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Señor Director
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Superintendencia de Industria y Comer
E. S. D.

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Evento : 379
Actuación : 444

Referencia : Expediente No. 05088317
Asunto : Solicitud de patente para: "Nueva modificación
cristalina del anhídrido de boscalida".
Solicitante : BASF AKTIENGESELLSCHAFT
Fecha de solicitud: 2 de Septiembre de 2005.

1. Yo, Luz Clemencia de PAÉZ, mayor de edad, domiciliada en Bogotá, D.C., identificada con la Cédula de ciudadanía N° 35.456.344 de Usaquén, obrando como apoderada del solicitante en el asunto antes identificado, me refiero al Oficio No. 621 notificado por fijación en lista del 14 de Enero de 2011. Mediante memorial radicado el 6 de abril de 2011 solicité un plazo de treinta (30) días para dar respuesta a este oficio.

2. Mediante el Oficio No. 621 se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la siguiente manera:

3. De la solicitud de patente.

Su Despacho enuncia:

- "La descripción de la solicitud no divulga la invención de manera suficientemente clara y completa para su comprensión. Así como tampoco presenta información suficiente para que una persona versada capacitada en la materia técnica pueda ejecutarla".
- "La descripción inicialmente presentada no tiene información suficiente, para la caracterización completa del polimorfo de interés. Las tres bandas en el infrarrojo medio, el punto de

fusión y los datos cristalográficos básicos no son suficientes para caracterizar de forma inequívoca el polimorfo".

- "Asimismo, la divulgación inicial debió haber presentado datos que demuestren la estabilidad del polimorfo durante el proceso de obtención de la composición en la forma de interés".
- "La materia reclamada en el capítulo reivindicatorio no esta definida y por tanto no es clara. Ni el punto de fusión, ni las tres bandas en el IR caracterizan inequívocamente el cristal del compuesto 2-cloro-N-(4'-clorobifenil-2-yl)-nicotinamida monoclinica de fórmula (1). Son necesarios más estudios analíticos, que en conjunto demuestren la existencia y la novedad del polimorfo".
- "El procedimiento de obtención del cristal, que como un todo sigue siendo una generalización amplia sin sustento en la descripción, presenta ahora una restricción que no se encuentra sustentada en la descripción. El intervalo específico 20 a 50°C no había sido indicado en la divulgación inicial".

Con respecto a lo señalado por su Despacho, mi representada desea señalar lo siguiente:

En primer lugar, deseamos poner de presente que no estamos de acuerdo con la afirmación del Señor Examinador en relación con el hecho que las tres bandas en el infrarrojo medio, el punto de fusión y los datos cristalográficos básicos no son suficientes para caracterizar de forma inequívoca un polimorfo. Lo anterior debido a que el Examinador únicamente sustenta su punto de vista a partir de apreciaciones personales y no proporciona ningún sustento o argumento científico que sustente dicha afirmación.

Ahora bien, con el fin de demostrar que los datos de infrarrojo y el punto de fusión son empleados para caracterizar polimorfos y que contrario a lo que afirma el Señor Examinador SI pueden caracterizar de forma inequívoca el mismo, se presentan a continuación citas de un libro ampliamente conocido en el área científica de polimorfos y cristales moleculares titulado "Polymorphism in Molecular crystals" anexo al presente memorial escrito por el Sr. Joel Bernstein.

El Sr. Joel Bernstein se especializa en estudios del estado sólido orgánico, con énfasis particular en entender y utilizar polimorfos, relaciones de estructura-propiedad, patrones de enlaces de hidrógeno y materiales orgánicos conductores. El Sr. Bernstein ha realizado aproximadamente 160 investigaciones y artículos relacionados sobre

estos temas y es autor del libro "Polymorphism in Molecular Crystals"; publicado por "Oxford University Press". Con el fin de demostrar la experticia del Sr. Bernstein en el área de los polimorfos, se presenta anexo al presente memorial su hoja de vida.

A continuación, presentaremos apartes del texto científico arriba mencionado con respecto a la validación de las metodologías para identificar la forma polimorfica II: Espectroscopia IR (bandas IR en la tabla 1) y cristalografía de rayos X (Parámetros de unidad de celda en la tabla 2):

3.1 Espectroscopia IR, bandas IR.

En su libro "Polymorphism in Molecular crystals", el Sr. Joel Bernstein claramente afirma que "la espectroscopia de infra rojo ha sido uno de los métodos ampliamente usados para investigar la propensión de materiales para formar polimorfos" (ver página 125). Adicionalmente, afirma que "el espectro IR de diferentes polimorfos muy a menudo exhiben varias características similares con diferencias que se muestran en bandas particulares (como en el presente caso), las cuales pueden...proporcionar marcadores distintivos para la caracterización polimorfica y distinción".

También esta el caso para la forma cristalina II de boscalid en el cual presenta tres bandas IR distintivas como se define en la descripción y en la reivindicación 1. Estas tres bandas han sido encontradas por medio de trabajo de investigación y constituyen bandas características de la forma II cristalina reivindicada.

Asimismo, el Sr. Bernstein también proporciona un ejemplo similar para bandas IR distintivas para polimorfos en la Figura 4.28 (ver página 127) para las formas 1 y 2 del clorhidrato de ranitidina, mostrando así que las bandas de IR pueden ser suficientes para caracterizar una forma polimorfica de una molécula orgánica como en el caso de la forma II de boscalid.

Adicionalmente, el Examinador cuestionó la pureza de las muestras y afirma que las bandas IR pueden ser causadas por impurezas. A este respecto, vale la pena resaltar que en el pliego descriptivo de la presente solicitud (ver página 3 de la solicitud internacional) claramente se menciona que la conversión del anhidrato del compuesto de formula I de forma I a la forma II se da a lugar cuantitativamente. Para una persona versada en la materia lo anterior muestra que el producto (modificación II) debe ser (esencialmente) pura en términos químicos así como en pureza del polimorfo. De modo que, el producto no contiene cantidades de la forma I.

Además, una persona versada en la materia sabe que las bandas IR de un compuesto químico (o polimorfo) no se ven influenciadas por un bajo contenido de impurezas. Por tanto, las diferencias en las bandas IR de ambos polimorfos solamente pueden resultar de perturbaciones de las vibraciones debido a variaciones en la conformación o por factores ambientales entre los arreglos cristalinos de ambos cristales (ver página 125 de libro de Bernstein) y se deben a formas polimórficas determinadas.

3.2 Parámetros de celda (constantes basadas en la cristalografía de rayos X).

En el estado del arte es ampliamente conocido que "los métodos de cristalografía de rayos X, los cuales reflejan directamente las diferencias en una estructura de un cristal, en la mayoría de los casos puede ser definitivo en la identificación y caracterización de polimorfos" y por tanto "la difracción de rayos X es considerado el método mas definitivo para identificar polimorfos y distinguirlos entre sí" (ver páginas 111 y 112 de texto de Bernstein).

En contraste a la opinión del Señor Examinador, la presente solicitud de patente SI contiene datos sobre la difracción de rayos X en la tabla 2 de la descripción, los cuales se incluyen como parámetros de celda derivados de medidas realizadas por difracción de rayos X. A este respecto, se aclara a su Despacho que es ampliamente conocido que la estructura de un cristal de un sólido molecular puede ser descrita en términos de su celda unitaria, la unidad periódica más pequeña que posee simetría y propiedades químicas. La celda unitaria se da por los parámetros de red que se refieren al espacio, longitud de los ejes de la celda y los ángulos entre las terminaciones. A este respecto, el Sr. Bernstein claramente afirma que "la difractometría de rayos X son (usualmente) empleadas para determinar detalles de la estructura molecular y cristalina del sólido- longitud de enlace, ángulos de enlace, interacciones intermoleculares, etc. y son la fuente más precisa de datos métricos sobre estas características estructurales" (Ver página 112).

Dichos datos acerca de los parámetros de la celda unitaria se divulgan en la tabla 2 de la descripción de la presente solicitud los cuales claramente demuestran que el polimorfo de interés es nuevo en comparación a la forma I del estado del arte debido a las diferencias en las longitudes a y c así como en el ángulo β .

De otro lado, el Sr. Bernstein también afirma que "aquellos resultados que deben ser empleados para simular en el computador el patrón de difracción de un polvo del mismo material. Dicho patrón puede servir

como un estándar para el patrón de difracción del polvo, no asociado con impurezas, la presencia de polimorfos, o las dificultades experimentales". Lo anterior, demuestra la validez de los parámetros de celda en términos de que caracterizan inequívocamente e identifican el polimorfo de interés. De modo que la descripción de la solicitud divulga la invención de manera suficientemente clara y completa para su comprensión y presenta información suficiente que en conjunto demuestran la existencia y la novedad del polimorfo.

