

Clarke, M

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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P-2265

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 09.083.638

Solicitud de patente a nombre de **MAKHTESHIM CHEMICAL WORKS, LTD.**

Yo, DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **MAKHTESHIM CHEMICAL WORKS, LTD.**, domiciliada en Beer Sheva, Israel, solicitante de la patente de la referencia, en respuesta al oficio No. 12835 notificado por fijación en lista el 25 de julio de 2012, cuyo término fue prorrogado mediante escrito radicado el 12 de septiembre de 2012, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio, el cual consta de 1 a 30 reivindicaciones y reemplaza en su totalidad el capítulo reivindicatorio presentado anteriormente.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones a la claridad, planteadas por el examinador en su concepto técnico.

2. Reivindicaciones de Uso

El examinador objeta las reivindicaciones 43 y 44 por considerarlas de uso y, por ende, no ser patentables en Colombia. Con el fin de subsanar esta objeción, el solicitante elimina dichas reivindicaciones del nuevo capítulo reivindicatorio adjunto.

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3. Claridad de la Solicitud

El solicitante adjunta un nuevo capítulo reivindicatorio con el cual subsana las objeciones presentadas por el examinador.

Particularmente, el solicitante quisiera hacer los siguientes comentarios:

- El artículo 51 de la decisión 486 establece que la descripción y las figuras se emplearán para interpretar la materia reclamada. Puesto que las figuras presentan patrones de difracción y espectros de Raman para los compuestos reclamados, no existe ninguna razón para incluir absolutamente todos los puntos relevantes de los mismos. Por otro lado, el experto con habilidad en la materia sabe que los polimorfos no difieren del compuesto base en muchos picos y su definición se puede hacer simplemente reclamando aquellos picos que son diferentes, ya que espectro base del compuesto a es conocido.

- El solicitante no entiende por qué razón el examinador sugiere que se incluyan en las reivindicaciones datos que no se encuentran en la solicitud como se presentó originalmente. ¿Acaso no sabe el examinador que esto constituye una ampliación de la materia?

- Los solventes son especificados en el capítulo reivindicatorio. Si bien la reivindicación principal los menciona por su familia, la reivindicación que le sigue los lista por nombre, por lo que el capítulo es suficientemente preciso.

- La descripción no menciona rangos o valores específicos para las temperaturas, no tampoco valores o rangos para las velocidades de enfriamiento o calentamiento. El solicitante considera que la persona versada en la materia tiene suficiente experiencia en la obtención de formas cristalinas polimorfas como para entender el significado de “enfriar gradualmente” o “calentar rápidamente”.

Para el solicitante no es claro exactamente de qué forma conocer la totalidad de los picos facilita el proceso de obtención del polimorfo. El experto con habilidad ordinaria sabe que lo importante es el tipo de solvente, la temperatura y demás factores de proceso.

3. Falta de Novedad

El solicitante considera que el capítulo reivindicatorio adjunto es novedoso por sobre las enseñanzas de cualquiera de las anterioridades D1, o D2.

Específicamente, el solicitante quisiera anotar que ninguno de los documentos

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citados enseña específicamente los patrones de difracción o espectros de Raman de la presente solicitud, por lo que la misma es novedosa por sobre el arte previo citado.

En este sentido, me permito manifestar que el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que la invención se considera como nueva cuando no está comprendida en el estado de la técnica.

Si de acuerdo con el espíritu de la norma legal indicada anteriormente, la invención no se considera como nueva si está “comprendida” en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la *totalidad del invento y no a alguno o a algunos de los componentes*. Para que la invención pierda su calidad de novedosa, es claro que **TODA ELLA**, ha de estar contenida en el “conjunto de conocimientos existentes que son aplicables al proceso industrial” como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Esto se conoce como **NOVEDAD ABSOLUTA**, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de **forma total** con lo revelado en un documento o anterioridad señalada, conclusión a la que se llega después de un análisis íntegro mediante una comparación entre el capítulo reivindicatorio de la invención en estudio y la anterioridad D1.

Es necesario resaltar que el examinador está considerando los aspectos generales de la invención, sin tener en cuenta que son las particularidades las que conceden la novedad.

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica, no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: “*hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria*” (Ibidem, páginas 53 y 54) (el subrayado es mío).

Por lo tanto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma **TOTAL y ABSOLUTA** en el documento que se menciona como anterioridad o de forma independiente en los documentos que se mencionan, si son varios; y

-Que la invención en estudio puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el valor agregado que aporta la invención con sus nuevas características al campo técnico al cual pertenece la invención en estudio.

Como se puede observar, la decisión no establece en ningún punto que la novedad de estudio se base a las características esenciales, como lo está evaluando el examinador. La novedad debe ser absoluta, en el sentido que todas y cada una de las características de la invención deben estar contenidas en la anterioridad para que ésta pueda afectar la novedad de la solicitud.

4. Falta de Nivel Inventivo

El examinador objeta la altura inventiva de la reivindicación 1 a la luz de las anterioridades D1 a D3. El examinador argumenta que para un experto con habilidad ordinaria en la materia sería obvio, conociendo el compuesto, su capacidad para formar polimorfos y métodos generales de cristalización, obtener los polimorfos reclamados en la presente solicitud.

Al respecto, el solicitante quisiera anotar que esto constituye una generalización carente de fundamento técnico. Si formar polimorfos fuera tan “obvio”, no se realizarían experimentos de cristalización de proteínas en gravedad cero, empleando las condiciones de la estación internacional.

La única forma en la que un experto puede llegar al método de obtención de las formas A y B reclamado en la presente solicitud es mediante un estudio retrospectivo de la misma. El solicitante adjunta dos escritos científicos en los cuales se demuestra que la obtención de polimorfos no es tan obvia como pareciera a simple vista. En dichos documentos se explica que la interacción de fuerzas como los enlaces internos de la molécula, su polaridad, la presencia de puentes de hidrógeno o fuerzas de Van der Waals hacen imposible predecir de antemano si dicha molécula va a formar un polimorfo específico, o incluso si los polimorfos que pueda formar van ser suficientemente estables o útiles en alguna medida.

Por otro lado, ninguna de las anterioridades citadas por el examinador enseña o sugiere polimorfos con los patrones reclamados, por lo que no sería posible para un experto con habilidad en la materia derivar de allí un proceso para obtener dos polimorfos específicos. No es lo mismo saber que un compuesto puede formar polimorfos y obtener dichos polimorfos. Lo uno no implica lo otro, como lo demuestra el hecho que para formar cristales de algunas proteínas no solo se deben escoger las condiciones termodinámicas apropiadas, sino además es necesario realizar el proceso en gravedad cero.

En vista de lo anterior, en ausencia de enseñanzas relacionadas con los polimorfos reclamados, resulta prácticamente imposible para un experto con habilidad en la materia derivar los polimorfos reclamados y más aún el proceso para obtenerlos, partiendo del conocimiento de la habilidad genérica del compuesto para formar polimorfos y un libro de teoría básica sobre procesos de cristalización.

En resumen, me permito decir que gracias a las modificaciones expuestas en el punto 1 de este memorial y los argumentos anteriormente mencionados, la presente solicitud cumple cabalmente con el requisito de claridad, novedad y altura inventiva respecto al método expuesto en el capítulo reivindicatorio adjunto. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

Señor Superintendente,



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REIVINDICACIONES

1. La Forma A polimorfa cristalina de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en donde la polimorfa exhibe un patrón de difracción por rayos X (método con polvo micro-cristalino) que tiene picos característicos expresados en grados 2θ ($\pm 0.20^\circ$) en cerca de 6.25, 13.8, 17.65, 19.05, 26.4 y 28.5.

2. La polimorfa cristalina de acuerdo con la reivindicación 1, en donde la polimorfa además exhibe picos característicos expresados en grados 2θ ($\pm 0.20^\circ$) en cerca de 11 y 14.4.

3. La polimorfa cristalina de acuerdo con la reivindicación 1, en donde la polimorfa exhibe un espectro infra-rojo (IR) que tiene picos característicos en cerca de 1378, 1328 y 1154 cm^{-1}

4. La polimorfa cristalina de acuerdo con la reivindicación 1, en donde la polimorfa exhibe una endoterma predominante única en un intervalo de cerca de 114-117 $^\circ\text{C}$ cuando se mide por Calorimetría por Escaneo Diferencial (DSC) a una tasa de escaneo de 10 $^\circ\text{C}$ por minuto.

5. La polimorfa cristalina de acuerdo con la reivindicación 1, en donde la polimorfa exhibe un espectro Raman que tiene picos característicos en cerca de 4398, 133029 y 22332 cm^{-1} .

6. La Forma B polimorfa cristalina de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en donde la polimorfa exhibe un patrón de difracción por rayos X (método con polvo micro-cristalino) que tiene picos característicos expresados en grados 2θ ($\pm 0.20^\circ$) en cerca de 7.5, 11.75, 13.20, y 19.65.

7. La polimorfa cristalina de acuerdo con la reivindicación 6, en donde la polimorfa además exhibe picos característicos expresados en grados 2θ ($\pm 0.20^\circ$) en cerca de 14.15, 17.1 y 23.6.

8. La polimorfa cristalina de acuerdo con la reivindicación 6, en donde la polimorfa exhibe un espectro infra-rojo (IR) que tiene picos característicos en cerca de 1389, 1335 y 1245 cm^{-1} .

9. La polimorfa cristalina de acuerdo con la reivindicación 6, en donde la polimorfa exhibe una endoterma predominante en un intervalo de cerca de 101-105 $^\circ\text{C}$ cuando se mide por Calorimetría por Escaneo Diferencial (DSC) a una tasa de escaneo de 10 $^\circ\text{C}$ por minuto.

10. La polimorfa cristalina de acuerdo con la reivindicación 6, en donde la polimorfa exhibe un espectro Raman que tiene picos característicos en cerca de 3098, 1335 y 2237 cm⁻¹.

11. Una mezcla de las Formas polimórficas A, de acuerdo con cualquiera de las reivindicaciones 1 a 5, y B, de acuerdo con cualquiera de las reivindicaciones 6 a 10, de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato.

12. Un (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato amorfo.

13. Un proceso para la preparación de una Forma A polimorfa cristalina de 3 (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato, de acuerdo a cualquiera de las reivindicaciones 1 a 5, el proceso comprende las etapas de cristalizar dicho compuesto a partir de un solvente seleccionado del grupo que consiste de un alcohol, un éter, una cetona, un éster, una amida, un nitrilo, y un hidrocarburo alifático o aromático.

14. El proceso de acuerdo con la reivindicación 13, en donde el solvente se selecciona del grupo que consiste de metanol, etanol, tetrahidrofurano, acetona, etileno glicol, acetonitrilo, acetato de etilo, metil isobutil cetona, xileno y tolueno.

15. El proceso de acuerdo con la reivindicación 13, que comprende las etapas de:

- a) Preparar una solución de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en un solvente seleccionado del grupo que consiste de un alcohol, un éter, una cetona, un éster, una amida, un nitrilo, y un hidrocarburo alifático o aromático.
- b) Enfriar gradualmente la solución hasta formar los cristales de dicho compuesto; y
- c) Separar los cristales.

16. Un proceso para la preparación de una Forma B polimorfa cristalina de 3 (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato, de acuerdo con cualquiera de las reivindicaciones 6 a 10, el proceso comprende las etapas de cristalizar dicho compuesto a partir de una mezcla de solventes que comprende agua y un solvente orgánico seleccionado del grupo que consiste de un alcohol y una amida.

17. El proceso de acuerdo con la reivindicación 16, en donde el solvente orgánico se selecciona del grupo que consiste de 1-propanol y N, N-dimetilacetamida.

18. El proceso de acuerdo con la reivindicación 16, que comprende las etapas de:

- a) Preparar una solución de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en un solvente seleccionado del grupo que consiste de un alcohol y una amida.
- b) Agregar agua a dicha solución hasta formar los cristales de dicho compuesto; y
- c) Separar los cristales.

19. Un proceso para la preparación de una mezcla de una Forma A polimorfa cristalina, de acuerdo con cualquiera de las reivindicaciones 1 a 5, y una Forma B, de acuerdo con cualquiera de las reivindicaciones 6 a 10, de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato, el proceso comprende las etapas de cristalizar dicho compuesto a partir de una mezcla solvente que comprende un alcohol y un anti-solvente seleccionado de un hidrocarburo alifático y aromático y separar los cristales resultantes.

20. El proceso de acuerdo con la reivindicación 19, en donde el alcohol se selecciona de del grupo que consiste de isopropil alcohol, 1-propanol y butanol.

21. El proceso de acuerdo con la reivindicación 19, en donde el anti-solvente es heptano.

22. El proceso de acuerdo con la reivindicación 19, que comprende las etapas de

- a) Preparar una solución de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en un alcohol;
- b) Agregar un anti-solvente seleccionado de hidrocarburo alifático y aromático a dicha solución hasta formar los cristales de dicho compuesto; y
- c) Separar los cristales.

23. Un proceso para la preparación de una mezcla de una Forma A polimorfa cristalina, de acuerdo con cualquiera de las reivindicaciones 1 a 5, y una Forma B, de acuerdo con cualquiera de las reivindicaciones 6 a 10, de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato, que comprende las etapas de

- a) Preparar una solución de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato en un alcohol;
- b) Enfriar rápidamente la solución hasta formar los cristales de dicho compuesto; y
- c) Separar los cristales.

24. El proceso de acuerdo con la reivindicación 23, en donde el alcohol es isopropil alcohol.

25. Un proceso para la preparación de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato amorfo, el proceso comprende las etapas de calentar dicho compuesto a una temperatura mayor que su punto de fusión; enfriar rápidamente; y separar el producto resultante.

26. El proceso de acuerdo con la reivindicación 25, en donde la temperatura es mayor que cerca de 100 °C.

27. Una composición para combatir los hongos que comprende una Forma A polimorfa cristalina de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato de acuerdo con cualquiera de las reivindicaciones 1-5; y un adyuvante aceptable.

28. Una composición para combatir los hongos que comprende una Forma B polimorfa cristalina de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato de acuerdo con cualquiera de las reivindicaciones 6 - 10; y un adyuvante aceptable.

29. Una composición para combatir los hongos que comprende una mezcla de Forma A polimorfa cristalina y Forma B de (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato de acuerdo con cualquiera de las reivindicaciones 11-12; y un adyuvante aceptable.

30. Una composición para combatir los hongos que comprende (E)-2-{2-[6-(2-cianofenoxi) pirimidin-4-iloxi] fenil}-3-metoxiacrilato amorfo de acuerdo con cualquiera de las reivindicaciones 13-14; y un adyuvante aceptable.

Organic Process Research & Development

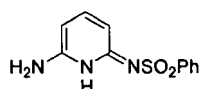
Organic Process Research & Development 2010, 14, 1

Editorial

Polymorphism - Still Unpredictable?

