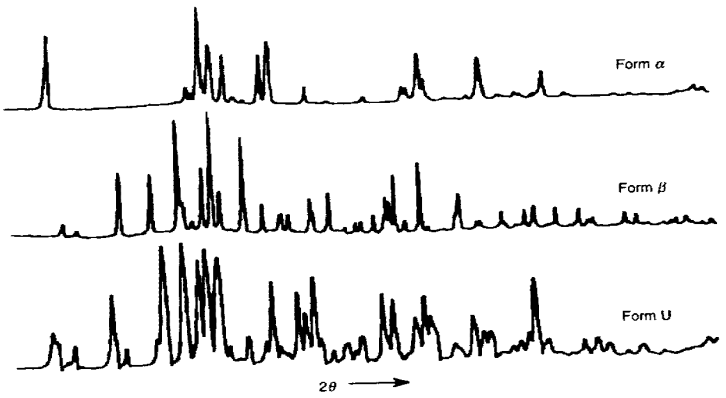


Figure 10.90 X-ray powder diffraction patterns of the α-, β-, and unknown forms of mannitol (Debord *et al.*, 1987).

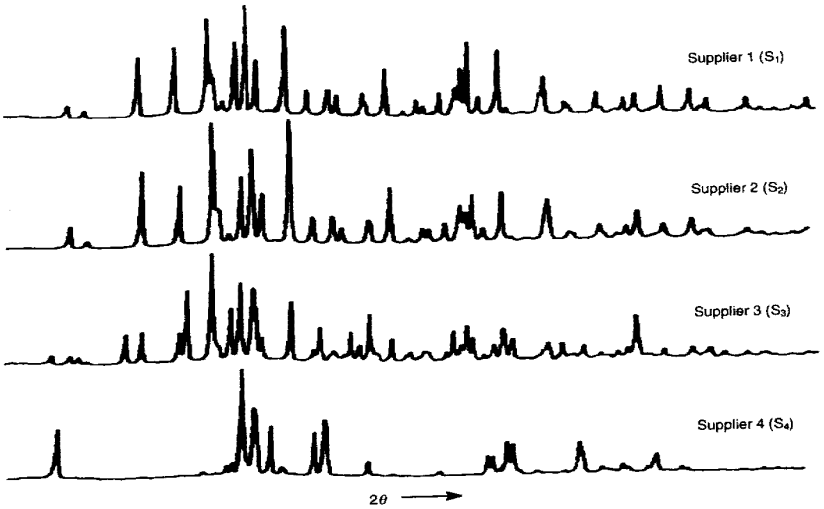


Figure 10.91 X-ray powder diffraction patterns of the commercial mannitol products S_1 through S_4 (Debord *et al.*, 1987).

10.9 POLYMORPHS OF A

Antibiotics exhibit polym
In addition, cephalosporin
solvates as discussed in C

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differences are not due to p
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Studies of nystatin s
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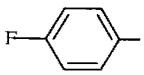
ences.

A. CONFORMATIONAL PO



Azibi *et al.* (1983) describ
compound exists in two cr
10.92–10.93 and Table 10.
°C. The infrared spectra of

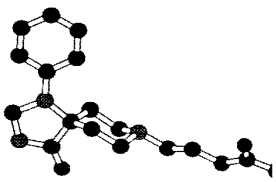


Figure 10.92 Stereoview of the
● N, ● O (Azib

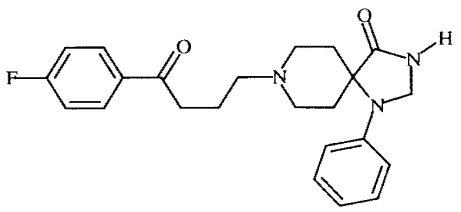
10.9 POLYMORPHS OF ANTIBIOTICS

Antibiotics exhibit polymorphism which could affect their stability and bioavailability. In addition, cephalosporin antibiotics crystallize in an extensive series of hydrates and solvates as discussed in Chapter 11.

For the polyene antibiotics, mepartricin and nystatin, different conditions of crystallization have resulted in products with different activity and acute toxicity. These differences are not due to particle size effects (Ghielmetti *et al.*, 1976). Evaporation of mepartricin in methylene chloride–methanol (9:1) at room temperature gave an oil which crystallized upon standing to form a solid which had one-fourth the oral activity and between one-sixth and one-tenth the LD_{50} (for mice) compared to the solid obtained by cooling an acetone–water–ether solution.