3.3. Proceso para la obtención del polimorfo de interés (forma II).

Con respecto al proceso para obtener la forma cristalina II, se pone de presente a su Despacho que no compartimos la opinión del Señor Examinador en relación con que no se revela información suficiente para ejecutar dicho proceso. Lo anterior por las siguientes razones:

La descripción de la presente solicitud de patente se refiere a dos procesos para la obtención de la forma cristalina II.

El proceso 1 no envuelve pasos de molienda, secado, granulación o mezcla bajo concentraciones específicas. La disolución del anhidrato de forma I en un solvente polar no requiere de concentraciones específicas para que sea comprensible para una persona versada en la materia.

Asimismo, el proceso 2 no envuelve pasos de molienda o secado, granulación. En este proceso se especifica la concentración de los cristales semilla: "de 0.01 a 20% en peso".

3.4 Estabilidad del polimorfo de interés.

Los resultados mostrados en la página 6 de la solicitud internacional demuestran que las suspensiones agroquímicas del anhidrato de forma II (formulación A) son diferentes a aquellas reveladas en el estado del arte previo (anhidrato I: formulación B) incluso después de 7 días de almacenamiento y resulta en una menor cantidad de precipitación de residuos.

3.5. Modificación de una solicitud en trámite.

Dada la importancia que tiene esta solicitud para el solicitante y su voluntad de avanzar en la discusión de las objeciones planteadas por su Despacho y con el fin de atender las anteriores observaciones y de acuerdo con el artículo 34 de la Decisión 486, se presenta un nuevo capítulo reivindicatorio como sustituto del anteriormente presentado conformado por 7 reivindicaciones. De tal manera que, las objeciones

formuladas a este respecto quedan superadas respectivamente con las modificaciones realizadas de la siguiente manera:

- Se ha revisado la redacción del capítulo reivindicatorio con el fin de hacer claridad sobre la materia que se solicita proteger y sobre el alcance de la misma.
- En particular, la reivindicación 1 ha sido redactada nuevamente y ahora especifica los parámetros de celda obtenidos por difracción de rayos X incluidos en la tabla 2 del pliego descriptivo de la presente solicitud de patente.
- Adicionalmente, en la reivindicación 2 se especifica que en el paso b) se disuelve 2-cloro-N-(4'-clorobifenil-2-il)-nicotinamida monoclinica de fórmula I, que funde a los 144 - 145°C, en un disolvente polar prótico seleccionado de alcoholes, glicoles, cetonas, éteres, ésteres, amidas, dimetilsulfóxido o mezclas de éstos o en un hidrocarburo aromático seleccionado de benceno, tolueno y xileno a una temperatura entre 20 a 150 °C, de conformidad con la enseñanzas del pliego descriptivo. De modo que la objeción formulada a este respecto se debe tener por superada.
- Asimismo, en la nueva reivindicación 2 ahora se especifica que el disolvente polar prótico se selecciona de metanol, etanol y propanol, etilen glicol, dietilen glicol, acetona, ciclohexanona, dioxano, tetrahidrofurano, etil acetato, dimetilformamida o dimetilsulfóxido.

Así entonces, con las aclaraciones arriba mencionadas y las modificaciones realizadas al capítulo reivindicatorio, el mismo es ahora claro y conciso y por tanto las objeciones formuladas a este respecto se deben tener por superadas. Sin embargo, en el evento que el Despacho considere que una modificación adicional sea necesaria, respetuosamente le solicito hacer uso de la facultad que le otorga el artículo 45 inciso 2. de la Decisión 486 de la Comisión de la Comunidad Andina a efecto de requerir nuevamente de nuestra parte cualquier complementación o aclaración.

Adicionalmente, mi representada desea poner de presente lo siguiente:

El efecto mejorado de la nueva forma cristalina ha sido demostrado en la descripción de la presente solicitud por comparación directa entre formulaciones idénticas conocidas en el estado del arte comprendiendo la forma cristalina I. La única diferencia entre las formulaciones

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comparadas es la forma cristalina de la boscalida usada. Por lo tanto, la contribución al estado del arte en términos de una menor formación de residuos es una contribución que se debe a una nueva forma cristalina II per se.

De otro lado, es importante resaltar que en el estado del arte no se sugiere o enseña re-cristalizar la boscalida. En efecto, se pone de presente que una persona versada en la materia no puede predecir con certeza absoluta la existencia de las posibles formas cristalinas de boscalida sin experimentación alguna. Por lo tanto, la re-cristalización de la boscalida con el fin de obtener una forma cristalina con una estabilidad mejorada no se puede derivar de manera obvia u evidente a partir del estado del arte toda vez que no se había revelado con anterioridad a la presente solicitud que al disolver 2-cloro-N-(4'-clorobifenil-2-il)-nicotinamida monoclinica de fórmula I, en un disolvente polar prótico a una temperatura entre 20 a 150 °C se obtendría una nueva forma cristalina de boscalida.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, respetuosamente solicito se continúe con su tramitación.

5. Anexos.

- Nuevo pliego reivindicatorio conformado por 7 reivindicaciones.
- Formulario de modificaciones.
- Copias de partes del libro: "Polymorphism in Molecular Crystals".

Señor Director,

Luz Clemencia de Paéz
LUZ CLEMENCIA DE PAÉZ
C.C. N° 35.456.344
T.P.A. No. 23.555

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4 Número de expediente: <u>05.088.317</u>			
5 Descripción de la corrección o modificación solicitada: Presento nuevo capítulo reivindicatorio compuesto por 7 reivindicaciones con el fin de superar las objeciones hechas por Su Despacho a la presente solicitud de patente y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.			
6 Comprobante de pago No. _____ Fecha: _____			
7 Anexos ☐ Comprobante de pago de la tasa por \$118.000, por concepto de modificaciones. ☐ Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.			

8

NOMBRE: LUZ CLEMENCIA DE PÁEZ

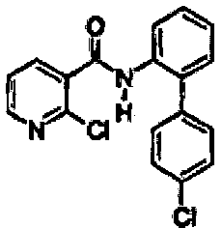
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REIVINDICACIONES.

1. 2-cloro-N-(4'-clorobifenil-2-il)-nicotinamida monoclinica de fórmula I:



caracterizado porque funde a los 147 - 148°C y en el espectro infrarojo muestra al menos una de las siguientes bandas características: 868cm-1, 917cm-1 y 1675cm-1; y presenta los siguientes parámetros de celda:

Clase = Monoclínico.
Grupo espacial = P21/c
Longitudes de la celda:
a=1162.5 pm
b=1134.2 pm
c= 1283.2 pm

Ángulos correspondientes de la celda:
 α (alfa)=90°
 β (beta)=114.52°
 γ (gamma)=90°

2. Procedimiento para la preparación del compuesto 1 de acuerdo con la reivindicación 1, **caracterizado** porque
- a) se disuelve 2-cloro-N-(4'-clorobifenil-2-il)-nicotinamida monoclinica de fórmula I, que funde a los 144 - 145°C, en un disolvente polar prótico seleccionado de metanol, etanol y propanol, etilen glicol, dietilen glicol, acetona, ciclohexanona, dioxano, tetrahidrofurano, etil acetato, dimetilformamida, dimetilsulfóxido o mezclas de éstos o en un hidrocarburo aromático seleccionado de benceno, tolueno y xileno a una temperatura entre 20 a 150 °C, y
 - b) se separa del disolvente por cristalización tras habérselo enfriado temperaturas entre 0 a 30°C.
3. Procedimiento para la preparación del compuesto I de acuerdo con la reivindicación 2, **caracterizado** porque como disolventes polares próticos se emplean alcoholes, ésteres o cetonas.
4. Procedimiento para la preparación del compuesto I de acuerdo con la reivindicación 3, **caracterizado** porque como alcohol se emplea el metanol o el etanol.
5. Procedimiento para la preparación del compuesto I de acuerdo con la reivindicación 2, **caracterizado** porque en la etapa a) se disuelve el compuesto de fórmula I a una temperatura de entre 40°C y 115°C.

6. Composiciones fungicidas **caracterizada** porque contienen el compuesto de fórmula I de acuerdo con la reivindicación 1 y aditivos inertes.
7. Composiciones fungicidas de acuerdo con la reivindicación 8, **caracterizadas** porque contienen de 0,1a 95% en peso del compuesto de fórmula I de acuerdo con la reivindicación 1.

Polymorphism in Molecular Crystals

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To Judy

Analytical techniques for studying and characterizing polymorphs

You can observe a lot just by watching (Yogi Berra)

4.1 Introduction

Since polymorphs represent different crystal structures essentially every physical or chemical property may vary among the polymorphic structures of a material. A consequence of this is the fact that virtually any technique that measures the properties of a solid material may in principle be used to detect polymorphism and to characterize the similarities and difference among polymorphic structures. Some techniques are more sensitive to the differences in *crystal structure* or molecular environment, as opposed to *molecular structure*, and in many cases these are to be preferred in detecting and characterizing polymorphs.