I have been fascinated by polymorphism ever since a routine preparation of a 2–4-nitrophenylhydrazone, during my undergraduate work in 1966–67, produced two different coloured crystals, with different melting points, depending on the crystallisation solvent used. More than 40 years on, this subject retains its fascination, partly because of the lack of predictability of polymorphism. A statement in a recent paper “Serendipity often plays a key role in the discovery of new forms, because no general methodology exists for producing new forms of a given compound”¹, will ring true to many process chemists, who may have seen a new crystalline form appear late in the development of a new drug substance. There are many examples of this in *Org. Process Res. Dev.* (OPRD) papers, one of the most interesting being the paper from Bristol Myers Squibb, where two new forms appeared after many batches had been made.²

Prediction of crystal structure from a given chemical substance, and hence its polymorphism, is a desired goal which has not been routinely achieved, despite one or two successes with specific molecules. Periodically, blind tests are organised where scientists are challenged to predict crystal structures of specific molecules, and the results are compared to the actual experimental results. Such a blind test in 2001 for the molecule shown below ended in failure, with none of the participants being able to predict the structure correctly. A later study found a second polymorph of the molecule, that was claimed to be the more thermodynamically stable form.



Now a reinvestigation of the polymorphism of this molecule,² which clearly has lots of H-bonding options, has revealed a new form III, and the relative stability of the three forms has been elucidated by slurry experiments. These have shown that form I, the structure originally reported as the blind-test solution, is in fact more stable than form II by 0.44 kcal/mol and more stable than form III by 0.23 kcal/mol. The results of all teams in the 2001 blind prediction trial were re-examined, and it was still shown that the two more stable forms (I and III) were absent from all predictions.

Therefore, structure prediction, which would be most valuable for process chemistry, has still a way to go, which is both good news and bad news. The good news is stated in the conclusion in the cited paper.² “After two decades, although improvements have been made, there is still considerable job security for the experimental chemist and crystallographer”—a much needed view in the current economic climate.

Trevor Laird
Editor

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(1) Roy, S.; Matzger, A. J. *Angew. Chem., Int. Ed.* 2009, 48, 8505–8508.

(2) Desikan, S.; Parsons, R. L., Jr.; Davis, W. P.; Ward, J. E.; Marshall, W. J.; Toma, P. H. *Org. Process Res. Dev.* 2005, 9, 933–942.

Making crystals from crystals: a green route to crystal engineering and polymorphism†

Dario Braga* and Fabrizia Grepioni*

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Supramolecular reactions between crystalline materials as well as reactions between a crystalline material and a vapour can be used to generate new crystalline substances. These solvent-free processes can be exploited to prepare both hydrogen-bonded co-crystals and coordination networks. Solid–vapour reactions do not differ from solid–vapour uptake/release processes, and can also be used to prepare polymorphs and solvates. It is argued that solvent-less reactions involving molecular crystals represent a green route to supramolecular solid-state chemistry and crystal engineering.

Introduction

Making crystals by design is the paradigm of crystal engineering.¹ The goal of this field of research is that of assembling functionalised molecular and ionic components into a target network of supramolecular interactions.² Such “bottom-up” process generates *collective* supramolecular properties (e.g. magnetism, non-linear optics, conductivity, nano-porosity, etc.) from the convolution of the physical and chemical properties of the individual building blocks with the periodicity and symmetry operators of the crystal (see Fig. 1).³

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† Dedicated to Professor Brian F. G. Johnson (Cambridge) on the occasion of his 67th birthday.

Dario Braga is Professor of Chemistry at the University of Bologna. Presently, his main scientific interests are in the study of crystal polymorphism and in the crystal engineering exploitation of hydrogen-bonding interaction between ions and in solvent-free gas–solid and solid–solid reactions. He received the Raffaello Nasini Prize from the Italian Society of Chemistry in 1988 for his studies on solid-state dynamic processes, and the FEDERCHIMICA Prize for 1995 for his research on the intermolecular interactions in organometallic systems. He has published more than 300 papers and reviews and organized several international conferences and schools on crystal engineering. He is Scientific Editor of the RSC journal *CrystEngComm*, a member of the international editorial board of *Chem. Comm.* and Director of the Collegio Superiore of the Alma Mater Studiorum University of Bologna.

Fabrizia Grepioni is Associate Professor of Structural and Functional Materials and of General Chemistry at the University of Bologna, after spending six years as Associate Professor at the University of Sassari. She received a PhD from the University of Bologna in 1990. She was awarded the 1997 Raffaello Nasini Prize from the Italian Society of Chemistry for her studies on intermolecular interactions in organometallic solids. She has published more than 200 papers. Her scientific interests are in the fields of crystal engineering and molecular crystal polymorphism.

The research work of many groups worldwide follows two main directions: coordination networks⁴ and molecular materials,⁵ with many relevant crossing points in between. The engineering of coordination networks can be described as *periodical coordination chemistry*,⁶ because the use of *divergent polydentate ligand–metal coordination*, as opposed to the more traditional *convergent coordination chemistry* of chelating ligands, extends coordination chemistry through space in 1-D, 2-D and 3-D architectures (see Fig. 2). Even though periodical coordination chemistry is at present dominating the field, in terms of scientific output and of number of groups involved, the roots of crystal engineering are in molecular organic solid-state chemistry.⁷

In molecular crystal engineering, on the other hand, the interactions of interest are mainly of the non-covalent type, e.g. van der Waals,⁸ hydrogen bonds,⁹ π -stacking¹⁰ etc. and their convolution with ionic interactions.¹¹

What is a molecular crystal,¹² then? An operative “crystal engineering” definition of a molecular crystal can be based on

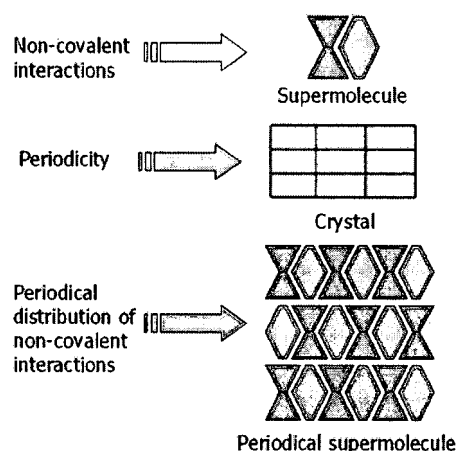


Fig. 1 From molecules to periodical supermolecules: the collective properties of molecular crystals result from the convolution of the properties of the individual molecular/ionic building blocks with the periodical distribution of intermolecular non-covalent bonding of the crystal.

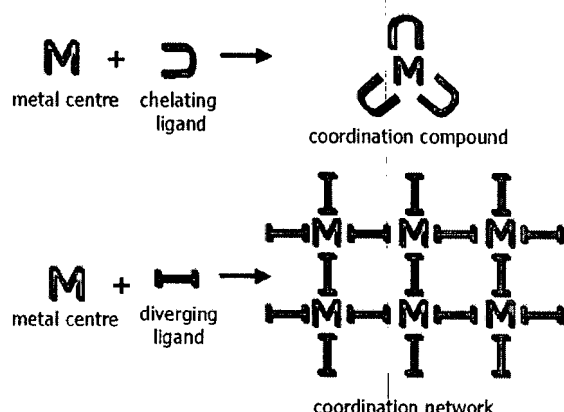


Fig. 2 Schematic representation of the relationship between molecular (top) and periodical (bottom) coordination chemistry: the use of bidentate ligand spacers allows construction of *periodical* coordination complexes.

the energy ranking of the bonding interactions: *the components of a molecular crystal are held together by intermolecular links that are weaker than the covalent chemical bonds within the individual components, whether molecules or molecular ions.* Hence, building blocks will retain, in general, their chemical and physical identity once evaporated or dissolved.

This definition encompasses also the possibility of obtaining *different crystal structures from the same building blocks*, viz. crystal polymorphism (see Fig. 3),¹³ by choosing different sets of non-covalent (supramolecular) bonds. We remind the reader that differences in supramolecular bonding may generate relevant differences in physical and chemical properties, such as solubility, melting point, density, *etc.*,¹⁴ as well as different behaviours under mechanical or thermal stress, with relevant consequences on packaging and tableting,¹⁵ hence on processing and marketing of commercial crystalline solids, such as pigments and drugs.¹⁶ A further element of variability to consider when dealing with molecular crystals and polymorphs is the co-crystallization¹⁷ of guest molecules, usually provided by the solvents of crystallization. Solvate crystals of a given chemical species, for which the unsolvated crystal is known, are also referred to (and not without controversy^{13b,18}) as pseudo-polymorphs.

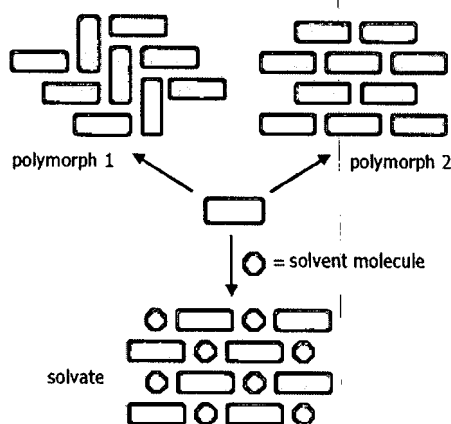


Fig. 3 From the same building block to polymorphs and to solvates

In this feature article we will focus on the idea that reactions between crystalline solids and between crystalline solids and vapours represent viable alternative methods to prepare new crystalline materials, *i.e. to make crystals from crystals*.

Our approach encompasses both the possibility of *reacting* a given crystalline material with another substance (which can be another crystalline materials, or a gas) and that of *transforming* a given crystalline material in a different one *via* a phase transition or *via* a loss of molecules (desolvation). Importantly, these “non-solution” approaches can be used not only to prepare new materials but also to generate new polymorphic or solvate modifications of the same substance.¹⁹

Making crystals from crystals

Crystal engineers are crystal *makers*. The ultimate step of a crystal engineering exercise is that of obtaining crystals, preferably single crystals of reasonable size that will allow to enjoy the speed and accuracy of single-crystal X-ray diffraction experiments. Even though amorphous molecular materials can be extremely interesting²² and constitute a serious problem in studies of polymorphism, in crystal engineering studies the desired materials need to be – *by definition* – in the crystalline form.

We have argued²³ that crystalline materials interesting for crystal engineering studies can also be obtained by reacting and transforming preformed crystals. This may be achieved by means of solvent-less processes,²⁴ such as those occurring between solids or between a solid and a vapour. Since processes of this type do not require recovery, storage and disposal of solvents, they are of interest in the field of “green chemistry”.²⁵ In our approach reactions between molecular crystals and gases or other crystals are regarded as *supramolecular reactions*, whereby interactions, including coordination bonds, between reactants are broken while those of the product are being formed.¹⁹ Solvent-free methods, however, still require that molecules are brought in contact for reaction. In general, fast and quantitative reactions can be achieved when finely ground powders (the large surface area helps molecular diffusion) are exposed to gaseous substances or co-ground with another powder. The two solvent-free processes are distinct but conceptually related, as depicted in the top part of Fig. 4.

In order to set the scope of this contribution, we should point out that “single crystal” and “polycrystalline powder” are relative definitions, which only express the size of the crystals *with respect to the technique in use*. A polycrystalline material is composed of small single crystals, typically too small for single-crystal X-ray diffraction experiments; on the other hand, crystals suitable for X-ray diffraction are often too small for neutron diffraction and so forth. In the context of this article the term “making crystals from crystals” will be used mainly to indicate processes involving polycrystalline powders. We should warn the reader that we will not discuss intra-solid reactions,¹⁹ such as topochemical reactions of the type explored by Schmid^{7b} in the early days of crystal engineering.⁷ These reactions are now experiencing a wave of renewed interest.²⁰ We shall also not discuss reactions involving single crystals.²¹

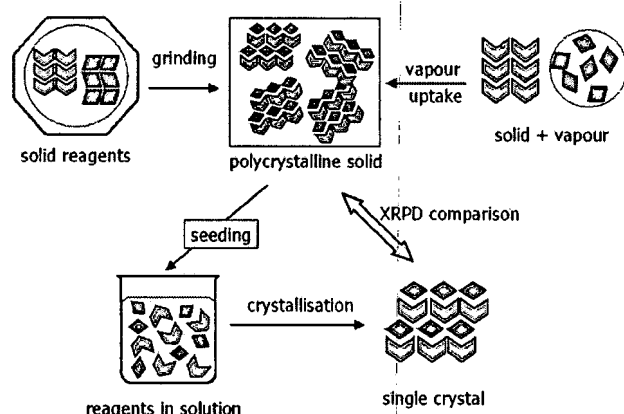


Fig. 4 Schematic representation of the solid–solid and solid–vapour processes and the strategy to obtain single crystals by recrystallisation via seeding.

Grinding, milling, kneading, seeding

Pioneering studies of reactions between molecular crystals were carried out by Rastogi *et al.* about forty years ago,²⁶ and extended by Curtin and Paul in the 1970s.²⁷ Etter and collaborators investigated formation of hydrogen-bonded co-crystals by grinding of the solid components,^{28a} even in the presence of a third solid component.^{28b} In the case of 2-aminobenzoic acid, Etter also showed grinding could determine polymorph interconversion.^{28c}

In spite of these early suggestive results methods based on (manual) *grinding* or (electromechanical) *ball milling*²⁹ are not very popular in academic chemistry labs, and are often dismissed as “non-chemical”, even though they are commonly used at industrial level mainly with inorganic solids and materials.³⁰ Another industrially relevant process that can be applied on a small-scale research lab is the so called *kneading*,³¹ i.e. the use of small amounts of solvent or of a liquid reactant to accelerate (when not make altogether possible) the solid-state reactions carried out by grinding or milling.³² *Kneading* has been described as a sort of “solvent catalysis” of the solid-state process, whereby the small amount of solvent provides a *lubricant* for molecular diffusion.^{19a} The method is commonly employed, for example, in the preparation of cyclodextrin inclusion compounds.³³

Whether a *kneaded* reaction between two solid phases can be regarded as a *bona fide* solid-state process is doubtful, as it is often the case with other mechanochemical reactions, because of the difficulty in controlling exact reaction conditions such as grinding time, temperature, pressure exerted by the operator, *etc.* Even though a discussion of these extremely relevant aspects is beyond the scope of this article, one should consider, for example, that the heat generated in the course of a mechanochemical process can induce local melting of crystals or melting at the interface between the different crystals, so that the reaction takes place in the liquid phase even though solid products are ultimately recovered. The same reasoning applies to formation of eutectic phases^{19e,f} and to reactions occurring with a minimal amount of solvent (*kneading*).