Studies of nystatin showed that crystals obtained by crystallization of a water–methyl ethyl ketone solution had approximately the same activity against microorganisms, but half the solubility and half to one-tenth the LD_{50} of crystals obtained from chloroform–methanol–ammonia. While the existence of nystatin polymorphs has not been proven by X-ray powder diffraction or other experimental techniques, it is likely that the differences in activity of the crystals are due to differences in solubility and solution rate. These solubility differences may, in turn, be due to polymorphic differences.

A. CONFORMATIONAL POLYMORPHISM OF SPIPERONE



spiperone

Azibi *et al.* (1983) described the conformational polymorphism of spiperone. This compound exists in two crystal forms (the structures and data are shown in Figures 10.92–10.93 and Table 10.29). Form I melted at 208.9 °C and Form II melted at 207 °C. The infrared spectra of the two crystal forms are different, and the crystal structure

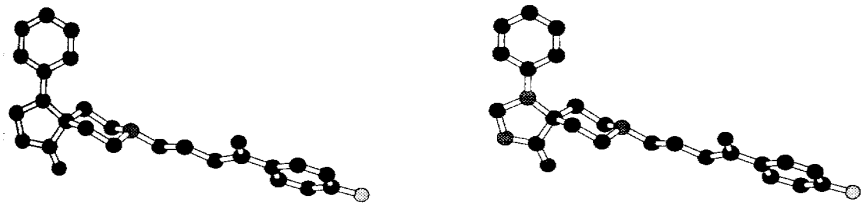


Figure 10.92 Stereoview of the molecular conformation of spiperone in Form I where: ● C, ○ F, ● N, ● O (Azibi *et al.*, 1983).

Figure 10.93 Stereoview of the molecular conformation of spiperone in Form II where: ● C, ◎ F, ● N, ● O (Koch and Germain, 1972).

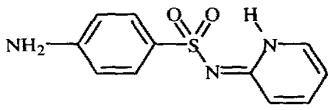
Table 10.29 Crystal Data of Spiperone Forms I and II

Parameter	Form I[a]	Form II[b]
Space Group	$P2_1/a$	$P2_1/c$
a (Å)	12.722	18.571
b (Å)	7.510	6.072
c (Å)	21.910	20.681
β	95.08°	118.69°
Z	4	4
V (Å^3)	2085.1	2045.7

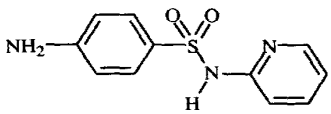
a Azibi *et al.*, 1983. *b* Koch and Germain, 1972.

showed that the conformation of the two forms are significantly different (see Figures 10.92–10.93). The authors analyzed the crystal packing and determined that hydrogen bonding was responsible for the polymorphism.

B. Sulfapyridine



"imide"



"amide"

Bar and Bernstein (1985) described the conformational polymorphism of 4-amino-*N*-2-pyridinylbenzenesulfonamide, sulfapyridine. The crystal structures of four forms of sulfapyridine were determined and are summarized in Table 10.30. The bond lengths and bond angles among the four structures are virtually identical, and are consistent with the imide structure. However, the conformations of the molecules are different in the different crystal structures, producing the phenomenon termed "conformational polymorphism." The conformations of the four different crystal forms are shown in Figure 10.94. It is clear that there is a different conformation about the —SO_2— bond in different molecules with some of the sulfapyridine rings pointing to the left in some forms and to the right in other forms.

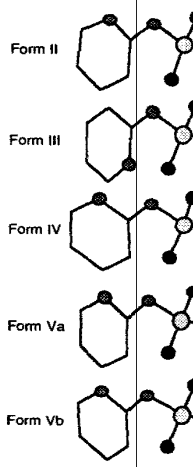


Figure 10.94 Stereoview of the
Bernstein, 1985; I

Table 10.30 Crystal Data for Su

Parameter	Form II[a]
Space group	$P2_1/c$
a (Å)	6.722
b (Å)	20.593
c (Å)	8.505
β	101.14°
Z	4
ρ_{calc} (g cm^{-3})	1.43
V (Å^3)	1155.1

a Bar and Bernstein, 1985. *b* Ba

Bar and Bernstein (19
dine in the different crystal
tions showed that all four fo