The intent of this chapter is to survey the most commonly employed of these analytical techniques with an eye to demonstrating how they are being used to discover and characterize polymorphs. There is considerable literature associated with each of these techniques and in the sense of being able to cover all the details and ramifications of each technique we do not intend to be comprehensive here. Rather, we will limit ourselves to briefly and qualitatively describing the principles of the technique, when necessary, to providing some leading references for further reading and entry to the literature, and to giving some examples of the application of the technique to the characterization and study of polymorphs. Because every technique provides different information and some techniques will not distinguish among a particular set of polymorphs, the importance of utilizing a wide variety of techniques for the identification and characterization of a polymorphic system cannot be overemphasized (Threlfall 1995; Brittain 1999a; Bugay 2001).

4.2 Optical/hot stage microscopy

Hot stage microscopy provides a rapid method for screening substances for the existence of polymorphism. In spite of the utility of this technique, it has not enjoyed the widespread use it deserves. Microscopy was much ignored during the

middle decades of the twentieth century, due, in part at least, to the subjective nature of the observations and 'measurement' and to the lack of practitioners to pass the knowledge and insight on to their scientific progeny. However, its utility and importance are being increasingly recognized (McLafferty 1990; Streng 1997; Bernstein and Henck 1998).

Three of the traditional centres of activity in chemical microscopy (Cornell University, University of Innsbruck and McCrone Associates) have provided a number of excellent literature sources for becoming acquainted with the polarizing microscope equipped with a hot stage and its use in studying polymorphism (Kofler and Kofler 1954; McCrone 1957; Kuhnert-Brandstätter 1971; Chamot and Mason 1973; McCrone *et al.* 1978; Kuhnert-Brandstätter 1982; Cooke 1998). The use of the microscope declined, in part at least, in an age of increasing quantification, due to the lack of quantitative measures that can be attached to visual observations. Photographic records of microscopic observations were more in the realm of geologists and biologists than that of chemists. However, the ready availability and relatively low cost of video recording with the capability of digitally capturing individual images or sequences of images bodes well for the future of chemical/thermal microscopy in the study of polymorphism.

The most general use of the microscope for the study of polymorphism is simply for observing the homogeneity or diversity of a crystalline sample. Variations in size, shape or colour may indicate the presence of polymorphism and the need for further examination (see, for instance Fig. 3.2). As noted in Section 2.4.1, differences in crystal habit are not necessarily indicative of polymorphism. Further physical characterization of the individual crystals may involve measurements such as optical constants (Hartshorne and Stuart 1960, 1964; Wahlstrom 1969; McCrone *et al.* 1978) or interfacial angles (Winchell 1943; Porter and Spiller 1951; Terpstra and Codd 1961).

By far the most useful accessory to polarized light microscopy is the hot stage originally invented by Lehmann (1877a,b, 1888, 1891, 1910) (Fig. 4.1) and now used in the versions developed by Kofler and Kofler (1954) and the Mettler Company in 1968 (Woodard 1970; Julian and McCrone 1971) (See also Kuhnert-Brandstätter 1971, 1982). Melting point determination on small samples is perhaps the most obvious application for hot stage microscopy. With practice, the true melting point (i.e. the temperature at which the solid and its melt are maintained at equilibrium) can be readily determined. Melting point is perhaps one of the longest used physical constants for characterizing solids, although as Borka (1991) has pointed out different polymorphs can have similar melting points. An outstanding example is that of trimorphic D-mannitol (Burger *et al.* 2000) for which the melting points are Form I 166.5 °C; Form II 166 °C and Form III 150–158 °C incongruently. A variety of other properties may be examined and studied with this versatile tool, which should be the first option for any characterization of a solid material, especially in the search for polymorphs.

The systematic use of the hot stage microscope employing mainly the Kofler hot stage was originally described in the book by Kofler and Kofler (1954) (the founders

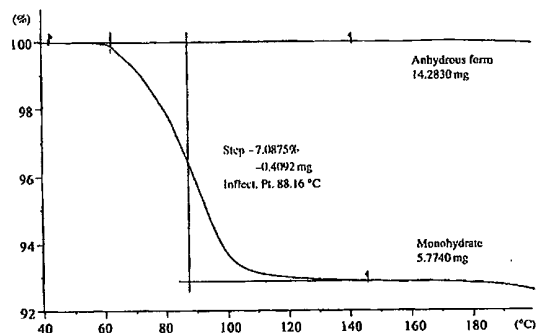


Fig. 4.16 TGA traces for the anhydrous and monohydrate forms of glucose. (Reprinted from Schwarz and de Buhr 1998, with permission.)

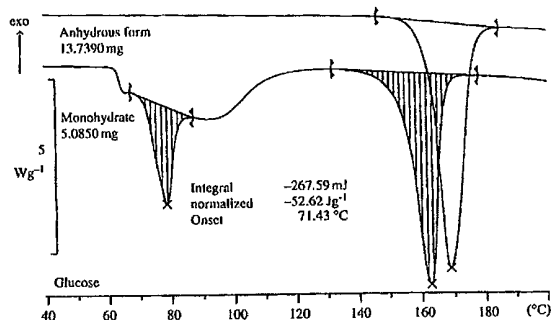


Fig. 4.17 DSC traces for the anhydrous and monohydrate forms of glucose. (Reprinted from Schwarz and de Buhr 1998, with permission.)

calculate the same quantity at a different temperature, T_2 , from the difference in the heat capacities of the two polymorphs:

$$\Delta H_{II}(T_2) \approx \Delta H_{II}(T_1) + (T_1 - T_2) \Delta C'_{p(I,II)}$$

Table 4.1 Heats of solution ΔH_s (kcal mol⁻¹) measured at 25 °C and calculated heats of transition ΔH_t for the two polymorphic forms of sodium sulphathiazole in two different solvents (adapted from Lindenbaum and McGraw 1985)

	Acetone	Dimethylformamide
$\Delta H_{s,I}$	2.853 ± 0.026	-1.113 ± 0.012
$\Delta H_{s,II}$	1.229 ± 0.016	-2.740 ± 0.023
ΔH_t (at 25 °C)	1.624 ± 0.042	1.627 ± 0.035

Some typical examples of these measurements are given by Lindenbaum *et al.* (1985). For quantitative analysis of mixtures, Botha *et al.* (1986) have demonstrated how the percentage composition of two polymorphs may be determined essentially over the entire range of composition by measurements of the heats of solution of the pure polymorphs. Additional details on many aspects of the applications of solution microcalorimetry to the study of polymorphs and solvates may be found in the book by Hemminger and Höhne (1984), the chapters by Grant and Higuchi (1990) and Brittain and Grant (1999) and the recent paper by Gu and Grant (2001).

4.4 X-ray crystallography

X-ray crystallographic methods, which reflect differences in crystal structure, in most cases can be definitive in the identification and characterization of polymorphs, and whenever possible should be included in the analytical methods utilized to define a polymorphic system.

In the application of X-ray diffraction methods to the study of molecular solids in general and polymorphic systems in particular a distinction is often made between powder methods and single crystal methods. Traditionally, the former have been used for the qualitative identification of individual polymorphic phases or mixtures of phases, while the latter have been employed for the determination of the detailed molecular and crystal structure. Fortunately, the gap between these two subdisciplines is being bridged, and much can be gained in the study of polymorphs by the cross-fertilization of these two techniques. For instance, single crystal structure solution techniques are being applied to powder data to solve larger and previously intractable crystal structures (Andreev *et al.* 1997; Shankland *et al.* 1997; Tremayne *et al.* 1997; David *et al.* 1998; Chan *et al.* 1999; Putz *et al.* 1999) with subsequent refinement by Rietveld methods (Young 1993), and this field is expected to grow rapidly with increasingly powerful X-ray sources and computing resources. The increasing application of synchrotron radiation to powder diffraction is also contributing significantly to closing this gap; in some cases revealing polymorphism not observed by laboratory scale X-ray sources (Sato 1999).

Recent and continuing developments in the field of electron diffraction of very small single crystals may also serve to bridge the gap between classical powder and single crystal diffraction techniques (Voigt-Martin *et al.* 1995; Dorset 1996; Dorset *et al.* 1998; Yu *et al.* 2000b).