Another point to consider is that the polycrystalline nature of mechanochemical products makes impossible the use of

straightforward single-crystal diffraction methods, which are indispensable for a precise description of the structure of the crystal (the ultimate product of a crystal engineering experiment). Beside *ab initio* structure determination from powder diffraction data,³⁴ which is not yet of widespread application, one has to resort to the *a posteriori* preparation of single crystals starting from the powdered product. In some cases, single crystals can be grown from solution by *seeding*, i.e. by using a small portion of the polycrystalline sample to “instruct” the crystallization process. Once the single-crystal structure is known, an X-ray powder pattern can be calculated and compared with the measured powder patterns of products obtained from subsequent preparations (see bottom part of Fig. 4). As for *grinding* and *kneading*, *seeding* procedures are commonly employed in industries to guarantee crystallization/precipitation of the desired crystal form. *Seeds* of isostructural or *quasi*-isostructural species that crystallise well can also been employed to induce crystallisation of unyielding materials (*heteromolecular seeding*).³⁵ Of course, unintentional *seeding* may also alter the crystallization process in an undesired manner.³⁶

These aspects will be developed by means of examples, taken mainly from our own work, organized in the following four sections:

- (i) mechanochemical preparation of hydrogen-bonded adducts and cages
- (ii) mechanochemical preparation of coordination networks
- (iii) solid–vapour reactions involving hydrogen-bonded crystals
- (iv) induced polymorphism and solvate formation

Mechanochemical preparation of hydrogen-bonded adducts

Hydrogen-bonding interactions play a central role in molecular crystal engineering as witnessed by the vast literature on hydrogen-bonded crystals.³⁷

We have recently exploited inter-solid reactions between molecular crystals to prepare hydrogen-bonded adducts of organic and organometallic molecules. For example, crystals of the ferrocenyl dicarboxylic acid complex $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ react with solid nitrogen-containing bases, such as 1,4-diazabicyclo[2.2.2]octane, 1,4-phenylenediamine, piperazine, *trans*-1,4-cyclohexanediamine and guanidinium carbonate, generating quantitatively the corresponding organic–organometallic adducts.³⁸ The case of the adduct $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{NH}][\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ (see Fig. 5) is particularly noteworthy because the same product can be obtained in three different ways: (i) by reaction of solid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ with vapours of 1,4-diazabicyclo[2.2.2]octane (which possesses a small but significant vapour pressure), (ii) by reaction of solid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ with solid 1,4-diazabicyclo[2.2.2]octane, $\text{C}_6\text{H}_{12}\text{N}_2$, i.e. by co-grinding of the two crystalline powders, and by reaction in MeOH solution of the two reactants. The fastest process is the solid–solid reaction. The base can be removed by mild thermal treatment, and the structure of the starting dicarboxylic acid is regenerated. The processes imply breaking and reassembling of hydrogen-bonded networks,

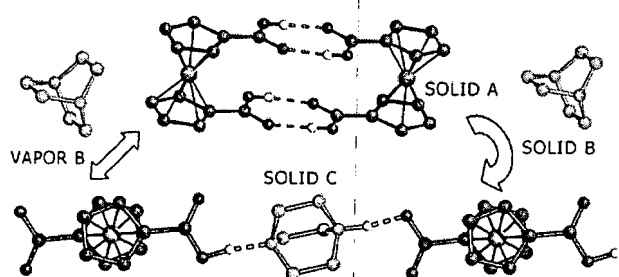


Fig. 5 The solid-vapour and solid-solid reactions involving 1,4-diazabicyclo[2.2.2]octane with formation of a linear chain of hydrogen-bonded $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]^-$ anions and monoprotonated $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{NH}]^+$ cations. (Reprinted from ref. 35a with permission.)

conformational change from *cis* to *trans* of the $-\text{COO}/-\text{COOH}$ groups on the ferrocene diacid, and proton transfer from acid to base.

In the organic chemistry area, the mechanochemical formation of hydrogen-bonded co-crystals between sulfonamide (4-amino-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide) and aromatic carboxylic acids has been investigated by Caira *et al.*³⁹

Mechanical mixing of solid dicarboxylic acids $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ ($n = 1-7$) of variable chain length together with the solid base 1,4-diazabicyclo[2.2.2]octane, $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$, generates the corresponding salts or co-crystals of formula $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{-H}[\text{OOC}(\text{CH}_2)_n\text{COOH}]$ ($n = 1-7$) (see Fig. 6).⁴⁰ The reactions imply transformation of inter-acid $\text{O}-\text{H}\cdots\text{O}$ bonds into hydrogen bonds of the $\text{O}-\text{H}\cdots\text{N}$ type between acid and base. The nature (whether neutral $\text{O}-\text{H}\cdots\text{N}$ or charged $(^-)\text{O}\cdots\text{H}-\text{N}^{(+)}$) of the hydrogen bond was established by means of solid-state NMR measurement.

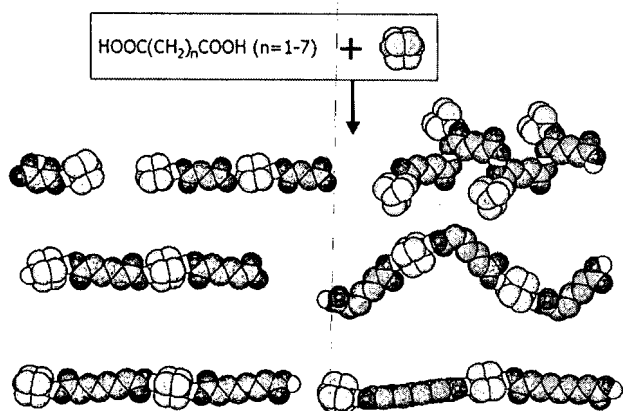


Fig. 6 The reaction of solid dicarboxylic acids $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ ($n = 1-7$) with the solid base 1,4-diazabicyclo[2.2.2]octane, $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$, generates the corresponding salts or co-crystals of formula $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{-H}[\text{OOC}(\text{CH}_2)_n\text{COOH}]$ ($n = 1-7$). The $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds present in the solid acid are replaced by neutral $\text{O}-\text{H}\cdots\text{N}$ and charged $(^-)\text{O}\cdots\text{H}-\text{N}^{(+)}$ interactions, with formation of dimeric units ($n = 1$) or infinite chains ($n = 2-7$) (H_{CH} atoms not shown for clarity).

We have also exploited the great versatility of the organometallic zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]^{41a}$ in the preparation of hybrid organometallic-inorganic salts, by reacting the solid complex with a number of M^+X^- salts ($\text{M}^+ = \text{K}^+, \text{Rb}^+, \text{Cs}^+, \text{NH}_4^+$; $\text{X}^- = \text{Cl}^-, \text{Br}^-, \text{I}^-, \text{PF}_6^-$) and obtaining compounds of general formula $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{M}^+\text{X}^-$.^{41b} In some cases ($\text{M}^+ = \text{Rb}^+, \text{Cs}^+$, $\text{X} = \text{Cl}^-, \text{Br}^-, \text{I}^-$) it has been necessary to resort to *kneading* by adding a few drops of water to the solid mixture in order to obtain the desired product. The polycrystalline products have been characterized by powder- and single crystal-X-ray diffraction as well as by a combination of solution and solid-state NMR methods. This class of compounds is characterized by the presence of a supramolecular cage formed by four zwitterionic molecules encapsulating the alkali or ammonium cations *via* $\text{O}\cdots\text{M}^+$ or $\text{O}\cdots\text{H}-\text{N}$ interactions. The cage is sustained by $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds between carboxylic $-\text{COOH}$ and carboxylate $-\text{COO}^{(-)}$ groups, and by $\text{C}-\text{H}\cdots\text{O}$ bonds between $-\text{CH}_2$ and $-\text{CO}$ groups, while the anions are layered in between the cationic complexes, as shown in Fig. 7 in the case of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{Cs}^+\text{I}^-$. It is fascinating to think of this inter-solid reaction as a sort of sophisticated solid-state “solvation” process of the cations by the organometallic complex.^{41c}

Mechanochemical preparation of coordination networks

Another relevant topic of crystal engineering is the preparation of coordination networks (the literature is growing

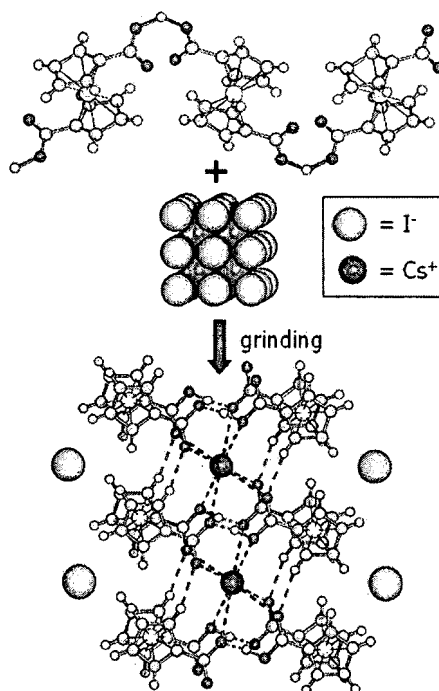


Fig. 7 A pictorial representation of the process leading from $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ and CsI to $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]_2\cdot\text{Cs}^+\text{I}^-$.

exponentially).⁴² In our lab, we have begun to explore the mechanochemical preparation of coordination networks by using bidentate nitrogen bases.⁴³ The coordination polymer $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}]\cdot 5\text{H}_2\text{O}$ has been obtained by co-grinding in the solid state and in the air of silver acetate and $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ in 1:2 ratio (see Fig. 8(a)). The preparation of single crystals of $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}]\cdot 5\text{H}_2\text{O}$ was obviously indispensable for the determination of the exact nature of the co-grinding product. One could thus establish that the coordination network in $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}]\cdot 5\text{H}_2\text{O}$ is based on chains of $\text{Ag}^+\cdots[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\cdots\text{Ag}^+\cdots[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\cdots\text{Ag}^+$, with each silver atom carrying an extra pendant $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ ligand and a coordinated water molecule in tetrahedral coordination geometry. When ZnCl_2 is used instead of AgCH_3COO in the equimolar reaction with $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$, different products are obtained from solution and solid-state reactions, respectively. Fig. 8(b) shows that the structure of $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$, crystallized from solution, is based on a one-dimensional zigzag coordination network constituted of alternating $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ and ZnCl_2 units, joined by Zn–N bonds. Crystals of the product obtained by grinding have not been obtained and the details of this compound remain unknown. However, we have been able to demonstrate that the phase obtained by co-grinding can be transformed into the known anhydrous phase $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$ by prolonged manual grinding.

Other examples of mechanochemical preparation of coordination complexes are known. Steed and Raston and co-workers have explored the use of mechanochemistry in the synthesis of extended supramolecular arrays.⁴⁴ Grinding of $\text{Ni}(\text{NO}_3)_2$ with 1,10-phenanthroline (phen) resulted in the facile preparation of $[\text{Ni}(\text{phen})_3]^{2+}$ accompanied by a dramatic and rapid colour change. Addition of the solid sodium salt of tetrasulfonatocalix[4]arene (tsc) gives two porous π -stacked supramolecular arrays $[\text{Ni}(\text{phen})_3]_2[\text{tsc}^{4-}]\cdot n\text{H}_2\text{O}$ and the related $[\text{Na}(\text{H}_2\text{O})_4(\text{phen})][\text{Ni}(\text{phen})_3]_4[\text{tsc}^{4-}][\text{tsc}^{5-}]\cdot n\text{H}_2\text{O}$ depending on stoichiometry. It has also been reported that the co-grinding of copper(II) acetate hydrate with 1,3-di(4-pyridyl)propane (dpp) gives a gradual colour change from blue to blue-green over *ca.* 15 min. The resulting material was

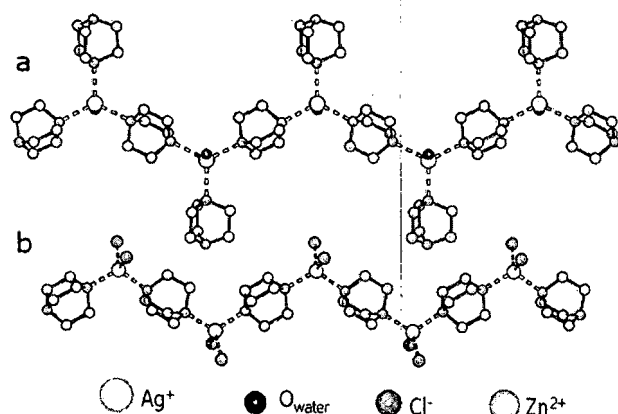


Fig. 8 The coordination network in $\text{Ag}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]_2[\text{CH}_3\text{COO}]\cdot 5\text{H}_2\text{O}$ (a) and in $\text{Zn}[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]\text{Cl}_2$ (b).

shown by solid-state NMR spectroscopy to comprise a 1D coordination polymer with water-filled pores. The same host structure, $[\{\text{Cu}(\text{OAc})_2\}_2(\mu\text{-dpp})]_n$, could be obtained from solution containing methanol, acetic acid or ethylene glycol guest species.⁴⁵

Solid–vapour reactions involving hydrogen-bonded crystals

Solid–vapour reactions are another solvent-free route to new materials. Reactions of this type have been extensively investigated in the organic field and nowadays hundreds of quantitative processes are known.⁴⁶ Applications to organometallic cases are less popular.⁴⁷

We have investigated the reactivity towards vapours of acids and bases of the organometallic zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$, because the presence of one $-\text{COOH}$ group, which can react with bases, and one $-\text{COO}^{(-)}$ group, which can react with acids, confers to this species a useful amphoteric behaviour. The reaction between a solid acid and a basic vapour was first investigated by the Italian scientist Pellizzari as early as in 1884.⁴⁸ In the 1970s Paul and Curtin, beside studying solid–solid reactions, investigated solid–vapour reactions in a series of elegant studies.⁴⁹

The zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ undergoes fully reversible heterogeneous reactions with the hydrated vapours of a variety of acids (*e.g.* HCl ,^{50a} CF_3COOH ,^{50b} HBF_4 ,^{50b}) and bases (*e.g.* NH_3 , NMe_3 , NH_2Me ,^{47a}), with formation of the corresponding salts.⁵⁰ Formation of the salts in the heterogeneous reactions was assessed by comparing observed X-ray powder diffraction patterns with those calculated on the basis of the single-crystal structures determined from crystals obtained from solution. In the case of vapours of aqueous HCl complete conversion of the neutral crystalline zwitterion into the crystalline chloride salt $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$ is attained in few minutes of exposure.^{50a} The polycrystalline product can be converted back to neutral $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ by heating the sample under low pressure (see Fig. 9(a)). The behaviour of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ towards NH_3 is similar: exposure to vapours of wet ammonia quantitatively transforms the neutral complex into the hydrated ammonium salt $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$.^{50a} Absorption of ammonia is also fully reversible: upon thermal treatment the salts convert quantitatively into the neutral zwitterion (see Fig. 9(b)). Analogously $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ reversibly reacts with CF_3COOH ,^{50b} CH_2ClCOOH ,^{50c} CHF_2COOH ,^{50c} HBF_4 and HCOOH ,^{50d} without decomposition or detectable formation of amorphous material. The materials are robust and stable and can be cycled through release/absorption without decomposition. The reactions of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ with HCl and CF_3COOH were also investigated by AFM on single crystals.^{50e}

The adduct with formic acid^{50d} deserves a closer look, because upon crystal formation proton transfer does not take place, and the product $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$ is a co-crystal rather than a salt

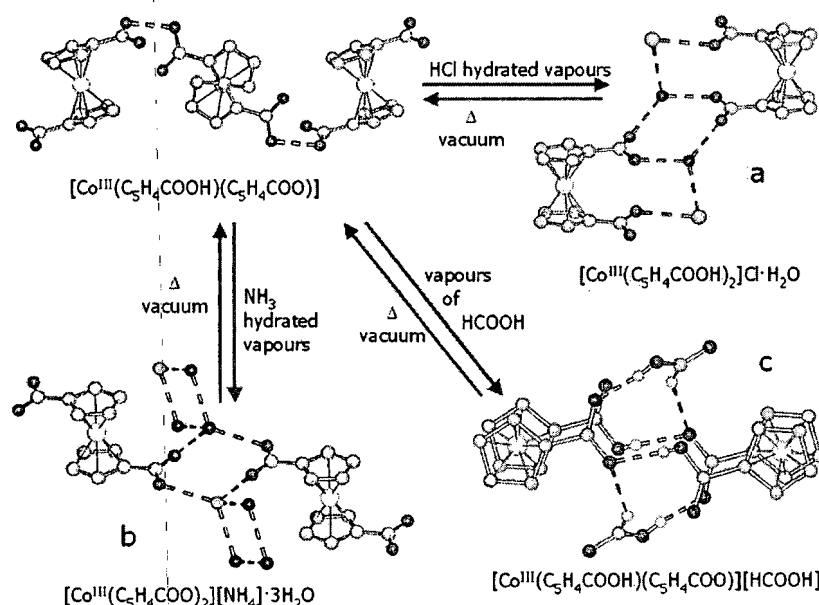


Fig. 9 The reversible reactions between anhydrous $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ and HCl (a), NH_3 (b), and HCOOH (c) leading to formation of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]\text{Cl}\cdot\text{H}_2\text{O}$, $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2][\text{NH}_4]\cdot 3\text{H}_2\text{O}$, and $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})][\text{HCOOH}]$, respectively.