Finally, the authors co
single crystal structures obt
the different crystal forms.
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of Form II and III did not a
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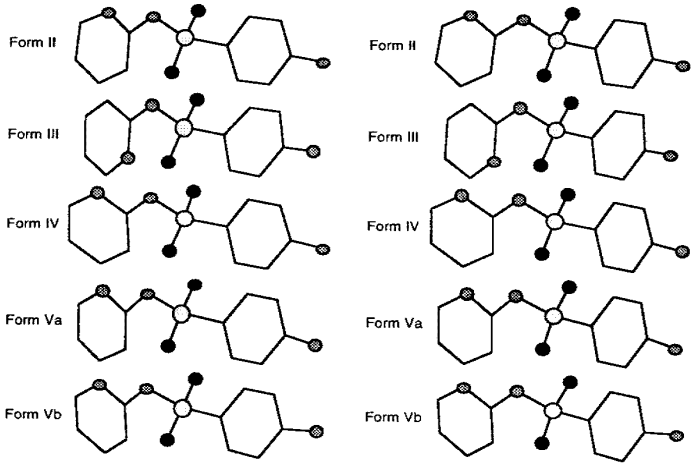

Figure 10.94 Stereoview of the molecular conformations in the four forms of sulfapyridine (Bar and Bernstein, 1985; Basak *et al.*, 1984; Bernstein, 1988).

Table 10.30 Crystal Data for Sulfapyridine

Parameter	Form II[a]	Form III[b]	Form IV[c]	Form V[a]
Space group	$P2_1/c$	$C2/c$	$P2_1/c$	$Pbca$
a (Å)	6.722	12.830	13.560	24.722
b (Å)	20.593	11.714	6.480	15.710
c (Å)	8.505	15.400	14.120	12.147
β	101.14°	94.12°	113.70	...
Z	4	8	4	16
ρ_{calc} (g cm^{-3})	1.43	1.44	1.46	1.41
V (Å^3)	1155.1	2308.5	1136.1	4717.7

a Bar and Bernstein, 1985. *b* Basak *et al.*, 1984. *c* Bernstein, 1988.

Bar and Bernstein (1985) also investigated the molecular energetics of sulfapyridine in the different crystal forms using extended Hückel calculations. These calculations showed that all four forms are within about 2.1 kJ/mol in energy.

Finally, the authors compared their data to research from other laboratories. The single crystal structures obtained allowed calculation of the X-ray powder patterns of the different crystal forms. The calculated X-ray powder pattern of Form I compared well with the published diffractogram. However, the calculated X-ray powder patterns of Form II and III did not agree with any previously reported patterns. This suggests that there are additional crystal forms. This study illustrates that the best way to prove that a given powder pattern is that of a pure polymorph is by comparing it with a calculated pattern from a single crystal structure. The powder pattern may be calculated either from observed single crystal diffraction intensity data or from the atomic coordinates using a program such as *Cerius*[2] (see Section 3.5).

10.10 POLYMORPHISM AND CHEMICAL STABILITY

Because polymorphs have different properties, including different melting points, densities, and crystal structures, it is not surprising that polymorphs have different chemical stabilities.

Perhaps the most striking effect of polymorphism on chemical reactivity is seen in the polymorphs of *trans*-2-ethoxycinnamic acid (see Figure 10.95). Irradiation of this compound in solution produces *trans*- to *cis*-isomerization, but no dimerization (Cohen and Green, 1973). Crystallization of this cinnamic acid yields three polymorphs, α, β, and γ. The α-form is obtained from ethyl acetate, ether, or acetone; the β-form is obtained from benzene or petroleum ether; and the γ-form is obtained from aqueous ethanol. Irradiation of the α-form gives the centrosymmetric dimer, irradiation of the β-form gives the mirror symmetric dimer, and irradiation of the γ-form produces no reaction. These reactions are summarized in Figure 10.95. Numerous examples of similar behavior have been found in other cinnamic acid derivatives and in anthracene dimerizations.

A number of pharmaceutical examples of different stabilities of polymorphs are also known. For example, methylprednisolone crystallizes in two forms. One form is stable while the other is reactive when exposed to heat, ultraviolet light, or high humidity (Munshi, 1973).