The fundamentals of X-ray powder diffraction techniques are summarized in a number of texts and reviews (Azaroff and Burger 1958; Bish and Reynolds 1989; Jenkins and Snyder 1996). The X-ray diffraction pattern from a solid results from the satisfaction of the Bragg condition ($n\lambda = 2d \sin \theta$), where λ is the wavelength of the X-ray radiation, and d is the particular spacing between individual parallel planes. The condition can be satisfied when the angle θ between the incident radiation and that set of planes results in constructive interference. The X-ray powder diffraction pattern of a solid is thus a plot of the diffraction intensity as a function of 2θ values (or equivalently, d spacings) and may be considered to be a fingerprint of that solid. The values of the d spacings reflect the dimensions of the unit cell, while the intensities are due to the contents of the unit cell and the way the atoms and molecules are arranged therein. As polymorphs comprise different solids with different unit cells and different arrangements of molecules within the unit cell they have different fingerprints—most often as different as the X-ray powder patterns of two different compounds. Thus X-ray powder diffraction is probably the most definitive method for identifying polymorphs and distinguishing among them. Typical experimental powder patterns for two polymorphs are given in Fig. 4.18.²

Single crystal X-ray crystallographic techniques are employed to determine details of the molecular and crystal structure of the solid—bond lengths, bond angles, intermolecular interactions, etc., and are the source of some of the most precise metric data on these structural features (Dunitz 1979; Giacovazzo 1992; Glusker *et al.* 1994). The three-dimensional results are obtained from the collection of three-dimensional diffraction data. Those results may be used to simulate computationally the two-dimensional diffraction pattern to be expected from a powder of the same material. Such a calculated powder pattern may serve as a standard for the powder diffraction pattern, unencumbered by impurities, the presence of other polymorphs, or the experimental difficulties enumerated below. The other side of this coin is the attempt to obtain the full three-dimensional crystal structure from the two-dimensional powder diffraction pattern, as noted above. Some of the important features of powder diffraction are discussed here. Those emanating from single crystal studies are alluded to in many other places throughout this work.

There are some reported cases of two genuinely polymorphic structures exhibiting very similar powder diffraction patterns. One of these cases, the two polymorphs

² There have been a number of reports of polymorphic systems in which the reader might be led to expect some similarity in the powder pattern of two polymorphs because they crystallize in the same space group. There is no physical basis for this expectation. Except for the systematic absences of certain reflections due to space group symmetry polymorphic structures in the same space group and different cell constants will have different powder diffraction patterns. On the other hand, polymorphs with similar cell constants but different space groups may exhibit some similarity in X-ray powder diffraction patterns, but these cases are very rare (*vide infra*). See also Section 2.4.3.

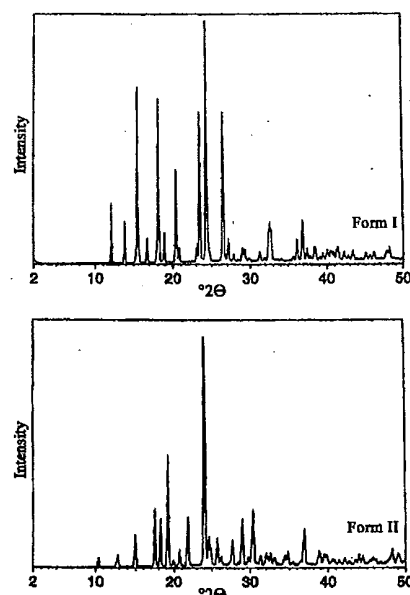


Fig. 4.18 X-ray powder diffraction patterns for the two polymorphs of paracetamol. (From Nichols and Frampton 1998, with permission.)

of terephthalic acid (Davey *et al.* 1994), is shown in Fig. 4.19. These two patterns are remarkably similar, save for the 2θ region just above the large peak at $\sim 30^\circ$. In such cases, there must be a structural explanation for the similarities in powder patterns. The two structures crystallize in the triclinic space group $P\bar{1}$ with different cell constants as given in Table 4.2 (Bailey and Brown 1967, 1984; Herbstein 2001). As shown in Fig. 4.20 and discussed by Berkovitch-Yellin and Leiserowitz (1982) and Davey *et al.* (1994) both structures are characterized by the formation of infinite hydrogen-bonded chains. The chains are organized into two-dimensional sheets that differ to some extent between the two polymorphs in the relationship between neighbouring chains. The offset of neighbouring sheets is more significant, and comprises the principal difference between the two structures. However, since the major

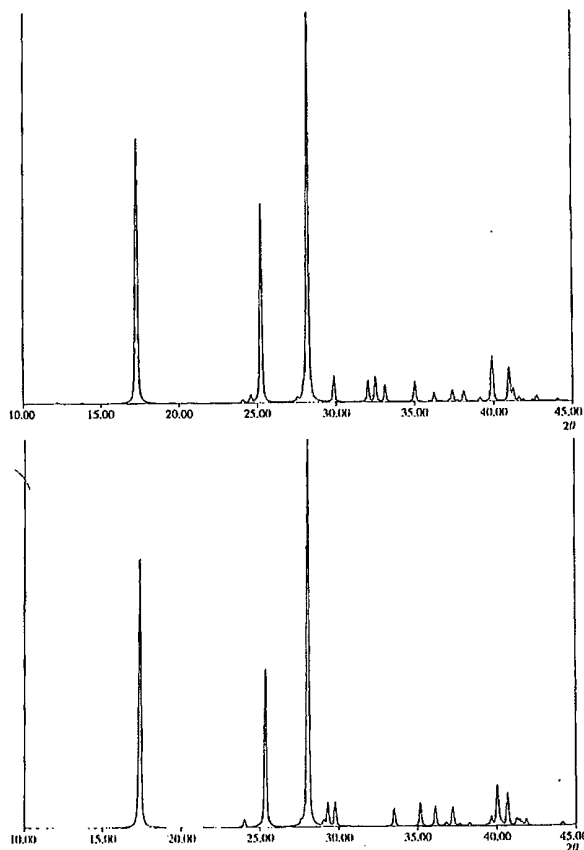


Fig. 4.19 X-ray powder diffraction patterns calculated from the crystal structures for the two forms of terephthalic acid. Upper, Form I; lower, Form II. (After Davey *et al.* 1994.)

Table 4.2 Crystallographic cell constants for the two polymorphs of terephthalic acid

	Reported cells ^a		Reduced cells ^b	
	Form I	Form II	Form I	Form II
<i>a</i> (Å)	7.73	9.54	3.76	5.027
<i>b</i> (Å)	6.443	5.34	6.439	5.36
<i>c</i> (Å)	3.749	5.02	7.412	6.991
α (°)	92.75	86.95	83.16	72.04
β (°)	109.15	134.6	80.87	76.03
γ (°)	95.95	104.9	88.53	87.09

^a After Bailey and Brown (1967, 1987).

^b Herbst (2001). The cell constants for the reduced cell are based on those reported by Colapietro *et al.* (1984) and Domenicano *et al.* (1990) (for Form I) and by Fischer *et al.* (1986) (by neutron diffraction) for Form II. Since they follow the convention for reporting reduced cells (International Tables 1987) they appear in a different order from the original; also by convention the cell angles are defined as acute.

contribution to the X-ray scattering is from the sheets, the similarity in structures is manifested in the similarity in powder patterns.³

Some other examples of very similar X-ray powder diffraction patterns have been noted. One of these is D,L-leucine (Mayukh *et al.* 1975) for which the spectral data are clearly distinguishable. Another is caffeine (Fig. 4.27) (Suzuki *et al.* 1985; Griesser 2000), which is discussed in the next section. Karfunkel *et al.* (1999) also quoted the 'surprisingly similar powder patterns' of some diketopyrrolopyrrole derivatives and have attempted to develop a model to describe the structural basis for similar powder patterns.

The preparation of samples for powder diffraction can lead to variations and inconsistencies among measurements on the same sample (e.g. Potts *et al.* 1994). Jenkins and Snyder (1996) have summarized the possible causes for compositional variations between the original sample and that prepared for the diffraction experiment; grinding of the sample (generally required to reduce preferred orientation) *vide infra* can lead to amorphisation, strain in individual particles, decomposition, solid state reaction or

³ A cautionary note is in order here. In principle there is considerable freedom in choosing the axial system in triclinic unit cells, and in some higher symmetry ones as well (International Tables 1987). The convention calls for choosing the so-called reduced cell (Mighell 1976; Burzlaff *et al.* 1983; Baer and Tillmanns 1986), and there are a number of computer programs available for doing carrying out this cell reduction (LePage and Donnay 1976; Macicek and Yordanov 1992). For example, both the unreduced and reduced cells are presented in Table 4.2. Most crystallographic databases now routinely check that the recorded cell is in fact the reduced one, and all data collection programs on automated diffractometers do the reduction. However, many literature values have not been checked for the presence or absence of the reduced cell. Cell reduction can also lead to the recognition of a cell of different symmetry (International Tables 1987). As a result, a comparison of unit cell constants which leads to the conclusion that two structures are polymorphs may be in error. One way to check for identity or difference in polymorphs is to calculate the powder pattern, which is invariant to the choice of cell, although different choices of cell will lead to different indexing of peaks for identical diffraction patterns.

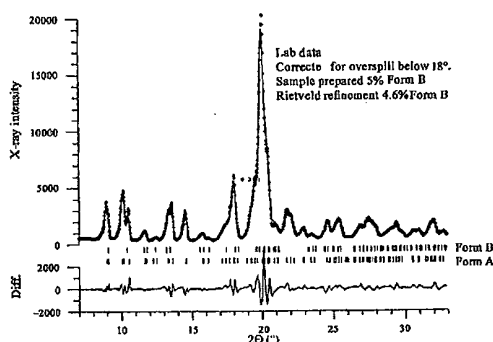


Fig. 4.25 A typical calibration run of a mixture of two polymorphs using the Rietveld analysis. The calibration sample was prepared using 5 per cent of Form B in a mixture of Forms A and B. The upper trace shows the laboratory data for this sample. The next two rows indicate the positions expected for the diffraction peaks of Forms B and A. The bottom trace shows the rms deviation resulting from the refinement of the combination of the full patterns for the two forms against the measured pattern. The best fit is obtained for a value of 4.6 per cent Form B. (From Newman *et al.* 1999, with permission.)