(Fig. 9(c)), as shown by both X-ray and CPMAS NMR spectroscopy.

In summary, the zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ can be said to behave as a solid amphoteric trap towards vapours of both acids and bases. Since the solid–vapour reactions occur with wet vapours, one may be brought to suppose that the reactions occur *via* a process of dissolution and recrystallisation, as the vapours are adsorbed by the crystalline powder. The reverse process, *i.e.* reconstruction of the zwitterion crystals, is more difficult to explain as it implies proton removal from the cationic acid. Moreover, the TGA experiments show that water of hydration is always released first, while the acid and the base come off only subsequently. Hence the participation in the reverse process of an intermediate liquid phase is unlikely.

On closing this section we would like to emphasize that heterogeneous solid–vapour reactions represent an alternative to nanoporosity (*i.e.* to zeolitic behaviour) for the controlled uptake and release of small molecules⁴⁷ and are being actively investigated in the quest for solid-state sensors, reservoirs, filters and sieves for detecting or trapping small molecules.⁵¹

Induced polymorphism and solvate formation

The paradigm of crystal engineering is the possibility of obtaining an ordered and periodical organization of molecules or ions through space from the self-assembly of building blocks (see Fig. 1). The control of the assembly process depends on our capacity of *instructing* molecules or molecular ions how to recognize each other and form stable crystal nuclei, that eventually lead to the desired crystalline material. Clearly, if the instructions are not very precise and/or if other (uncontrolled or less controlled) external factors affect the process, the result can be unpredictable or admit multiple

solutions, *i.e.* serendipitous polymorphism. The problem is further complicated by the possibility of obtaining different solvate forms. One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to *predict* whether a new species may crystallize from solution with one or more molecules of solvent. However, while serendipitous polymorphism and solvate formation are very common (“it happens” to crystallize the same substance as different crystals or solvates), intentional polymorphism is more difficult, as it requires the purposed investigation of the conditions to obtain different crystals for the same species.^{13,52}

Thus far we have provided evidence that the solvent-free reaction of a molecular crystal with a vapour can be exploited to make new crystalline supramolecular aggregates. A useful notion is that the same approach can be used to prepare a new *polymorph* or *solvate*.⁵³ This section of the *Feature Article* will expand on this idea. We will show how mechanical treatment, vapour uptake and release and seeding can all be used to obtain new crystal forms. We will also discuss the useful possibility of obtaining interconversion of crystal forms as a function of pressure and temperature.

We have come across a case of relationship between polymorphism and pseudo-polymorphism during the initial preparation of the zwitterion $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$.^{38a} Single crystals of this molecule could be obtained by *seeding* a water solution obtained by dissolving the trihydrate $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]\cdot 3\text{H}_2\text{O}$ with *seeds* prepared by step-wise dehydration of the hydrated species.^{38b} A thermogravimetric experiment showed that $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]\cdot 3\text{H}_2\text{O}$ reversibly releases one water molecule at 378 K, while the loss of the two remaining water molecules occurs at *ca.* 506 K and is immediately followed by a phase transition. Subsequent

comparison of the calculated and measured powder diffractograms of the anhydrous phase confirms that the powder obtained at 506 K and the single crystals precipitated at room temperature after *seeding* possess the same structure. Importantly, crystallization in the absence of seeds of $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]$ yields the initial trihydrate form $[\text{Co}^{\text{III}}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]\cdot 3\text{H}_2\text{O}$.

In a similar process, crystals of $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2$ can be crystallized from nitromethane as the solvate form $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2\cdot\text{MeNO}_2$. These solvate crystals, if exposed to air, rapidly convert to the unsolvate form $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2$. The nature of this latter compound was established from single crystals obtained from water in the presence of seeds of the powder material obtained from desolvated crystals $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2\cdot\text{MeNO}_2$.⁵⁴

The opposite process, namely solvent uptake, can often be activated by mechanical treatment of unsolvated crystals. There are several reports on that even gentle grinding of a powder product to prepare a sample for powder diffraction may lead to the formation of a hydrated product.⁵⁵ In our lab, we have seen that the hydrated salt $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]^- \cdot \text{H}_2\text{O}$ is obtained by simply grinding in the air the crystalline powder of $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]^-$ that precipitates from THF or nitromethane on reacting $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]$ with $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$.^{56a} Once $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})(\eta^5\text{-C}_5\text{H}_4\text{COO})]^- \cdot \text{H}_2\text{O}$ has been obtained by grinding, its single crystals can be grown from water or nitromethane, while crystals of the anhydrous form are no longer observed. However, on heating, the hydrated form loses water at 373 K and reverts to the starting material.

A related situation has been observed on reacting solid $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ with solid malonic acid $[\text{HOOC}(\text{CH}_2)\text{COOH}]$ in the molar 1:2 ratio.^{56b} Two different crystal forms of the salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{CH}_2)\text{COOH}]_2$ are obtained depending on preparation technique (grinding or solution) and crystallization speed. Form I, containing mono-hydrogen malonate anions forming conventional intramolecular $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds and inter-ionic $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds, is obtained by solid-state co-grinding or by rapid crystallization, while form II, containing *both* intermolecular and intramolecular $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds, is obtained by slow crystallization (see Fig. 10). Form I and II do not interconvert, while form I undergoes an order-disorder phase transition on cooling. One can envisage the two crystalline forms as *hydrogen-bond isomers* of the same solid supermolecule.

Proton transfer along a hydrogen bond poses an interesting question about polymorph definition. In fact, proton mobility along a hydrogen bond (say from $\text{O}-\text{H}\cdots\text{N}$ to $(^-)\text{O}\cdots\text{H}-\text{N}^{(+)}$) may not be associated with a phase transition, even though it implies the formal transformation of a molecular crystal into a molecular salt. This situation has been observed, for instance, for the proton migration along an $\text{O}-\text{H}\cdots\text{O}$ bond in a co-crystal of urea-phosphoric acid (1:1) as a function of temperature.^{57a} Mootz and Wiechert, on the other hand, have isolated two co-crystals of pyridine and formic acid: in the 1:1 co-crystal proton transfer from formic acid to pyridine does not take place, while in the 1:4 co-crystal $\text{N}-\text{H}^{(+)}\cdots\text{O}^{(-)}$

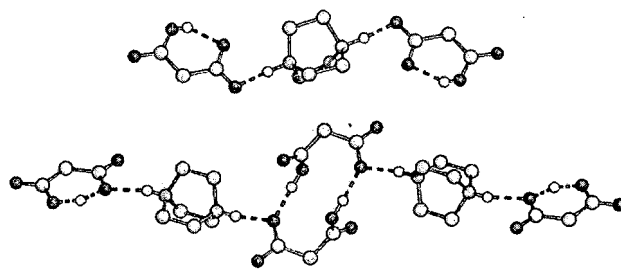


Fig. 10 Form I (top) and II (bottom) of $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{CH}_2)\text{COOH}]_2$ and the hydrogen-bonded anion-cation chains present in their crystals. Form I is obtained by solid-state co-grinding or by rapid crystallization, while form II is obtained by slow crystallization.

interactions are present.^{57b} Examples of this kind are rare, but serve to stress how the phenomenon of polymorphism can be, at times, full of ambiguity.

An intriguing case of interconversion between unsolvate and solvate crystals is observed when $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ is reacted with maleic acid $[\text{HOOC}(\text{HC}=\text{CH})\text{COOH}]$. The initial product is the anhydrous salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]$, which contains chains of $(^+)\text{N}-\text{H}\cdots\text{N}^{(+)}$ bonded cations $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}]^+$ and "isolated" $[\text{OOC}(\text{HC}=\text{CH})\text{COOH}]^-$ anions.⁵⁸ Upon exposure to humidity the anhydrous salt converts within few hours into the hydrated form $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]\cdot 0.25\text{H}_2\text{O}$, which contains more conventional "charge-assisted" $(^+)\text{N}-\text{H}\cdots\text{O}^{(-)}$ hydrogen bonds between anion and cation (see Fig. 11). This latter form can also be obtained by co-grinding.

The two isomorphous crystalline complexes $[\text{M}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ ($\text{M} = \text{Co}, \text{Fe}$) afford a textbook example of an enantiotropic system, *i.e.* of polymorphs that interconvert as a function of temperature.⁵⁹ The room temperature phases of these crystals have been shown, by variable-temperature X-ray diffraction experiments and differential scanning calorimetry (DSC), to undergo two reversible solid-to-solid phase changes

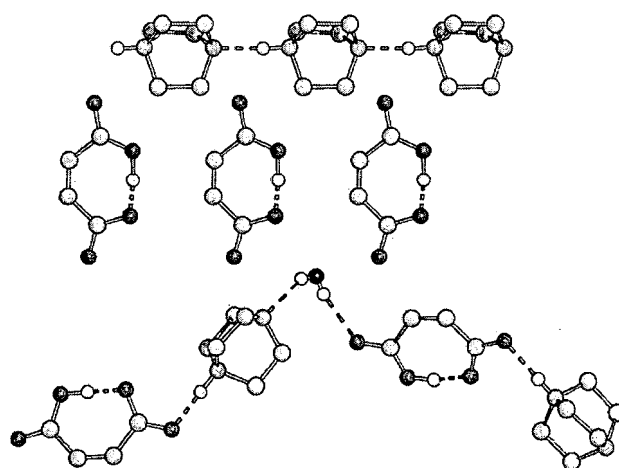


Fig. 11 Views of the packing and hydrogen bonding in the anhydrous salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]$ (top) and of the hydrated salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]\cdot\text{H}_2\text{O}_{0.25}$ (bottom).

towards a low-temperature monoclinic phase and a high-temperature cubic phase, respectively. The only difference between Co and Fe is in the temperatures of the transitions: $M = \text{Fe}$, *ca.* 213.1 and 347.1 K, $M = \text{Co}$, *ca.* 251.8 and 313.9 K measured in the heating cycles, respectively. Therefore, the range of thermal stability of the intermediate phase is *ca.* 62 K in the case of Co and *ca.* 134 K in the case of Fe. The phase transitions could be studied on the single-crystal X-ray diffractometer by collecting data sets on the same crystal specimen. While the room- and low-temperature phases are ordered, the high-temperature phase of $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ contains ordered $[\text{PF}_6]^-$ anions and orientationally disordered $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ cations (see Fig. 12), while, in the case of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$, both cations and anions are disordered.

The close structural similarity between the two complexes $[\text{M}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ ($M = \text{Co, Fe}$) prompted us to explore the possibility of growing crystals from solutions containing mixtures of the two cations. We have discovered that, in the solid state, the two cations are fully miscible in the whole range of composition and that the composition is the same as that of the water solutions from which the mixed-crystals are precipitated, *e.g.* the mixed salts can be formulated as $[\text{Co}_x\text{Fe}_{1-x}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ (with $0 < x < 1$).⁶⁰ Moreover, the phase transition behaviour depends linearly on the composition (see Fig. 12). The temperatures at which the two solid-to-solid phase transitions occur vary regularly, as a direct function of the molar ratio, between the two extremes defined by the homo-cationic crystals.

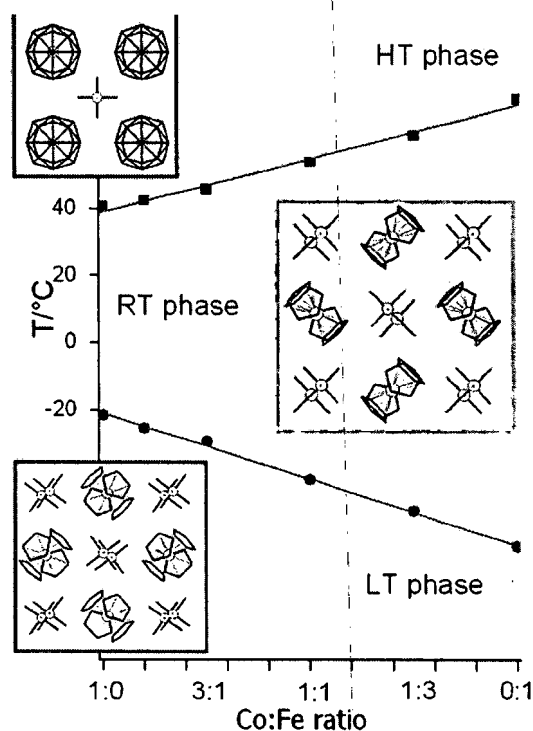


Fig. 12 Schematic representation of the relationship between the three structures of crystalline $[\text{M}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ ($M = \text{Co, Fe}$) and the dependence of the phase transition temperatures on the alloy composition, when $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ and $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ are co-crystallized to give $[\text{Co}_x\text{Fe}_{1-x}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ (with $0 < x < 1$).