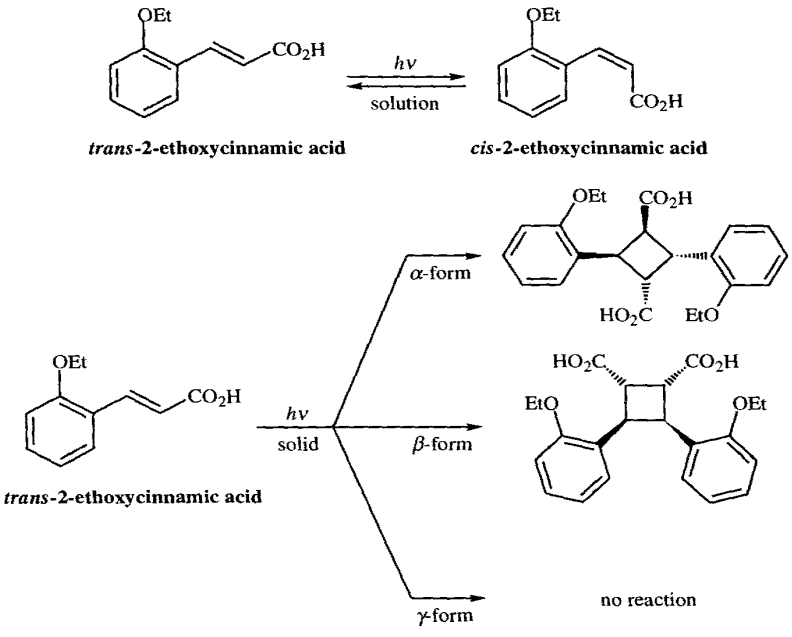

Figure 10.95 Summary of the reactivities of the α-, β-, and γ-crystalline forms of *trans*-2-ethoxycinnamic acid upon exposure to ultraviolet light (Cohen and Green, 1973).

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10.11 POLYMORPHISM AN

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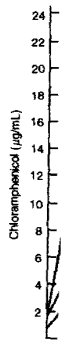

Figure 10.96 Comparison
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In closely related studies, different stabilities of polymorphs and solvates have been reported. In our laboratory, we have reinvestigated the behavior of the various polymorphs of hydrocortisone 21-*tert*-butylacetate. This steroid crystallizes from ethanol in three crystalline forms, one anhydrous and two solvates. When exposed to light, one of the solvates is reactive while the other two forms are stable. In addition, there are numerous cases where amorphous forms are much more reactive than the crystalline form. Macek (1965) has reported that the amorphous forms of sodium and potassium penicillin G are significantly less stable than the crystalline forms. Crystals of the potassium salt can withstand heating for several hours, while identical treatment of the amorphous form results in a significant loss of activity. Pfeiffer *et al.* (1976) have found similar differences between amorphous and crystalline cephalosporins applied to sensitivity discs. The reactivity of amorphous drugs is discussed in more detail in Chapter 12 (see Sections 12.1C–D).

This discussion clearly shows that in cases where chemical stability is a problem, there is a need for careful control of the polymorph or solvate.

10.11 Polymorphism and Bioavailability

The rate of absorption of a drug is sometimes dependent upon the dissolution rate. The dissolution rate is affected by the polymorph present, with the most stable form having the lowest solubility and, in most cases, the slowest dissolution rate. Other less stable polymorphs will usually have higher dissolution rates. Thus, if polymorphism is ignored, significant dose-to-dose variations can occur (Haleblian and McCrone, 1969).

In a particular striking example, a suspension of chloramphenicol palmitate containing various ratios of Form A and B showed significant variations in bioavailability (*i.e.*, blood levels) (Aguiar *et al.*, 1967). Figure 10.96 shows a comparison of mean

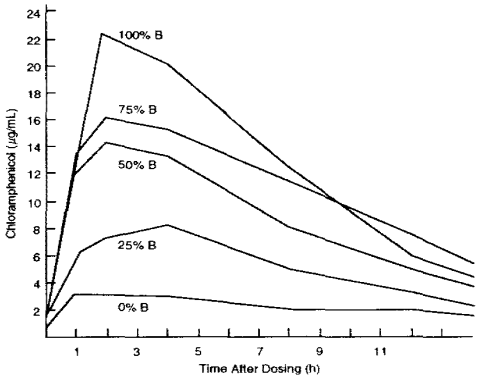

Figure 10.96 Comparison of the mean serum levels obtained with chloramphenicol palmitate suspensions containing varying ratios of the A and B polymorphs following a single oral dose equivalent to 1.5 gm of chloramphenicol palmitate. As the blood level increases, the percent of polymorph B increases. The lowest curve corresponds to 0% B, the next 25% B, the next 50% B, then 75% B, and the highest 100% B (Haleblian and McCrone, 1969).

blood serum levels of suspensions containing varying ratios of Form A and B. Clearly, the maximum blood levels are quite different, ranging from 3 to 22 μg/mL or by approximately a factor of seven. (Interestingly, a plot of peak blood levels versus percent Form B gave a straight line, as shown in Figure 10.97.) These data show that bioavailability is influenced by the type and concentration of the polymorph present. Obviously, if products are manufactured containing Form A, they will be largely inactive, while products containing Form B will show activity.

In another study, serum levels of the amorphous form and Form A of chloramphenicol palmitate have been compared in both children and Rhesus monkeys. Table 10.31 lists the results of these studies (Banerjee *et al.*, 1971) which show that the amorphous form has greater bioavailability than Form A.