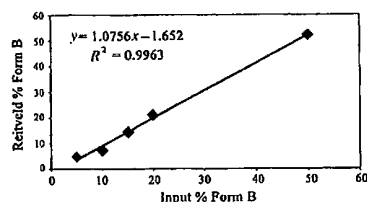


Fig. 4.26 Calibration curve for mixtures of polymorphs A and B using laboratory X-ray data and Rietveld analysis. The value for the 50 per cent mixture was obtained from synchrotron data. (From Newman *et al.* 1999, with permission.)

of the system values at least as low as 1 per cent are obtainable using quantitative X-ray analysis (Tammelin and Yliruusi 1992).

Artificial neural network (ANN) theory (Zupan and Gusteiger 1991), which has been applied to other areas of quantitative chemical analysis (Bos and Weber 1991)

has recently been claimed to be useful in the quantitative analysis of mixtures of polymorphs using X-ray diffraction methods (Agatonovic-Kustrin *et al.* 1999, 2000). In studying the two polymorphs of ranitidine hydrochloride, and comparing the method to the more conventional method employing polynomial regression, the authors showed that the ANN methods yielded a smaller standard deviation and relative error, especially for the region of lower concentrations of Form 2, as low as 1–2 per cent. Depending on its general applicability, the ANN methodology may be a potential alternative to the more traditional methods of quantitative analysis of mixtures, and the authors suggest extending the use to entire patterns (rather than a few selected peaks as in their study) as has been done with partial least squares methods in the quantitative analysis of mixtures using IR methods (see the next section).

4.5 Infrared spectroscopy

Infrared spectroscopy is of course a standard technique for the characterization of compounds in the current context of solid materials. Because it is based on the measurement of the vibrational modes generally of bonded atoms, with absorptions usually in the range of 400–4000 cm^{-1} it is primarily a tool for investigating *molecular* properties rather than solid state properties.

Nevertheless, for half a century (Ebert and Gottlieb 1952), it has been one of the most widely used methods for investigating the propensity of materials to form polymorphs (Kuhnert-Brandstätter and Junger 1976), including thermodynamic details such as transition points and number of components (Gu 1993). Fourier transform infrared spectroscopy (FTIR) is clearly the current method of choice, having replaced traditional grating and prism spectrophotometers (Krishnan and Ferraro 1982; Brittain 1997). Since the characteristics of bonds or bonded atoms are monitored with this method, it is the perturbations of those vibrations due to variations in conformational or environmental factors among polymorphs that can lead to the differences in spectra. In general, many molecular features are constant from polymorph to polymorph and the effect of environment on particular bonds and their vibrational manifestation may not be sufficiently large to be evident as differences in the IR spectra among polymorphs (Fig. 4.27), e.g. caffeine (Suzuki *et al.* 1985; Griesser 2000) and trovafloxacin mesylate (Norris *et al.* 1997), especially when presented in graphical form on a reduced scale. Hence, IR spectra of different polymorphs quite often exhibit many similar features with differences showing up in particular bands, which may, however, provide distinctive markers for polymorphic characterization and distinction (Fig. 4.28). The FTIR instrumentation and technique provides precise location of absorption bands, and that information, coupled with the IR assignments and comparisons for the various polymorphs, allows a means of characterization and comparison which is not available to the reader who is presented with a series of graphical spectra. Much information about the similarities and differences among polymorphs is often lost in such a graphical presentation. An example of the preferred mode of presentation is in Fig. 4.29 and Table 4.4 for two forms of lamivudine. While it is not always possible to make assignments of the bands to molecular bonding or

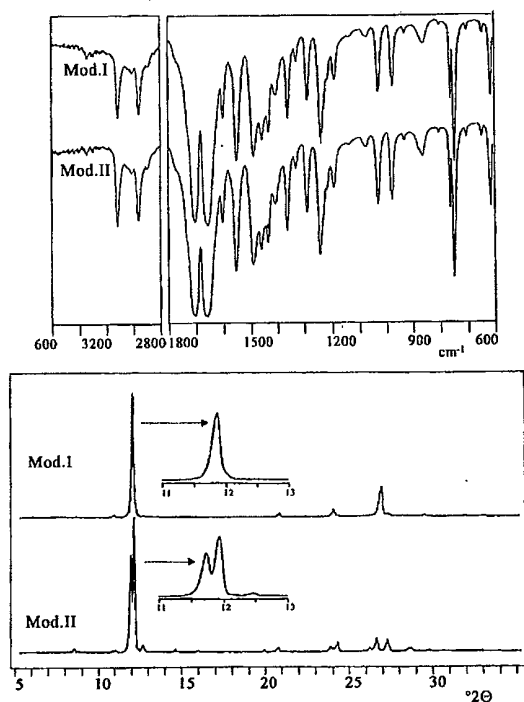


Fig. 4.27 Upper: FTIR spectra of the two anhydrous modifications of caffeine, exhibiting very similar features. Lower: X-ray powder diffraction patterns of the same modifications, showing considerable similarity, but distinguishable with the use of an expanded scale in the region $11^\circ < 2\theta < 13^\circ$. Other differences can be detected upon close inspection. (From Griesser 2000, with permission.)

functional groups, the tabulation of distinguishing peaks among polymorphic systems should be encouraged as standard practice. Evaluation of the statistical significance of similarities and differences in the spectra is considerably facilitated by the inclusion of information on the experimental precision of peak location.

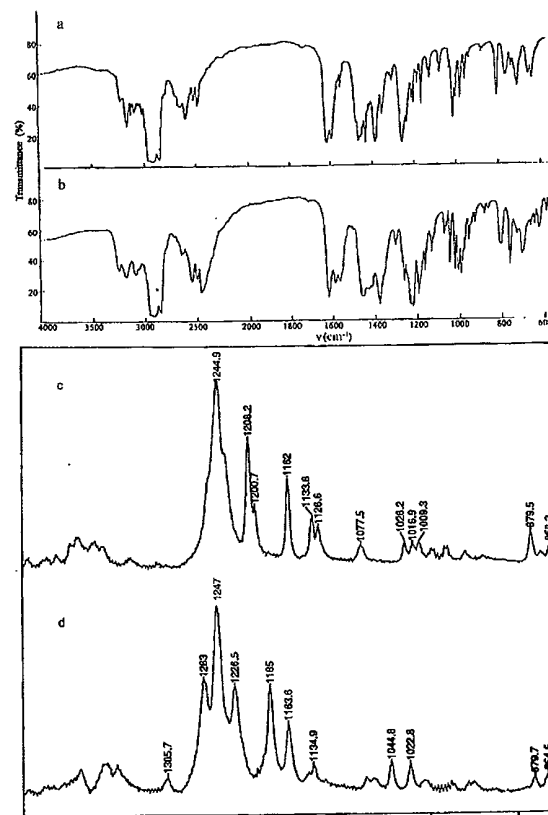


Fig. 4.28 (a, b) IR spectra of (a) Form 1 and (b) Form 2 of ranitidine hydrochloride. The are very similar (though not identical) in many respects, with one particularly distinguishing band at 1045 cm^{-1} in the spectrum of Form 2. (From Chiderton *et al.* 1984, with permission.) Detail of the (c) Form 1 and (d) Form 2 FTIR spectra of the two polymorphs of ranitidine hydrochloride, including the instrument-determined location of individual peaks. (From

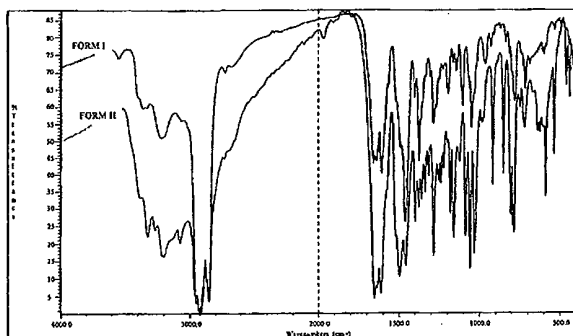


Fig. 4.29 FTIR spectra of the two forms of lamivudine. Note that the two spectra are presented as nearly overlaid as possible to facilitate comparison. In addition, the vibrational origin of significant peaks has been identified and the peak positions for the two polymorphs are compared in Table 4.4 (Harris *et al.* 1997). (Figure from Lancaster 1999, with permission.)

Table 4.4 IR assignments and frequencies for the two polymorphs of lamivudine (From Harris *et al.* 1997, with permission.)