The close structural similarity between the two complexes $[\text{M}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ ($M = \text{Co, Fe}$) prompted us to explore the possibility of growing crystals from solutions containing mixtures of the two cations. The resulting mixed salts $[\text{Co}_x\text{Fe}_{1-x}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ (with $0 < x < 1$) show that the two cations are fully miscible in the whole range of composition and that the composition is the same as that of the water solutions from which the mixed-crystals are precipitated. Moreover, the phase transition behaviour depends linearly on the composition, *i.e.* the temperatures at which the two solid-to-solid phase transitions can be selected by choosing the molar ratio in solution. Thus, the mixed-crystal $[\text{Co}_x\text{Fe}_{1-x}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$, though composed of molecular ions and soluble in water, possesses the features of an alloy of the A_xB_{1-x} type.

The seeding procedure can also be exploited to attempt crystallization of unyielding materials if seeds of isostructural or quasi-isostructural species that crystallise well are available.⁶¹ This sort of heteromolecular seeding has been instrumental to the separation of two concomitant polymorphs.⁶² Precipitation of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2]^+$ as its $[\text{AsF}_6]^-$ salt generates two concomitant crystal phases: a trigonal phase (Fe-T) and a monoclinic phase (Fe-M). In order to separate the two polymorphs two solutions were seeded with crystals of the trigonal phase of $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2][\text{AsF}_6]$ and of the monoclinic phase of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$, yielding the corresponding trigonal and monoclinic forms of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{AsF}_6]$, respectively. The seeding was successful and yielded good quality single crystals of Fe-T and Fe-M (see Fig. 13), which proved to be sufficiently robust to undergo a full cycle of four phase transitions directly on the diffractometer, (Fe-T $\rightarrow$ Fe-M $\rightarrow$ Fe-C (cubic phase) $\rightarrow$ Fe-M $\rightarrow$ Fe-T), a rather uncommon situation that permitted a whole rationalization of the phase transitional behaviour.

On closing the section devoted to polymorphism, we ought to point out that the ongoing intensive research on coordination network crystal engineering is opening new avenues to the investigation of polymorphs and solvates. As a matter of fact the same divergent ligand may yield topologically different coordination networks with the same metal, which will have

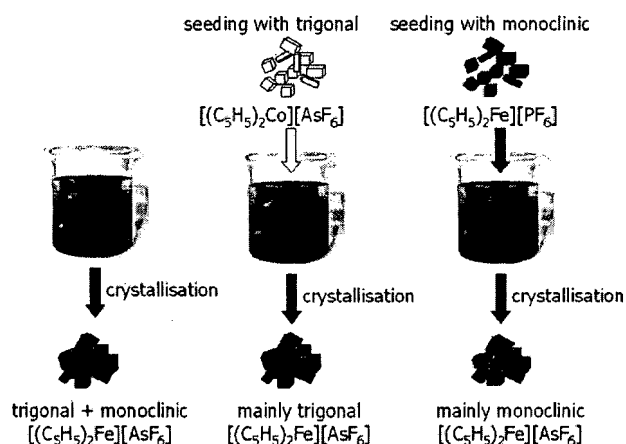


Fig. 13 The seeding procedure where crystals of trigonal $[\text{Co}(\eta^5\text{-C}_5\text{H}_5)_2][\text{AsF}_6]$ were used to grow the trigonal form of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{AsF}_6]$, while crystals of monoclinic $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{PF}_6]$ were used to obtain the monoclinic form of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_5)_2][\text{AsF}_6]$.

the same composition but different architecture (polymorphs or supramolecular isomers?). Moreover, the same network can co-crystallize with a different number and type of molecules in the voids and channels, and these molecules can be desorbed or substituted often without network destruction or reconstruction.⁶³ Solvent and/or guest dependent topological isomerism in coordination polymers has been recently reviewed.^{4a}

Concluding remarks

In this *Feature Article* we have shown that “crystals can be made from crystals” by mechanical mixing of molecular and ionic crystals and by reacting crystals and vapours in solvent-free conditions. This awareness is useful in crystal engineering not only because it provides alternative routes to the synthesis of new crystalline materials but also because it can be exploited to obtain different forms of a given substance, *e.g.* crystal polymorphs or solvates. Polymorphism, with its high degree of serendipity, contrasts the ideas of control and reproducibility dear to the crystal engineer. Hence, for both scientific and utilitarian reasons, any step forward towards a higher degree of control of polymorphism and solvate formation is useful.

Solid–solid and solid–vapour reactions have been the subject of investigation for decades in the fields of organic and of inorganic chemistry and are commonly used in industrial processes. In spite of this, or – perhaps – because of this, these processes are not very popular in the field of organometallic and coordination chemistry. Clearly, the control on solid-state reactions, that can be used to trap environmentally dangerous or poisonous molecules, is an attractive goal for solid-state chemistry and crystal engineering. For instance, one may purposefully plan to assemble molecules that are capable of absorbing molecules from the gas phase and, possibly, to react with them. This implies *sensing* and could be exploited to detect molecules if there is a measurable response from the solid state. If the reaction is quantitative and reversible, the same processes (whether based on weak non-covalent bonding or on some type of covalent/ionic, high enthalpy, process) can be used to trap gases and deliver them where appropriate.

Since the solid–solid and solid–vapour reactions described in this article involve formation or disruption of non-covalent interactions, they can be looked at as *supramolecular reactions* between a two periodical supermolecules (crystals) or between a periodical supermolecule and a molecule in the gas phase. The concept can be stretched to encompass also solvation/desolvation processes, because the uptake/loss of solvent molecules requires supramolecular bond breaking and forming, as for the formation of a co-crystal or a supramolecular adduct.

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Crystal Polymorphism and Multiple Crystal Forms

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Abstract This chapter discusses the phenomenon of polymorphism in organic and organometallic compounds. Polymorphism is first introduced and then, to give the work some context, background information is given concerning properties and techniques for characterizing the solid phases. In particular, desolvation and interconversion are examined, and the gas–solid reactions are presented as a successful route to obtaining new crystalline phases. Co-crystal definition is then described and the problem in distinguishing co-crystals and salts is evaluated.

Keywords: Co-crystal · Hydrogen bond · Organic salt · Polymorphism · Solid-gas reaction · Solid-state NMR · Solvate · X-ray diffraction

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1 Introduction

The isolation, identification and characterization of different crystal forms (polymorphs, solvates, salts and co-crystals) of the same molecule or of aggregates of the same molecule with other molecules represents one of the most active areas of modern solid state chemistry. The investigation of crystal forms impacts on fundamental science as well as on utilitarian objectives because different crystal forms may display a range of different physico-chemical properties, which may affect application and utilization of the solid materials.

Polymorphism [1] is one of the most fascinating phenomena of solid state chemistry and indeed is a "difficult" phenomenon, studied for many decades mainly, and separately, in the fields of organic and inorganic chemistry. In spite of the huge efforts of many researchers our knowledge of the phenomenon is still embryonic, and the relationship between growth of a crystalline phase and nucleation of the first crystallites is often mysterious. It is a fact that, despite the ambitions of the scientist, crystal construction is not yet strictly under human control. Many examples exist of *appearing* and *disappearing* polymorphs, some of which have had great practical consequences. The reader is addressed to the review by Dunitz and Bernstein for a number of intriguing examples [2].

2 Definition of Crystal Forms

Although the existence of three different crystal forms of calcium carbonate (calcite, vaterite and aragonite) was identified by Klaproth in 1788 [3], formal recognition of the phenomenon of *crystal polymorphism* is attributed to the work of Mitscherlich in 1823 [4]. In more general terms, the solid phase of a material, whether formed of organic molecules, inorganic ions or extended covalent networks, can exhibit different structures which, although possessing the same chemical composition, may manifest different properties. In addition to these polymorphic modifications the material may also lack long-range order and appear as an amorphous solid, which can be considered as another polymorph.

A number of authors have suggested that polymorphism is ubiquitous in crystal chemistry. McCrone stated long ago that: "...every compound has different polymorphic forms" and that, "...in general, the number of forms known for a given compound is proportional to the time and energy spent in research on that compound" [5]. In 1951 Findlay noted in his book that polymorphism: "...is now recognized as a very frequent occurrence indeed" [6]. Buerger and Bloom stated: "...polymorphism is an inherent property of the solid state and it fails to appear only under special conditions" [7]. Similarly, Sirota wrote in 1982: "Polymorphism is now believed to be characteristic of all substances, its actual non-occurrence arising from the fact that a polymorphic transition lies above the melting point of the substance or in the area of as yet unattainable values of external equilibrium factor or other conditions providing for the transition" [8].

In 1965 Kuhnert-Brandstätter investigated by hot stage microscopy three common classes of drug: 70% of barbiturates, 60% of sulphonamides and 23% of steroids exist in various polymorphic or solvate forms [9, 10].

A number of statistical estimates of the extent of polymorphism have also been carried out. A search of the Cambridge Structural Database on the keywords “polymorph”, “form”, “modification” and “phase” indicated that about 3.5% of the ~350,000 entries fall into this category. Approximately 25% of the entries are either solvates or hydrates. Other studies based on different selection criteria reveal a much larger occurrence [11–13]. For instance, Griesser and Burger have collected information on about 600 polymorphic forms and solvates (including hydrates) of pharmaceutical compounds that are solid at 25°C [14].

Even though crystal forms have been and are the subject of intense investigations, polymorphism as a *phenomenon* still represents a substantial scientific challenge. Indeed it is hard to predict whether a given molecule will crystallize in one or several crystal forms, whether it will form solvates with different stoichiometries or will ever be “happy” to link up with other molecules and form stable co-crystals. Such variability and unpredictability have been taken by some scientists as an intrinsic drawback of being able to construct desired crystal structures (and obtain relevant properties) from a purposeful choice of the molecular components, which is the paradigm of molecular crystal engineering [15–19].

In recent times the concept of crystal polymorphism has expanded beyond its original boundaries to encompass crystal forms of the same molecule with different molecular partners. These may be solvent molecules in solvates [20], or counterions if the molecule can be made non-neutral (by say proton or electron transfer [21]), or other molecules in co-crystals [22]. It is worth noting that the formation of solvate and hydrated forms is commonly observed during polymorph screening, therefore the use of the term “pseudopolymorphism” to describe solvate forms of a given molecular crystal ought to be discouraged, at least because solvates may, in turn, be polymorphic [23–25].

In this paper we shall discuss all four different types of crystal forms of the same molecule: polymorphs of the mere molecule, solvates and hydrates, molecular salts and co-crystals (when the same molecule can be co-crystallized with different co-crystal formers). All these crystal forms are summarized in Fig. 1.

3 Properties of Crystal Forms

From thermodynamic principles, under specified conditions only one polymorph is the stable form (except at a transition point) [26]. In practice, however, due to kinetic considerations, metastable forms can exist or coexist in the presence of more stable forms. The relative stability of the various crystal forms and the possibility of interconversion between crystal forms, between crystals with different degree of solvation, and between an amorphous phase and a crystalline phase can have very

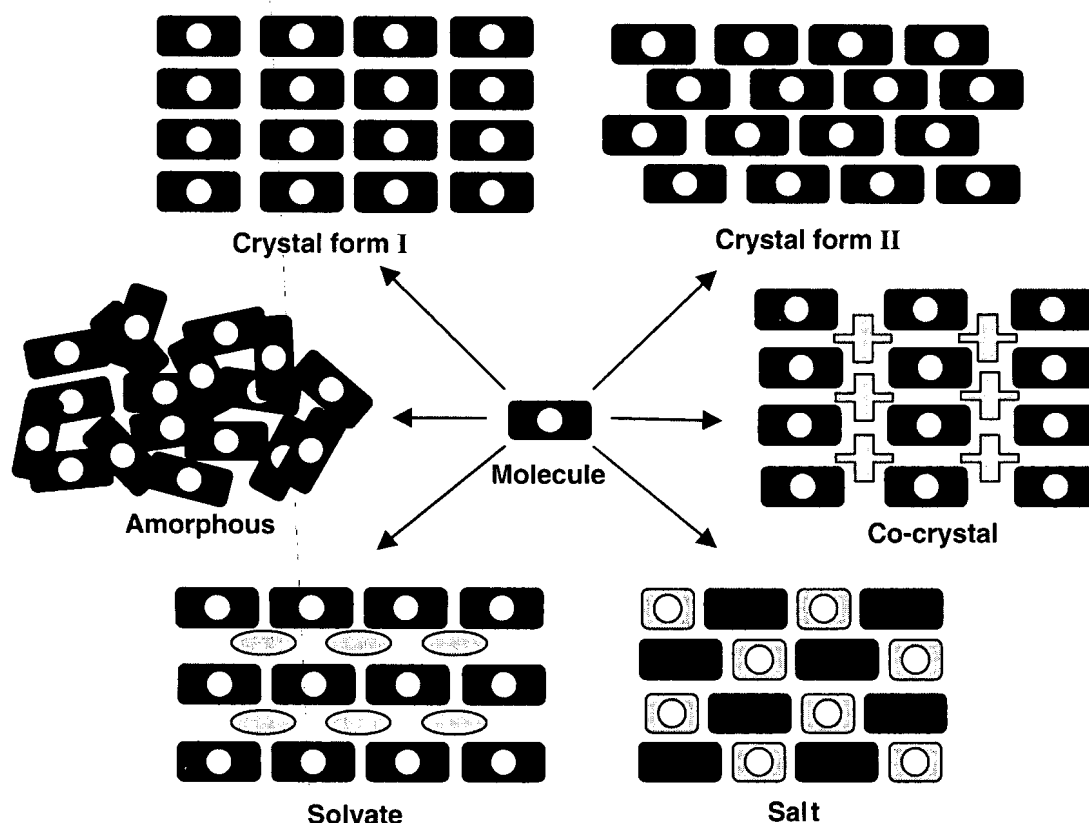


Fig. 1 Schematic representation of the structural relationship between “true” polymorphs, solvates, co-crystals, salts and the amorphous phase

serious consequences on the life and effectiveness of a polymorphic product and the persistence over time of the desired properties. The variety of phenomena related to polymorphism requires a thorough mapping of the “crystal space” of a substance that is ultimately intended for some specific applications (e.g. drugs, pigments, agrochemicals and food additives, explosives, etc.).

The industrial production and marketing lines need to know not only the exact nature of the material in the process, but also its stability with time, the variability of its chemical and physical properties as a function of the crystal form, etc. The search for and characterization of crystal forms is therefore a crucial step in the development of a new chemicals with relevant consequences on intellectual property issues [1, 27–29].

Different crystal forms are often recognized by differences in the colour and shape of crystals. A striking example of these two properties is provided by the differences in colour and form of the crystal forms of ROY (ROY = red, orange, yellow polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophene carbonitrile) [30, 31]. Colour and shape are only some of the possible differences and Table 1 summarizes some major possible differences in chemical and physical properties between crystal forms and solvates of the same substance. In addition, one has to consider that new and different properties may derive from a change in the nature and chemical composition of the same molecule as a consequence of salt formation or co-crystallization. For each new crystal form obtained, a full characterization

PHYSICAL AND THERMODYNAMIC PROPERTIES	density and refractive index, thermal and electrical conductivity, hygroscopicity, melting points, free energy and chemical potential, heat capacity, vapor pressure, solubility, thermal stability
SPECTROSCOPIC PROPERTIES	electronic, vibrational and rotational properties, nuclear magnetic resonance spectral features
KINETIC PROPERTIES	rate of dissolution, kinetics of solid state reactions, stability
SURFACE PROPERTIES	surface free energy, crystal habit, surface area, particle size distribution
MECHANICAL PROPERTIES	hardness, compression, thermal expansion
CHEMICAL PROPERTIES	chemical and photochemical reactivity

Fig. 2 Examples of chemical and physical properties that can differ among crystal forms and solvates of the same substance

should be done since the new form can have different properties, such as higher solubility or higher melting point (Fig. 2).