Fluprednisolone crystallizes in three polymorphs and two solvates. These forms were pressed into pellets and implanted into rats, and their *in vivo* dissolution rates

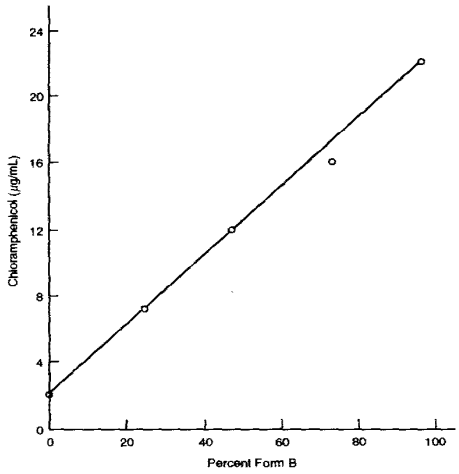

Figure 10.97 Plot of the peak chloramphenicol palmitate blood levels versus the percent of polymorph B (Haleblian and McCrone, 1969).

Table 10.31 Blood Levels (μg/100 mL) for Various Suspensions of Chloramphenicol Palmitate[a]

Suspension used	Hours after Feeding 2	4	6	8
		In Children		
Amorphous	102	60	42	26
Polymorph A	34	35	57	23
		In Rhesus Monkeys		
Amorphous	58	39	18	
Polymorph A	22	17	17	

a Banerjee *et al.*, 1971.

were measured (Haleblian and McCrone, 1969). The dissolution rates showed the following order and value: Form I (0.237 mg cm^{-2} M^{-1}) > Form III (0.209 mg cm^{-2} M^{-1}) > Form II (0.186 mg cm^{-2} M^{-1}) > β-monohydrate (0.162 mg cm^{-2} M^{-1}) > α-monohydrate (0.147 mg cm^{-2} M^{-1}). Thus, the variation in dissolution rate is approximately a factor of 1.6 when comparing Form I to the α-monohydrate.

The examples discussed in this section show that the polymorph present can dramatically affect the bioavailability of a drug.

10.12 Polymorphism and Its Pharmaceutical Application

Because polymorphs have different physical properties, it is often advantageous to choose the proper polymorph for the desired pharmaceutical application (see Section 22.10). In general, the pharmaceutical applications of polymorphism depends on the answers to the following questions:

1. What are the solubilities of each form?
2. Can pure, stable crystals of each form be prepared?
3. Will the form survive processing, micronizing, and tableting?

Furthermore, several more basic questions about polymorphs also need to be answered:

1. How many polymorphs exist?
2. What is the chemical and physical stability of each of these polymorphs?
3. Can the metastable states be stabilized?

These basic questions can be answered as follows: The number of polymorphs can be determined by microscopic examination and by subsequent analytical studies using DSC, IR, solid-state NMR, X-ray powder diffraction, and single-crystal X-ray studies (see Section 22.3). The physical stability of each form can be determined using the solution phase transformation method. This method involves placing two polymorphs in a drop of saturated solution under the microscope. Under these conditions, the crystals of less stable form will dissolve and crystals of the more stable form will grow until only the most stable form remains. Comparison of the relative stabilities of pairs of forms in succession gives the order of stability of the various forms. This method can also be used to prepare metastable forms. In this case, the temperature is increased or decreased to the temperature where the metastable form is most stable and then the experiment repeated.

There are numerous activities in the pharmaceutical industry that require consideration of polymorphism; these have been reviewed by Haleblian and McCrone (1969). Tableting behavior depends upon the polymorph present. For example, Simmons *et al.* (1972) showed that tolbutamide exists in Forms A and B. Form B is plate-like and causes **powder bridging** in the hopper and **capping** problems during tableting. Form A, which is not plate-like, showed no problems during tableting.

The behavior of suspensions also depends upon the polymorph present. If the wrong polymorph of a drug is used, a phase transformation to a more stable form may occur producing a change in crystal size and possibly caking. A change in particle size is often undesirable as it may cause serious caking problems, as well as changes in the syringeability of the suspension. In addition, the new polymorph may have altered

dissolution properties and, thus, bioavailability. Caking is a particularly serious problem since a caked suspension cannot be resuspended upon shaking. For example, oxyclozanide, upon standing in quiescent (undisturbed) suspensions, undergoes an increase in particle size (Pearson and Varney, 1969). This is due to a solvent-mediated phase transformation between two polymorphs. As discussed earlier, under these conditions, crystals of the more stable form grow and those of the less stable form dissolve. This produces cakes that cannot be resuspended by shaking.

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