Assignment	Form I	Form II
ν_{OH}^a	3545	—
ν_{NH}, ν_{OH}	3404, 3365, 3341, 3232	3376, 3328, 3270, 3201
ν_{CO}	1662	1652
ν_{CN}	1643	1636
ν_{CC}	1613	1613
ν_{CO}/δ_{OH}	1053	1060

^a Of a hydration water molecule.

Since determination of the IR spectra of polymorphs is often carried out for the purpose of comparison, sample preparation becomes a particularly important factor in the experimental procedure (Bugay 2001). Threlfall (1995) has reviewed many of the factors that must be taken into consideration in this regard, including labelling of polymorphic form (obvious, but in view of the confusion in polymorph nomenclature (see Section 1.2.3) still a potential problem), sample purity (both chemical and polymorphic purity), crystal size, crystal habit and orientation (Griesser and Burger 1993; Kobayashi *et al.* 1994), instability to pulverization and grinding (Farmer 1957; Hoard and Elkovich 1996; Threlfall 1999), solubility in the mulling medium or hydration (Kuhnert-Brandstätter and Riedmann 1989), desolvation of a solvate (Burger and Ramburger 1979*a,b*) or instrumental variables (Free and Miller 1994).

A number of experimental alternatives to traditional IR transmission spectroscopy are suitable for overcoming some of these complicating experimental factors. In the technique of diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) (Hartauer *et al.* 1992; Neville *et al.* 1992) the sample is dispersed in a matrix of powdered alkali halide, a procedure which is less likely to lead to polymorphic transformations or loss of solvent than the more aggressive grinding necessary for mull preparation or pressure required to make a pellet (Roston *et al.* 1993). For these reasons, Threlfall (1995) suggests that DRIFTS should be the method of choice for the initial IR examination of polymorphs. He has also discussed the possible use of attenuated total reflection (ATR) methods in the examination of polymorphs and provided a comparison and discussion of the results obtained on sulphathiazole polymorphs from spectra run on KBr disks, Nujol mulls and ATR.

In spite of many of the potential experimental pitfalls and difficulties (which should be viewed here as caveats rather than as deterrents), IR spectroscopy is still one of the simplest and most widely and routinely employed analytical tools in the study and characterization of polymorphs. Some other modifications, developments and 'hyphenated techniques' are worthy of note here, since they often considerably enhance the potential of the technique while reducing the drawbacks. Perhaps the most obvious of these is the combination of microscopy with FTIR spectroscopy for visual examination and spectral characterization of small areas in heterogeneous samples or identity and analysis of the spatial distribution of components of mixtures (e.g. pharmaceutical formulations) (Messerschmidt and Harthcock 1988).

Photoacoustic spectroscopy is based on the absorption of modulated, rather than direct, radiation; hence, it is independent of the linear absorption, thus eliminating attenuation due to excessive sample thickness or high extinction coefficients. Spectra can be measured on neat samples without dilution (Vidine 1982; Graham *et al.* 1985; McClelland *et al.* 1992). This avoids the polymorphic changes that might be brought about by grinding, but particle size plays a role in such measurements (Rockley *et al.* 1984). An example of a study of a polymorphic system by photoacoustic spectroscopy on polymorphic forms sensitive to mechanical perturbations has been given by Ashizawa (1989).

Just as polarized light enhances the utility of optical microscopy in the study of polymorphic systems, so polarization can be used in conjunction with IR spectroscopy. As we shall show later in greater detail (see Section 6.3.2) polarized spectroscopic methods provide detailed information on the *directional* properties which distinguish the spectral features of polymorphs. Thus, for instance, the directional properties of a polymorphic transformation of fatty acids (Kaneko *et al.* 1994*a-c*) and inferences about the differences in packing modes (Yano 1993) have been investigated with polarized IR methods.

As with other analytical techniques previously widely used for polymorph characterization (i.e. polymorph identity), IR spectroscopy is being increasingly employed as a technique for quantitative analysis (e.g. polymorphic purity) (Aldridge *et al.* 1996; Blanco *et al.* 2000; Bugay 2001; Stephenson *et al.* 2001; Patel *et al.* 2001).

A typical example has recently been given by Bugay (1999) for cefepime dihydrochloride (Bugay *et al.* 1996). The question of polymorphic purity (more correctly in this case purity of crystal modification) involved in determining the amount of a dihydrate in a marketed monohydrate form. As seen in Fig. 4.30(a), the two modifications have quite distinct IR spectra in the 3000–4000 cm^{-1} range, and a mixture of 5 per cent dihydrate in the monohydrate clearly shows how the peak of the former just below 3600 cm^{-1} may be used to quantify its presence. To extract quantitative information, a calibration curve of known w/w mixtures was prepared in the working range of 1.0–8.0 per cent, using diffuse IR reflectance. The statistical analysis led to the graph shown in Fig. 4.31, with a limit of detection of 0.3 per cent, a minimum quantifiable level of 1.00 per cent, and a good cross-validation with an independently developed assay based on X-ray powder diffraction (see Section 4.4).

For the cases of the quantitative analysis of mixtures of crystal modifications in which the distinction between two spectra is not as favourable or where unambiguous identification of many of the characteristic absorption peaks is desired (Zenith 1994), the method of partial least squares (Haaland and Thomas 1988) may be required. This technique originally developed for the use in the near IR spectral region uses the entire (digitized) spectrum, rather than an individual peak or small number of peaks. Some applications to the quantitative analysis of mixtures of polymorphs have been given by Geladi and Kowalski (1986), Hartauer *et al.* (1992), Tudor *et al.* (1993) and Jaslowsky *et al.* (1995) (the latter two with Raman spectroscopy), and it appears that this is a method that will see increasingly widespread use.⁵

An alternative procedure for the recognition of a minor polymorphic component in a polymorphic mixture has been reported by Aldridge *et al.* (1996). This method employs pattern recognition of the near-IR spectra of the polymorphs (Ciurezak 1987) to distinguish between them. Near-IR spectroscopy may be advantageous over mid-IR since sample preparation procedures have less chance of inducing polymorphic conversion and there may be spectral differences in the former which are not apparent in the latter (Bugay 2001). In this study the authors compared the near-IR reflectance spectra in the range 1100–2500 cm^{-1} of the desired polymorph, and undesired polymorph, a hydrate, a solvate and the free acid of the material using two pattern recognition algorithms, the Mahalanobis distance method and the SIMCA residual variance method (Gemperline and Boyer 1995) to determine the preferred method for detecting unwanted small quantities of undesired crystal forms. The former algorithm gave better results, indicating that levels as low as 2% of the undesired polymorph may be detected, although the number of samples studied was too low to determine proper limits of detection.

⁵ The desirability of using the entire spectrum (and hence every absorption peak) for both identification and quantification is particularly relevant in light of a recent court decision which required the plaintiff in a patent infringement litigation involving a particular polymorphic form to show that all the peaks in the patent were present in the defendant's accused infringing product. In that litigation the peaks were X-ray powder diffraction maxima, but the same principles would apply to peaks in IR spectra (see Section 10.2).

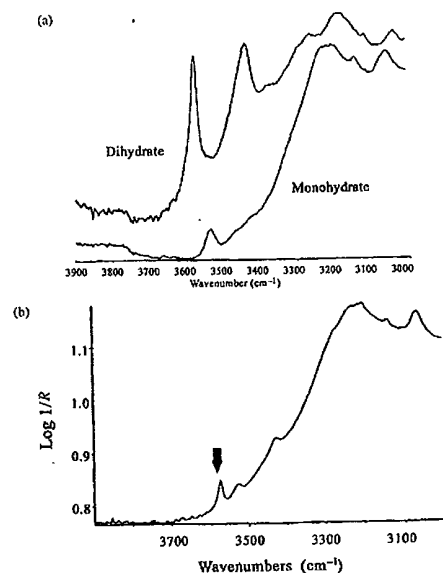


Fig. 4.30 (a) IR spectra for the monohydrate and dihydrate of cefepime dihydrochloride; (b) spectrum of a 5/95 w/w mixture of the dihydrate in the monohydrate. The arrow indicates the distinct dihydrate absorption used in the quantitative analysis. (From Bugay 1999, with permission.)