4 Characterization of Multiple Crystal Forms

The exploration of the “crystal form space” of a substance is the search of polymorphs and solvates in order to identify the most stable form and the existence of unstable forms that interconvert (enantiotropism) or do not (monotropism) as a function of the temperature. This also applies to amorphous and solvate forms. The relationships between the various phases and commonly used industrial and research laboratory processes are schematically illustrated in Fig. 3.

It is worth stressing that polymorph assessment in industrial research and development as well as during processing is part of the system of quality control. Therefore it is necessary to make sure that the scale-up from laboratory preparation to industrial production does not introduce variations in crystal form. Polymorph assessment also guarantees that the product conforms to the guidelines of the appropriate regulatory agencies and does not infringe the intellectual property protection that may cover other crystal forms [32].

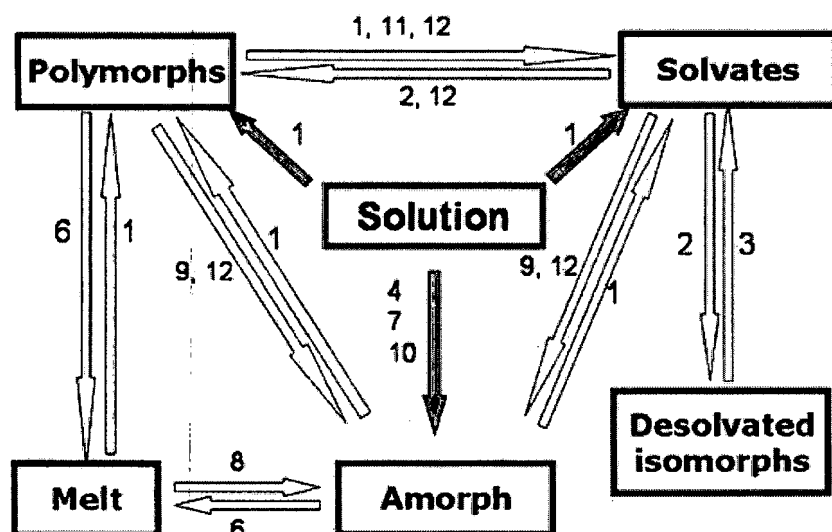


Fig. 3 Some general relationships between polymorphs, solvates and amorphous phases and the type of research laboratory or industrial or process for preparation and interconversion: 1 crystallization; 2 desolvation; 3 exposure to solvent/vapour uptake; 4 freeze drying; 5 heating; 6 melting; 7 precipitation; 8 quench cooling; 9 milling; 10 spray drying; 11 kneading; 12 wet granulation. Analogous relationships apply to polymorphic modifications of solvate forms. Note that the figure represents general trends rather than every possible transformation; the presence or absence of an arrow or number does not represent the exclusive existence or absence of a transformation

The screening of crystal forms is best achieved by the combined use of several solid-state techniques, such as hot stage microscopy, differential scanning calorimetry, thermogravimetric analysis and X-ray diffraction. Powerful complementary tools are also provided by solid-state spectroscopic techniques such as solid state nuclear magnetic resonance spectroscopy [33] and Raman spectroscopy [1]. Of great relevance is the possibility of determining the molecular and crystal structure of a crystal form by means of single crystal X-ray diffraction. This technique, although much more demanding than powder diffraction in terms of experiment duration and data processing, has the great advantage of providing detailed structural information on the molecular geometry. Furthermore, it affords insight into the factors controlling the packing of the molecules in the crystal and the nature and structural role of solvent molecules. Knowledge of the single-crystal structure allows a direct comparison between the X-ray powder diffraction pattern, calculated on the basis of the structure, with the one measured on the polycrystalline sample as it will be diffusely used in the following description of specific cases.

Importantly, the calculated diffraction pattern is not affected by the typical sources of errors of experimental powder diffraction (preferential orientation, mixtures, presence of amorphous phase) that often complicate or render uncertain the interpretation of measured powder diffractograms; hence the calculated powder pattern is often referred to as the “gold standard” pattern for a crystal form.

The search for various crystal forms requires that the behaviour of a solid phase is investigated as a function of the variables that can influence or determine the outcome of the crystallization process, e.g. temperature, choice of solvents,

crystallization conditions, rate of precipitation, interconversion between solid forms (from solvate to un-solvate and vice versa), pressure and mechanical treatment, absorption and release of vapour, etc. [24]. Techniques such as hot stage microscopy, DSC and micro-DSC can be used to obtain a semiempirical energy–temperature diagram [34, 35] that can be helpful in designing protocols for screening for crystal forms.

Another powerful tool for the investigation of the structural relationship between crystal forms is variable temperature X-ray diffraction that provides information on phase transitions and on adsorption/desorption of solvent molecules (and chemical reactivity, of course, but this is of less concern in this context).

Beside the traditional thermal and solution methods for obtaining new crystal forms, many other methods are being used or developed in the quest for multiple crystal forms. Some of these methods are based on the knowledge of crystal structures in the literature [16], the application of crystal engineering principles (based on hydrogen-bonding patterns) to the preparation of new multicomponent solids [36,37], the induction of crystal forms by using polymeric substrates [38], the development of high-throughput crystallization technology [39], the utilization of solid–solid and solid–gas reactions [40], solvent-free synthesis [41,42], the desolvation of solvated crystals [43] and crystallization from a supercritical solvent [44,45]. These methods, combined with the development of new technology [39], the attempts to design and control crystal structure [46], combined with some spectacular encounters with new (and undesired) crystal forms [47] (see Sect. 5) and some high profile pharmaceutical patent litigations [1], have led to many new techniques for exploring the crystal form space of any particular substance.

5 Examples of Crystal Form Identification and Characterization

There is no protocol of polymorph screening that can guarantee the identification of *all* crystal forms of a given molecule. As pointed out in the previous section, the understanding of a system exhibiting multiple crystal forms is best achieved by studying the system with a wide variety of analytical tools. We have chosen to illustrate this aspect by means of two recent examples coming from our own work.

The first example is that of cinchomeric acid, which has been known for almost a century [48]. The cinchomeric acid 3,4-dicarboxypyridine is one of the six isomers of the acid pyridinedicarboxyl; all isomers are widely utilized in the construction of coordination networks [49–51]. The presence of two of cinchomeric forms is reported in the PDF-2 [52], while the crystal structure has been determined only for one form [53]. We have investigated the structural relationship between these two crystal forms by a combined use of single-crystal X-ray diffraction, IR and Raman spectroscopy, and solid state NMR spectroscopy [54]. Form I crystallizes in an acentric orthorhombic group, while form II crystallizes in a centric monoclinic group (Fig. 4), due to a static disorder for the nitrogen position (Fig. 5). The zwitterionic nature of the acid in both forms has been confirmed by ^1H MAS,

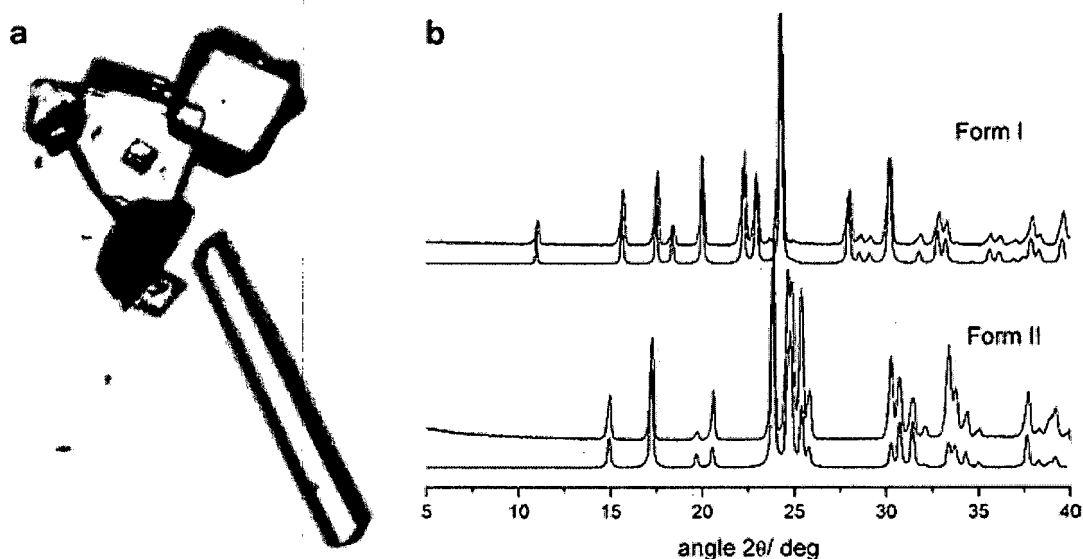


Fig. 4 Concomitant polymorphs obtained from an ethanol/water solution: *rods* form I, *blocks* form II **a** Comparison between the experimental and calculated powder diffractograms of form I and form II **b**

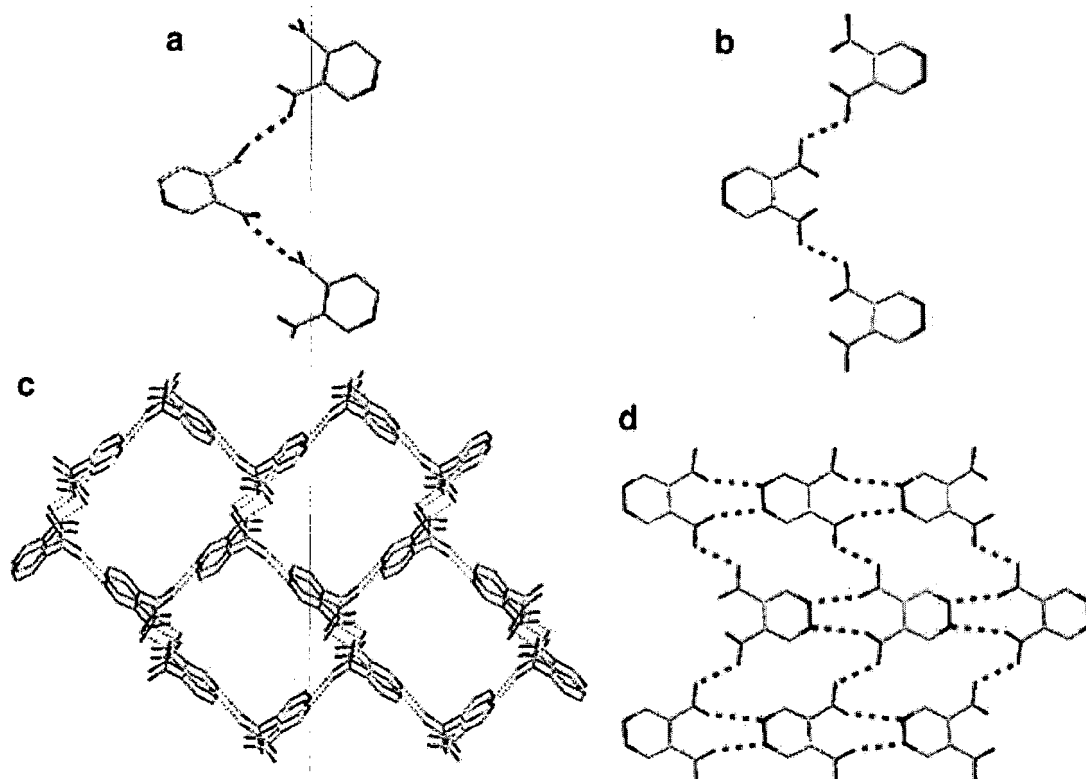


Fig. 5 Chains present in form I **a** and form II **b**; the adamantoid network formed by N-H $\cdots$ O— hydrogen bonds among the chains and the overall crystal structure formed by the three interpenetrating networks in form I **c**; interactions N-H $\cdots$ O— and C-H $\cdots$ O— among the chains and the 2D-network present in form II **d**

^{13}C CPMAS and ^{15}N CPMAS (Fig. 6). The single crystal structures give us a view of the hydrogen bonds formed by the molecule of cinchomeronic acid in the solid state; in both structures the molecules of cinchomeronic acid form infinite chains via

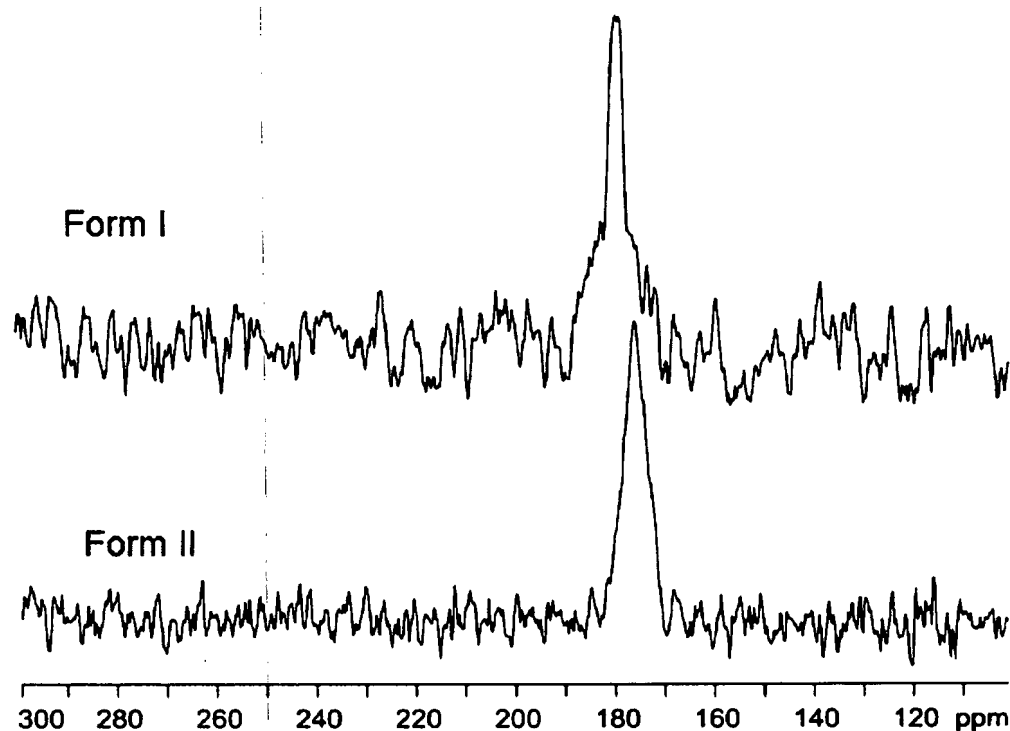


Fig. 6 ^{15}N CPMAS spectra of cinchomeronic acid: form I (*top*) and form II (*bottom*) recorded at 27.2 MHz with a spinning speed of 5 kHz which confirm the zwitterionic nature of cinchomeronic acid in both crystal phases

short O—H—O hydrogen bonds between the carboxylic and carboxylate groups (see Fig. 5). In form I the zwitterion chains are ordered and are connected via N—H—O interactions to form a threefold interpenetrating networks. In form II, on the other hand, the presence of static disorder leads to crystallographic equivalence between the $-\text{COO}$ and $-\text{COOH}$ groups (see Fig. 5) and the nitrogen atom is disordered over two positions, which leads to a longer and weaker N—H—O hydrogen bond consistent with the IR and Raman spectra. Both forms decompose before melting without any interconversion, which suggests the presence of a monotropic system, while the slurry experiment indicates that form I is the thermodynamically stable form. The crystal structure and spectroscopic analysis indicate that the difference in stability can be ascribed to the strength of the hydrogen bonding patterns established by the protonated N-atom and the carboxylic/carboxylate O-atoms. The possibility of optimizing the hydrogen bond interaction in form I, with respect to the somewhat *looser* interactions allowed by the packing in form II might be responsible for the stabilization of the crystal structure of form I.

Another example is provided by the two different crystal forms of the salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{NH}] [\text{OOC}(\text{CH}_2)_2\text{COOH}]_2$ obtained depending on preparation technique (grinding or solution) and crystallization speed. Form I, containing mono-hydrogen malonate anions forming conventional intramolecular O—H $\cdots$ O hydrogen bonds and inter-ionic N—H $\cdots$ O hydrogen bonds, is obtained by solid-state co-grinding or by rapid crystallization, while form II, containing *both* intermolecular and intramolecular O—H $\cdots$ O hydrogen bonds, is obtained by slow crystallization

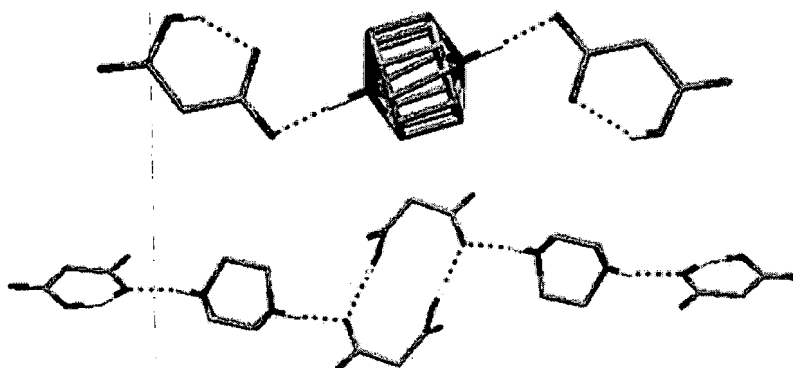


Fig. 7 Form I (*top*) and II (*bottom*) of $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{NH}][\text{OOC}(\text{CH}_2)\text{COOH}]_2$ and the hydrogen bonded anion $\cdots$ cation chains present in their crystals. Form I is obtained by solid-state co-grinding or by rapid crystallization, while form II is obtained by slow crystallization

(see Fig. 7). Form I and II do not interconvert, while form I undergoes an order-disorder phase transition on cooling. One can envisage the two crystalline forms as *hydrogen bond isomers* of the same *solid supermolecule* [55].

6 Examples of Solvate Crystal Forms and Interconversion

An intriguing case of interconversion between unsolvate and solvate crystals is observed when $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ is reacted with maleic acid $[\text{HOOC}(\text{HC}=\text{CH})\text{COOH}]$. The initial product is the anhydrous salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]$, which contains chains of $(^+)\text{N}-\text{H}\cdots\text{N}^{(+)}$ bonded cations $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}]^+$ and “isolated” $[\text{OOC}(\text{HC}=\text{CH})\text{COOH}]^-$ anions [56].

Upon exposure to humidity the anhydrous salt converts within few hours into the hydrated form $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}] \cdot 0.25\text{H}_2\text{O}$, which contains more conventional “charge-assisted” $(^+)\text{N}-\text{H}\cdots\text{O}^{(-)}$ hydrogen bonds between anion and cation (see Fig. 8). This latter form can also be obtained by co-grinding.

In a similar process, crystals of $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2$ have been crystallized from nitromethane as the solvate form $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2 \cdot \text{MeNO}_2$. These solvate crystals, if exposed to air, rapidly convert to the unsolvate form $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2$. The nature of this latter compound was established from single crystals obtained from water in the presence of seeds of the powder material obtained from desolvated crystals $[\text{Ru}(\eta^6\text{-C}_6\text{H}_6)_2][\text{BF}_4]_2 \cdot \text{MeNO}_2$ [57]. The opposite process, namely solvent uptake, can often be activated by mechanical treatment of unsolvate crystals. There are several reports that even gentle grinding of a powder product may lead to the formation of a hydrated product [58–60].

Another example is provided by the hydrated salt $[\text{Co}(\eta_5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}(\eta_5\text{-C}_5\text{H}_4\text{COOH})(\eta_5\text{-C}_5\text{H}_4\text{COO})]^- \cdot \text{H}_2\text{O}$, which is obtained by simply grinding in air the crystalline powder of $[\text{Co}(\eta_5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}(\eta_5\text{-C}_5\text{H}_4\text{COOH})(\eta_5\text{-C}_5\text{H}_4\text{COO})]^-$ that precipitates from THF or nitromethane on reacting $[\text{Co}(\eta_5\text{-C}_5\text{H}_5)_2]$ with $[\text{Fe}(\eta_5\text{-C}_5\text{H}_4\text{COOH})_2]$ [61]. Once $[\text{Co}(\eta_5\text{-C}_5\text{H}_5)_2]^+[\text{Fe}$

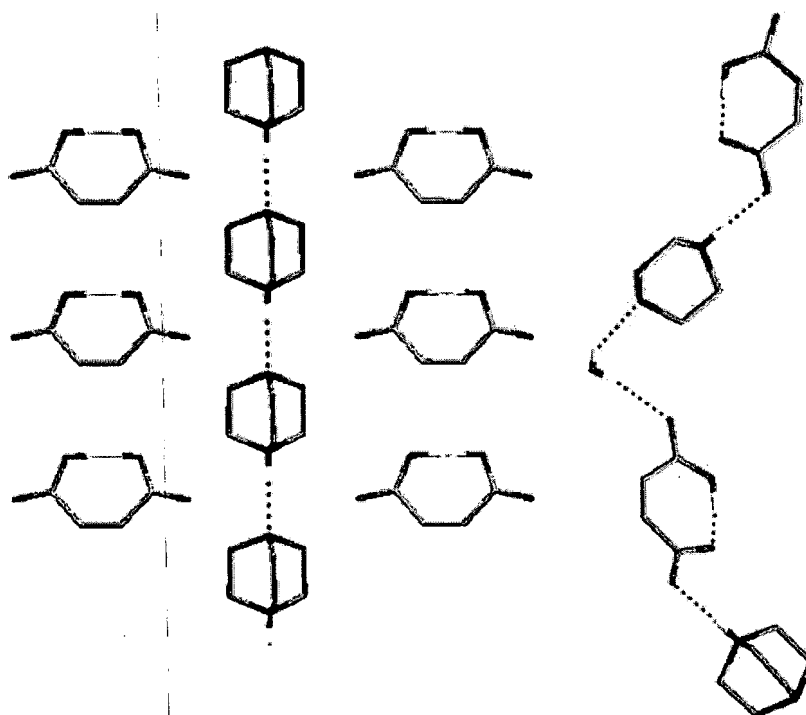


Fig. 8 Views of the packing and hydrogen bonding in the anhydrous salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]$ (left) and of the hydrated salt $[\text{HN}(\text{CH}_2\text{CH}_2)_3\text{N}][\text{OOC}(\text{HC}=\text{CH})\text{COOH}]\cdot\text{H}_2\text{O}_{0.25}$ (right)

$(\eta_5\text{-C}_5\text{H}_4\text{COOH})(\eta_5\text{-C}_5\text{H}_4\text{COO})^- \cdot \text{H}_2\text{O}$ has been obtained by grinding, its single crystals can be grown from water or nitromethane, while crystals of the anhydrous form are no longer observed. However, on heating, the hydrated form loses water at 373 K and reverts to the starting material.

7 Solid–Gas Reactions: A Route to New Crystal Forms

Solid–gas reactions have been known for a long time and have recently attracted a renewed interest in the strive to find environmentally friendly processes. Since the reactant is a crystalline solid, the issue of whether different crystal forms would react in the same or a different way towards a gaseous reactant is of interest to the discussion. We have tackled this question by exploiting solid–gas reactions between crystal polymorphs of the same acidic substance and vapours of volatile bases, investigating in turn the inverse process, i.e. removal of the vapours from the crystal structures by thermal treatment.

The possibility of different chemical behaviour of polymorphic modifications has been explored before only in the case of indomethacin amorphous and crystal forms reacted with ammonia by Stowell, Griesser, Byrn et al. [62]. We have investigated two rather different systems, namely the polymorphic forms of barbituric acid [63] and of ferrocene dicarboxylic acids [64], which have been reacted with

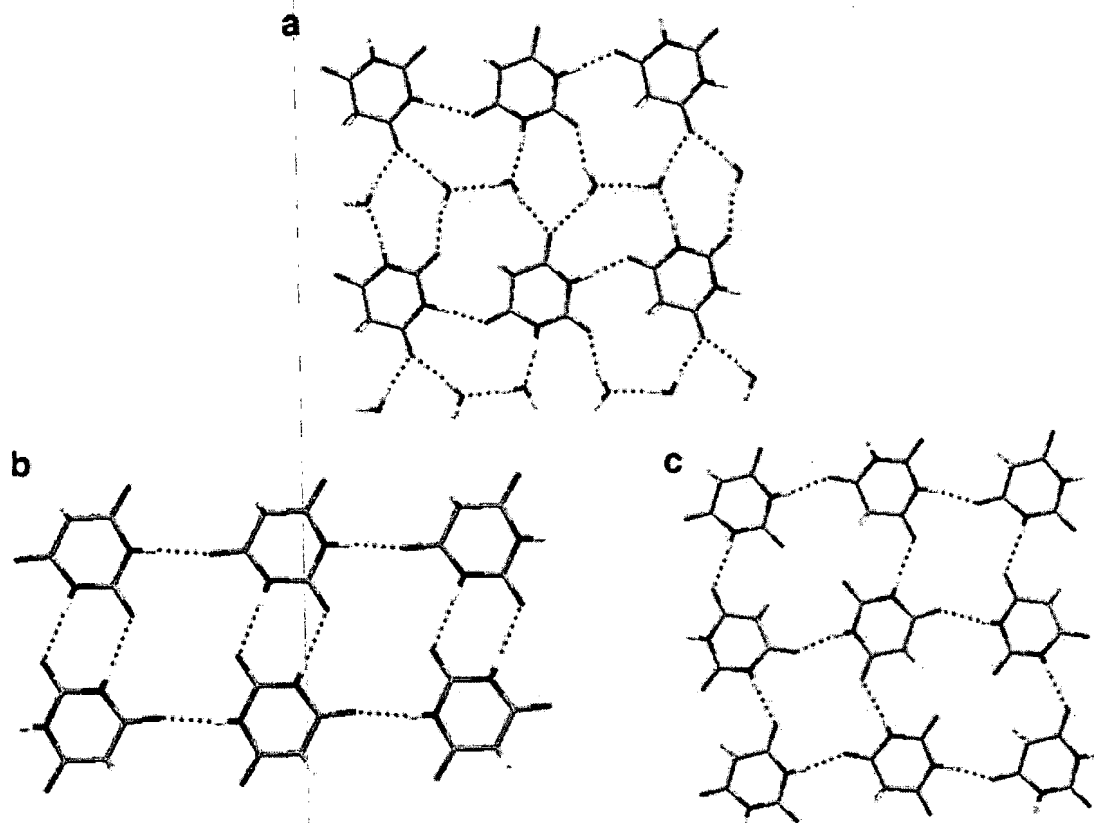


Fig. 9 Hydrogen bond networks present in the dihydrate form a, form I b and form II c of barbituric acid

volatile bases. Solid barbituric acid is known as two polymorphic forms (forms I and II) and as a dihydrate form for which single crystal data are available allowing computation of the theoretical powder diffractograms [65–68]. Views of the packings of the three forms are shown in Fig. 9. De-hydration of the dihydrate form has also been investigated, showing that it releases water to yield exclusively crystals of form II. We have been able to show that forms I, II and the dihydrate form of barbituric acid react with ammonia leading to the same crystalline ammonium barbiturate salt $\text{NH}_4(\text{C}_4\text{H}_3\text{N}_2\text{O}_3)$, while the gas–solid reactions of form II with methylamine and dimethylamine yield the corresponding crystalline salts $\text{CH}_3\text{NH}_3(\text{C}_4\text{H}_3\text{N}_2\text{O}_3)$ and $(\text{CH}_3)_2\text{NH}_2(\text{C}_4\text{H}_3\text{N}_2\text{O}_3)$, respectively. The processes are shown in Fig. 10.

Thermal desorption of the bases at ca. 200°C leads to formation of a new crystal form of barbituric acid, form III, as confirmed by ^1H -NMR spectroscopy and by chemical behaviour. Unfortunately several attempts to crystallize compound III yielded only the formation of the dihydrate form (Fig. 11).