4.6 Raman spectroscopy

Infrared and Raman spectroscopy are often grouped together, since both techniques provide information on the vibrational modes of a compound. However, since the two spectroscopic techniques are based on different physical principles the selection rules are different. Infrared spectroscopy is an absorption phenomenon, while the Raman spectroscopy is based on a scattering phenomenon (Raman and Krishnan 1928). In general, infrared energy is absorbed by polar groups, while radiation is more effectively scattered in the Raman effect by symmetric vibrations and nonpolar groups (Colthup *et al.* 1990; Ferraro and Nakamoto 1994). For most molecules other

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M.Sc.	Yale University	1962-1964
Ph.D.	Yale University	1964-1967

Advisor: Basil G. Anex

Thesis title: "Spectral Properties of *trans*-Azobenzene and *trans*-Stilbene"

EMPLOYMENT HISTORY

<u>Institution</u>	<u>Rank</u>	<u>Years</u>
Cornell University	Teaching assistant	1962
Weizmann Institute of Science	Summer student	1962
Yale University	Teaching assistant	1962-66
Univ. of California (Los Angeles)	Postdoctoral	1967-69
Weizmann Institute of Science	Postdoctoral	1969-71
Ben-Gurion University	Lecturer	1971-73
Ben-Gurion University	Senior Lecturer (tenure)	1973-79
University of Illinois (Urbana)	Visiting Scientist	1977-78
Ben-Gurion University	Associate Professor	1979-88
Cornell University	Visiting Professor	1983-84
University of Minnesota	Visiting Professor	1988-89
Ben-Gurion University	Professor	1988-
University of Barcelona	Visiting Professor	7/97-9/97
Cambridge Crystallographic Data Centre	Visiting Fellow	9/97-9/98
Rand Afrikaans University	Visiting Professor	8/99-9/99
University of Bologna		
Institute of Advanced Study	Visiting Professor	3/05-4/05; 07/08; 07/09
University of Barcelona	Visiting Professor	5/05-6/05
University of Johannesburg	Visiting Professor	07/05-08/05
Ben-Gurion University	Barry and Carol Kaye Professor	

Australian National University
University of Western Australia
University of Western Australia

of Applied Science
Craig Visiting Professor
Gledden Senior Fellow
Professor at Large

04/08-
10/09-11/09
11/09-01/10
2010-2011

RESEARCH INTERESTS

Organic solid state chemistry, chemical crystallography, polymorphism, hydrogen bonding, graph sets, structure-property relations in organic solids and pharmaceuticals.

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Undergraduate Studies Committee, 1971-1977, 1986-88.
Undergraduate Advisor, 1971- .
Director of Undergraduate Studies, 1973-1975.
Graduate Studies Committee, 1971-1973; 1978-1986 .
Director of Graduate Studies, 1978-1980.
University Computer Policy Committee, 1971-1973; 1976-1977.
University Computer Evaluation and Selection Committee, 1972-1977.
University Athletics Committee, 1975-1977.
Faculty of Natural Sciences ad hoc Committee for Implementation of the Credit System of Studies, 1974-1975.
Department of Chemistry Executive Committee, 1985-88, 1994-
Rector's Select Committee on Undergraduate Curriculum and Education, 1986-87.
Chairman, Graduate Studies Committee, Faculty of Natural Sciences, 1987-88.
Vice-chairman, Department of Chemistry, 1987-88.
Dozor Visiting Professors Fund Committee, 1989-, Chairman, 1991-1995
Steering Committee, Board of Governors, 1990-1992, 1993-1997
University Supreme Committee on Appointments and Promotion, 1993-1997
Chairman, University Committee to Establish a Program of Studies in Hotel, Hospitality and Tourism Management, 1992-1994
Department of Chemistry Executive Committee, 2005-2007
Faculty of Natural Sciences Promotion and Tenure Committee, 2006-2008.

PROFESSIONAL FUNCTIONS OUTSIDE THE UNIVERSITY

President, Israel Crystallographic Society, 1979-1983, 1993-1997
Israeli representative to European Crystallographic Committee, 1980-1982, 1992, 1993, 1994.
Israeli representative to International Union of Crystallography XII Congress, 1981.
Chairman, Organizing Committee, Seventh European Crystallography Meeting, Jerusalem, August, 1982.
Member, Selection Committee, Gerhard Schmidt Memorial Prize, 1984-87.
Israeli Chairman, Organizing Committee for Joint Israeli-Italian Meeting on "The Influence of Steric and Electronic Effects on Molecular Crystalline Structures", Florence, Italy, 1987.
Co-Chairman, Second Midwest Meeting on Organic Solid State Chemistry, Minneapolis, 1989.
Chairman, Microsymposium on "Crystal Engineering", XV Congress, International Union of Crystallography, Bordeaux, July, 1990.
Member, Joint Committee on Powder Diffraction Standards-International Centre for Diffraction Data, 1990-.
Member, Steering Committee for Israeli National Center on Protein Crystallography, Hebrew University, Jerusalem, 1990-1994 .
Member, International Program Committee, VIIIth Symposium on Organic Crystal Chemistry, Rydzyna, Poland, 1992.
Chairman, Organizing Committee, Second Joint Israeli-Italian Meeting on "The Influence of Steric and Electronic Effects on Molecular Crystalline Structures", held in Israel, February, 1992.

Member, Program Committee, XI International Conference on the Chemistry of the Organic Solid State, Jerusalem, Israel, July, 1993.

Member, International Advisory Committee, Third International Conference on Crystal Growth of Materials, Washington, D.C., August, 1995.

Israeli Co-Chairman, Organizing Committee, Joint Italian-Israeli Conference on Crystal Structure and Molecular Recognition", held in Ferrara, Italy, February, 1996.

Vice President, European Crystallographic Committee, 1994-2000

Co-Chairman, Microsymposium on "Organic Materials", XVII Congress, International Union of Crystallography, Seattle, August, 1996.

Chairman, Program Committee, Xth Symposium on Organic Crystal Chemistry (OCC-97) held in Rydzyna, Poland, August, 1997.

External Ph.D. Examiner, University of Copenhagen, Denmark, February, 1997.

Co-Chairman, Microsymposium on "Polymorphism", 17th European Crystallographic Meeting, Lisbon, Portugal, August, 1997.

Chairman, Microsymposium on "Polymorphism and Isomorphism", XVIII Congress and General Assembly of the International Union of Crystallography, Glasgow, Scotland, August, 1999.

Member, Organizing Committee, PhandTA4 – 4th Symposium/Workshop on Pharmacy and Thermal Analysis, Karlsruhe, German, March, 1999.

Chairman, First European Crystallography Prize Committee, 2000.

External Ph.D. Examiner, Technical University of Denmark, Lyngby, Denmark, February, 2000.

Organizer and Chairman, Session on "Crystallization, Polymorphism and Properties of Organic Crystals", at the Gordon Research Conference on "Organic Structures and Properties: Extended Systems", held at New London, CT, June, 2000.

Member, International Program Committee, 11th Symposium on Organic Crystal Chemistry, Rydzyna, Poland, 2001.

Member, International Program Committee, 20th European Crystallography Meeting, Krakow, Poland, August, 2001.

Coconvener and Cochairman, European Polymorphism Network, 2001-2004

Chairman, Organizing Committee, XIX Congress and General Assembly of International Union of Crystallography (IUCr XIX), held in Geneva, Switzerland, August 2002.

External Ph.D. Examiner, Department of Chemistry, Rand Afrikaans University, Johannesburg, South Africa, 2003

Chairman, Microsymposium on "Polymorphism and Isomorphism", XXI European Crystallography Meeting, Durban, South Africa, August, 2003.

Director, NATO Advanced Study Institute and International School of Crystallography on "Polymorphs and Solvates" held in Erice, Sicily, June, 2004.

Co-Chairman, Symposium honoring awardees of ACA Fankuchen Prize and Trueblood Prize at the annual meeting of the American Crystallographic Association, Salt Lake City, July, 2007

Co-Chairman, Microsymposium on "Functional crystallography: tuning molecular behavior" held at the 24th European Crystallographic Meeting, Marrakech, Morocco, August, 2007

Chairman, Poster Prize Committee, 24th European Crystallographic Meeting, Marrakech, Morocco, August, 2007

Member, International Committee for Frevel Scholarship Awards, International Centre for Diffraction Data, Newton Center, PA, USA, 2004-

EDITORIAL BOARDS

Member, Editorial Advisory Board, *Israel Journal of Chemistry*, 1993 - .
Member, International Editorial Advisory Board, *Structural Chemistry*, 1993 - .
Member, International Editorial Advisory Board, *Zeitschrift für Kristallographie*, 1997 -2003
Member, International Editorial Advisory Board, *Crystal Engineering*, 1997 -2003
Member, International Advisory Board, *Crystal Engineering Communications*, 2000-2002
Topic Editor, Polymorphism and Polytypism, *Crystal Growth & Design*, 2000-.

Member, Oxford University Press/International Union of Crystallography Book Series Committee, 2002-.

PROFESSIONAL CONSULTING

Cephalon, U.S.A. 2009-
Johnson & Johnson 2008 - 2009
Astra Zeneca, U.K. 2007
Roche, U.S.A. 2007-2009
Organon, U.K. and Holland, 2004-2006
sanofi-aventis, U.S.A., U.K., Korea, France and South Africa 2003-
Eli Lilly, U.S.A., 2004; 2007-2008
Chemagis, Israel, 2003
Agan Chemicals, Israel, 2003, 2009
Rechter Gideon, Hungary, 2002-2005
Pfizer Pharmaceuticals, U.S.A., 2001-2003
Warner-Lambert Pharmaceuticals, U.S.A., 2000-2003
TransForm Pharmaceuticals, U.S.A., 2000-2006
Millenium Pharmaceuticals, U.S.A., 1999
Abbott Laboratories, U.S.A., 1997, 2002
SmithKline Beecham, United Kingdom and U.S.A., 1996 - 1998
Unipharm, Tel Aviv, Israel, 1993-1994.
GlaxoSmithKline, U.S.A, U.K., Australia, Denmark and Canada, 1992-.
Teva Pharmaceuticals, Petah Tikva, Israel, 1991-1995.
3M Company, St. Paul, Minnesota, 1980-84.
Bethlehem Steel Corporation, Bethlehem, Pennsylvania, 1981.
Plantex Pharmaceuticals, Ltd. Netanya, Israel, 1980.
Department of Chemical Physics, Weizmann Institute of Science, Rehovot, Israel, 1977-80.

COURSES TAUGHT

At Ben-Gurion University:

General Chemistry for chemistry majors and chemical engineers
Introduction to Analytical Chemistry
General and Analytical Chemistry Laboratory
Physical Chemistry Laboratory
Advanced Integrated Laboratory for third year (senior) students, including
conception and preparation of the course.
X-ray Crystallography for graduate students
Solid State Chemistry for graduate students
Molecular Symmetry for graduate students

At Cornell University:

X-ray Crystallography for graduate students (with J. Clardy)

At the University of Minnesota

MEMBERSHIPS IN PROFESSIONAL SOCIETIES

American Chemical Society, 1974- .
Sigma Xi, 1966 -.
American Association for the Advancement of Science, 1967 -; Elected Fellow, 1999.
American Crystallographic Association, 1968 -.
Royal Society of Chemistry (London), 1972 -.
American Physical Society, 1968 -.
Israel Crystallographic Society, 1971 - (President 1979-1983; 1993-1997)

AWARDS, HONORS, RESEARCH FELLOWSHIPS:

National Institutes of Health Predoctoral Fellow, 1963-67
Institute Fellow, Weizmann Institute of Sciences, 1969-71.
BGU - UCLA Exchange Fellow, February, 1983.
Israel - Italy National Council for Research and Development Senior Scientist Exchange Fellow,
March-April, 1983.
Israel - Italy National Council for Research and Development Senior Scientist Exchange Fellow,
June, 1991.
"Tberdrola – Cincia y Technologia: Visiting Professor, University of Barcelona, July-September 1997
Eric Samson Chair, Rand Afrikaans University, August-September, 1999
Fellow, American Association for the Advancement of Science, 1999-
Fellow, Institute for Advanced Study, University of Bologna, 2005
Fellow, HPC-Europa Transnational Access, University of Barcelona, 2005
Barry and Carol Kaye Endowed Professorship in Applied Science, Ben-Gurion University, 2008-
David P. Craig Visiting Professor, Australian National University, 10/09-11/09
Gledden Visiting Fellowship, University of Western Australia, 11/09 – 01/10
Professor-at-Large, University of Western Australia, 2010-2011

SCIENTIFIC PUBLICATIONS (*Citations as of January, 2009 in bold italics at end of entry;*
Hirsch Index = 34)

Book

J. Bernstein

"Polymorphism in Molecular Crystals", Oxford University Press, ISBN 0 19 850605, (2002) 410 pages.
(Russian translation edition, 2008) **(574)**

Chapters in collective volumes

1. "Structural Chemistry of Quinones"
J. Bernstein, M.D. Cohen and L. Leiserowitz
A chapter in the book "The Chemistry of Quinones", S. Patai, ed., Wiley Interscience, New York, 1974, pp. 37-110. **(96)**
2. "Crystal Forces and Molecular Conformation"
J. Bernstein
Chapter in book "X-ray Crystallography and Drug Action: Current Perspectives", A.S. Horn and C.J. De Ranter, eds., Oxford University Press, New York, 1984, pp. 23-44. **(11)**
3. "Conformational Polymorphism"
J. Bernstein
Chapter 14 in the book "Organic Solid State Chemistry", G. Desiraju, ed., Elsevier, Amsterdam, 1987, pp. 471-518. **(173)**
4. "Polymorphism in Drug Design and Delivery"
J. Bernstein
In "Computer Assisted Modeling of Receptor-Ligand Interactions: Theoretical Aspects and Applications to Drug Design", A. Golombek, ed. Alan R. Liss, New York (1989), pp. 203-215. **(2)**
5. "Polymorphism and the Investigation of Structure-Property Relations in Organic Solids"
J. Bernstein
In "Organic Crystal Chemistry", J.B. Garbarczyk and D. W. Jones, eds. Oxford University Press, Oxford. 1991, pp.6-26. **(9)**
6. "Effect of Crystal Environment on Molecular Structure"
J. Bernstein
In "Accurate Molecular Structures", A. Domenicano and I. Hargittai , eds. Oxford University Press, Oxford. 1992, pp 469-497. **(40)**
7. "The Role of Hydrogen Bonding in Molecular Assemblies"
J. Bernstein, M.C. Etter and L. Leiserowitz
In "Structure Correlations", J.D. Dunitz and H.-B. Bürgi, eds. Volume 2, VCH, Weinheim, 1994, pp 431-507. **(158)**
8. "Structural and Crystallographic Aspects of Supramolecular Engineering: Structure-Property Relations, Polymorphism and Crystal Growth"
J. Bernstein
NATO Advanced Research Workshop on Supramolecular Engineering of Synthetic Metallic Materials: Conductors and Magnets, J. Vaciato, C. Rovira, and D.B. Amabilino (editors), NATO ASI Series, Series C: Mathematical and Physical sciences – Vol. 518, Kluwer Academic Publishers, Dordrecht (1999),

9. "Graph Set Analysis of Hydrogen Bond Motifs"
J. Bernstein and R.E. Davis
In "Implications of Molecular and Materials Structure for New Technologies"
J.A.K. Howard, F.H. Allen and G.P. Shields (editors)
NATO Science Series, Series E, Applied Sciences – Volume 360
Kluwer Academic Publishers, Dordrecht (1999), pp. 275-290. (1)
10. "Pharmaceuticals"
J. Bernstein and J.-O. Henck
Chapter 21 of *Industrial Applications of X-ray Diffraction*, edited by D. Smith and F. Chung,
Marcel Decker, New York (2000), pp. 527-538. (4)
11. "Polymorphism"
J. Bernstein
In "Strength from Weakness: Structural Consequences of Weak Interactions in Molecule, Supramolecules and Crystals"
A. Domenicano and I. Hargittai (editors)
NATO Science Series, Kluwer Academic Publishers, Dordrecht (2002), pp. 247-260.
12. "Crystal Structure Prediction and Polymorphism"
Joel Bernstein
Transactions of the American Crystallographic Association, 39, 1-10 (2004).
Actual date of publication, November 2005.
13. "Polymorphism and Patents from a Chemist's Point of View"
J. Bernstein
In "Polymorphism in Pharmaceutical Technology"
R. Hilfiker (editor)
Elsevier, Amsterdam, (2006), pp. 365-384. (2)
14. "Crystal Polymorphism: Challenges at the Crossroads of Science and Technology"
D. Braga and J. Bernstein
Chapter in the book "Making Crystals by Design – Methods, Techniques and Applications", edited
by D. Braga and F. Grepioni,
Wiley-VCH, Weinheim, (2006), pp. 293-314.
15. "Crystal Polymorphism"
J. Bernstein
Chapter in the book "Engineering of Crystalline Materials Properties", edited by J.J. Novoa, D.
Braga and L. Addadi,
Springer, Dordrecht (2008), pp. 87-109.

Refereed articles in scientific journals

16. "The Infrared Absorption of Normal and ^{18}O -Labelled Triphenylarsine Oxide"
J. Bernstein, M. Halmann, S. Pincus and D. Samuel
Journal of the Chemical Society (London) 1964, 821-824. (43)
17. "Absorption and Fluorescence Spectra of Crystalline *trans*-Stilbene"
J. Bernstein and B.G. Anex
Journal of Physics, Section C 1970, L137-139. (3)

Book Reviews

1. "Historical Atlas of Crystallography" J. Lima-de-Faria, editor, Kluwer Academic Publishers, Dordrecht, Holland, 1992.
Reviewed for Structural Chemistry 4, 67-68 (1993).
2. "Crystallography in Modern Chemistry - A Resource Book of Crystal Structures" by T.C.W. Mak and Gong-Du Zhou, published by Wiley Interscience, 1992.
Reviewed for Molecular Crystals and Liquid Crystals, 237, 496-498 (1993).
3. "Crystal Structure Analysis for Chemists and Biologists" by J.P. Glusker, M. Lewis and M. Rossi, published by VCH Publishers, 1994.
Reviewed for Acta Crystallographica B51, 382-384 (1995).
4. "Applications of Graph Theory and Topology in Inorganic Cluster and Coordination Chemistry" by R.B. King, published by CRC Press, 1993
Reviewed for Structural Chemistry 6, 403 (1995).