Similarly, the reactions between solid 1–3 dimethylbarbituric acid (dmb) with vapours of NH_3 and of the volatile amines $\text{NH}_2(\text{CH}_3)$, and $\text{NH}(\text{CH}_3)_2$ have been investigated [69]. The barbiturate salts $[\text{NH}_4]\text{dmb}$, $[\text{NH}_3(\text{CH}_3)]\text{dmb}$ and $[\text{NH}_2(\text{CH}_3)_2]\text{dmb}$ have been characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry and thermogravimetric analysis. The solid–gas reactions were monitored by UV–Vis spectroscopy in the solid state. In the case of $[\text{NH}_2(\text{CH}_3)_2]\text{dmb}$, recrystallization from methanol yields the salt

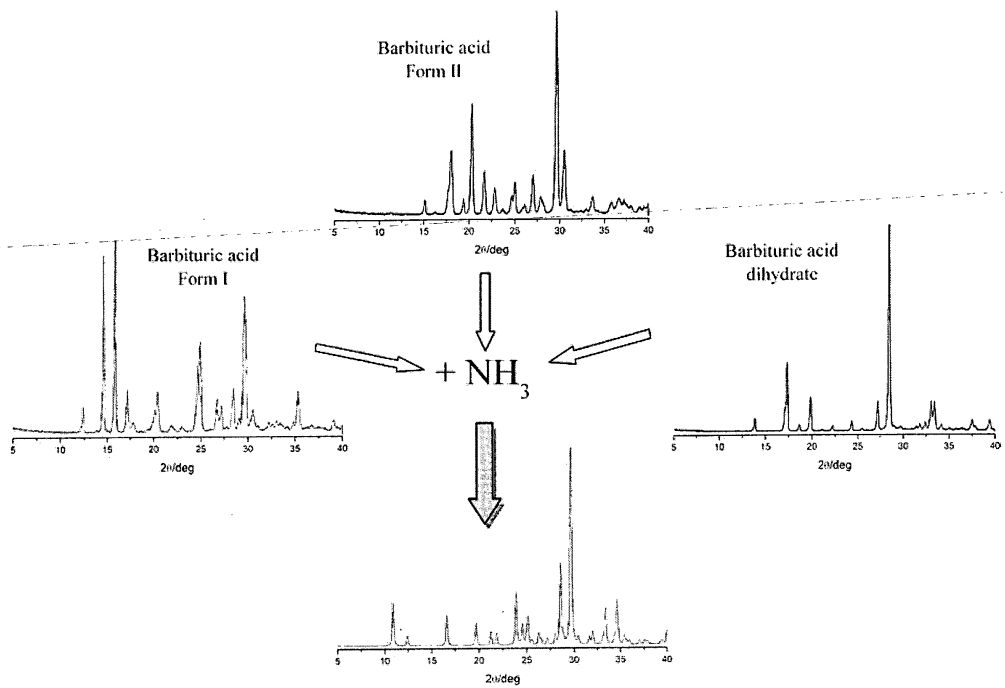


Fig. 10 Schematic representation of the XRPD patterns of the polymorphic forms of barbituric acid I and II and that of the dihydrate form. The interaction with NH_3 leads to the formation of the same product, $\text{NH}_4(\text{C}_4\text{H}_3\text{N}_2\text{O}_3)$

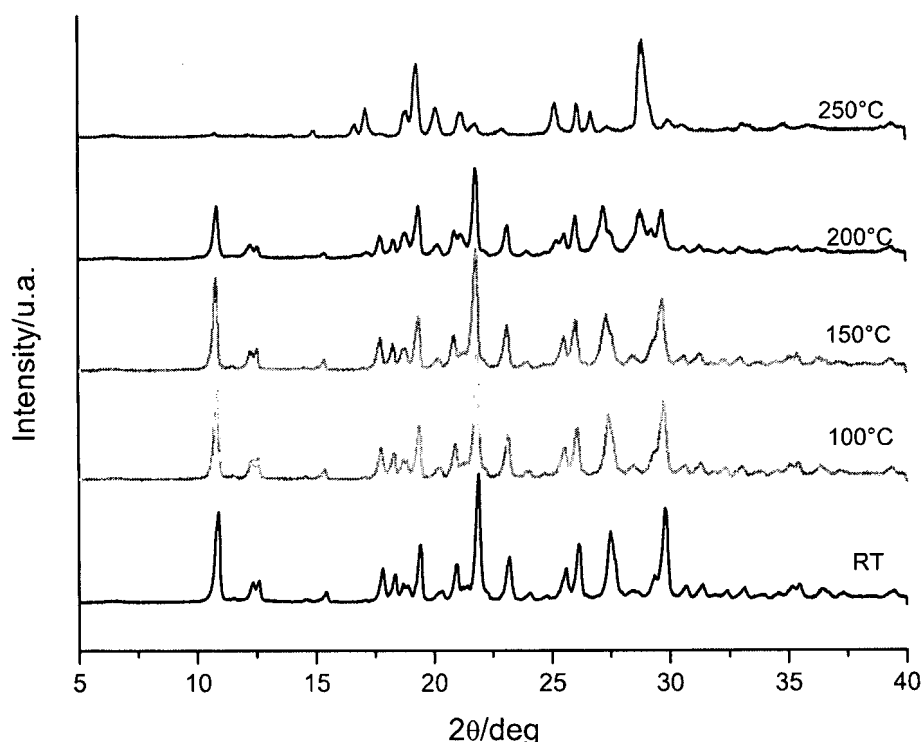


Fig. 11 XRPD recorded at different temperatures from room temperature to 250°C on crystalline $\text{NH}_4(\text{C}_4\text{H}_3\text{N}_2\text{O}_3)$ showing the presence of new reflections at 200°C

$[\text{NH}_2(\text{CH}_3)_2][\text{DMB}] \cdot 2[\text{DMBA}]$, while recrystallization of $[\text{NH}_3(\text{CH}_3)]\text{dmb}$ yields both the dimerization product $[\text{NH}_3(\text{CH}_3)][(\text{C}_6\text{O}_3\text{N}_2\text{H}_6)_2\text{-OH}] \cdot 2\text{H}_2\text{O}$ and the hydurate salt $[\text{NH}_3(\text{CH}_3)]_2[(\text{C}_6\text{O}_3\text{N}_2\text{H}_6)_2]$, i.e. the product $[\text{NH}_3(\text{CH}_3)]\text{dmb}$ is only accessible via the solid-gas reaction.

In an analogous study, crystalline form I (monoclinic) and form II (triclinic) of ferrocene dicarboxylic acid $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ have been reacted at room temperature with the gaseous bases NH_3 , $\text{NH}_2(\text{CH}_3)$ and $\text{NH}(\text{CH}_3)_2$ [64]. The two crystal forms behave in exactly the same way in the solid-gas reaction generating the same products, identified as the anhydrous crystalline salts $[\text{NH}_4]_2[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]$, $[\text{NH}_3\text{CH}_3]_2[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]$, and $[\text{NH}_2(\text{CH}_3)_2]_2[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COO})_2]$. Interestingly though, all these crystals revert via vapour release exclusively to the metastable crystalline form I, as shown in Fig. 12.

This is not surprising per se, because there is no reason why, if the reaction is quantitative, the crystalline salt product should “remember” which crystal form it comes from. It is instead of relevance that forms I and II of $[\text{Fe}(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2]$ are not known to interconvert via a solid-solid phase transition, hence they constitute a monotropic system. The ammonia absorption/release process, therefore, can be seen as a solid state way to convert the thermodynamically stable form II into the metastable form I. The process is schematically represented in Fig. 13.

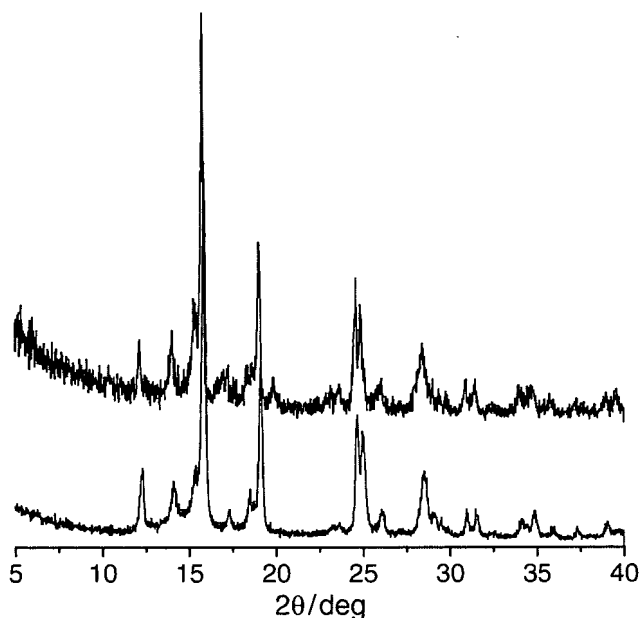


Fig. 12 Comparison between the experimental powder diffractograms of compound 1, obtained from the solid–gas reaction with ammonia of form I (*top*) and form II (*bottom*), respectively

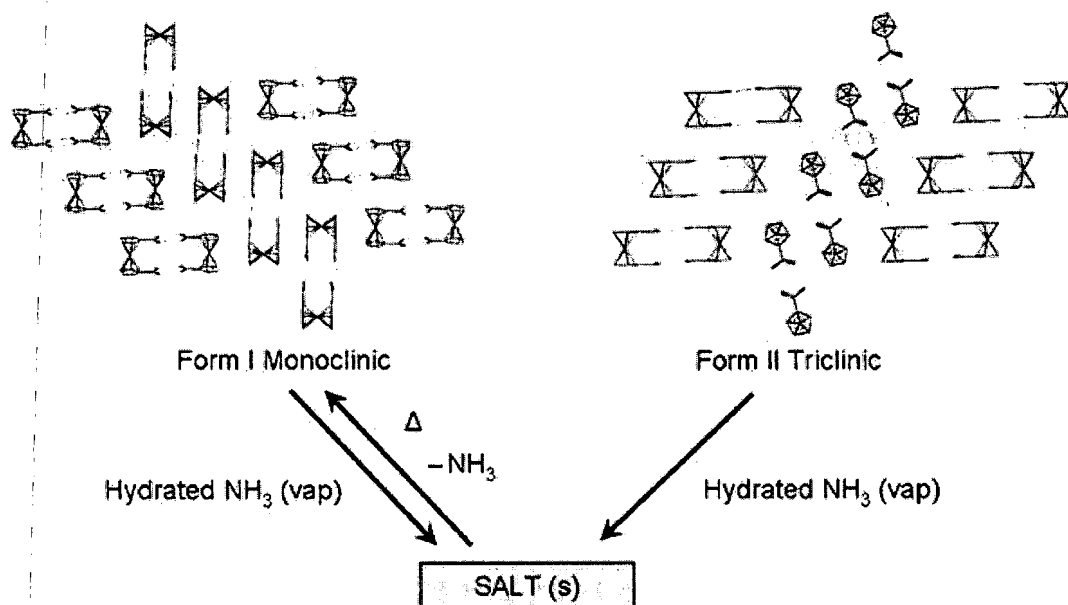


Fig. 13 Reaction of crystalline forms I and II with vapours of NH_3 yields the same salt, which upon heating and removal of NH_3 generates only the monoclinic form I

8 Co-Crystals and Salts, Co-Crystals or Salts?

In this last section we focus on co-crystals. Although co-crystals, i.e. multicomponent crystals containing chemically different molecular units in the asymmetric unit have long been known [70], they have recently become an important field of new discoveries and innovation under the strive to find new drugs and the potential of extension of IP protection on existing ones [71–73].

The definition of a co-crystal is still matter of debate [74, 75]. The definition initially put forward by Aakeroy focused on the aggregation state: "co-crystals are made from reactants that are solids at ambient conditions" [76] and has also been taken up by others [71, 77]. This definition, however, is not without ambiguity (see below). We prefer to take up Dunitz' more liberal view of co-crystals as "encompassing molecular compounds, molecular complexes, solvates, inclusion compounds, channel compounds, clathrates, and other types of multi-component crystals." This view has been echoed recently by Stahly [78] who wrote that: "co-crystals consist of two or more components that form a unique crystalline structure having unique properties." At the bottom line, these multicomponent systems ought to be looked at as crystals of supermolecules whereby the component units interacting via non-covalent interactions generate collective physico-chemical properties that are different from those of the homo-molecular crystals formed by the components.

One may wonder whether solvates would fall under the same broad definition. We would argue in favour, not only because solvent molecules themselves form their own crystalline materials at appropriate temperature (ice!) but also because, as we have argued above, solvate crystals do not necessarily come from solutions since vapour or any other volatile molecule can be taken up from the ambient atmosphere and become incorporated into the crystal. Since we are dealing with crystal forms, it is useful to also remind the reader that the term pseudopolymorphism is not appropriate to refer to solvate forms of a given molecular crystal [23, 79, 80] because solvate crystals can themselves be polymorphic!

In a recent paper, Bond listed a number of interesting controversial examples of co-crystals [81]. For example, dioxane, $C_4H_8O_2$, forms isostructural 1:1 two-component crystals with I_2 , Br_2 or Cl_2 , which at room temperature and 1 bar pressure are solid, liquid, and gas, respectively [82–84]. Clearly a distinction based on the aggregation state of one component has little significance.

The crystal structures of 13 co-crystals formed by *n*-alkylcarboxylic acids and pyrazine in 2:1 stoichiometry have been reported [85, 86]. The acids include formic acid, which is liquid at room temperature, up to the tridecandioic acid which is solid. Pyrazine is also a solid. Clearly, the early members of this series cannot be called solvates only because the co-former is liquid, while from decanoic to tridecandioic the acid/pyrazine systems are co-crystals. Another example is the two-component crystals formed by picric acid forms and benzene, naphthalene and anthracene (amongst others), which contain stacks of alternating molecular components that are clearly comparable in all three structures [87–89]. All of these crystals are stable at room temperature.

Not only it is difficult to distinguish between a co-crystal and a solvate (as a matter of fact all molecules are solid and form crystals at sufficiently low temperature) but it is also often difficult to distinguish between a crystal and a salt. As discussed above in the case of hydrogen-bonded systems between acids and bases the *transition* between a salt and a co-crystal may be a very semantic issue depending exclusively on the position of a proton along a $N \cdots O$ supramolecular link [90].

Proton transfer along a hydrogen bond poses an interesting question about polymorph definition. In fact, proton mobility along a hydrogen bond (say from

$\text{O}-\text{H} \cdots \text{N}$ to $(-)\text{O} \cdots \text{H}-\text{N}^{(+)}$) may not be associated with a phase transition, even though it implies the formal transformation of a molecular crystal into a molecular salt. This situation has been observed, for instance, for the proton migration along an $\text{O}-\text{H} \cdots \text{O}$ bond in a co-crystal of urea-phosphoric acid (1:1) as a function of temperature [91, 92].

Mootz and Wiechert have isolated two co-crystals of pyridine and formic acid: in the 1:1 co-crystal, proton transfer from formic acid to pyridine does not take place, while in the 1:4 co-crystal $\text{N}-\text{H}^{(+)} \cdots \text{O}$ interactions are present (see Fig. 14) [93]. Examples of this kind are rare, but serve to stress how the phenomenon of polymorphism can be, at times, full of ambiguity.

In order to tackle the problem of the co-crystal or salt nature of acid-base adducts we have used the same approach illustrated above in the case of the polymorphs of barbituric and cinchomeric acid, namely a combined use of diffraction and spectroscopic methods in the investigations. We have shown that mechanical mixing of a di-nitrogen base $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]$ (dabco) and of dicarboxylic acid $\text{HOOC}(\text{CH}_2)_n\text{COOH}$ ($n = 1-7$) affords a series of hydrogen-bonded adducts of general formula $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]-\text{H}-[\text{OOC}(\text{CH}_2)_n\text{COOH}]$ ($n = 1-7$, that is to say **1C3**, **1C4**, **1C5**, **1C6**, **1C7**, **1C8**, and **1C9**) (see Fig. 15) [21].

These compounds can be classified as co-crystals or salts depending on whether proton transfer from oxygen to nitrogen takes place or not along the $\text{O}-\text{H}-\text{N}$ bonds [94]. In order to address this issue we have compared the results of an X-ray investigation carried out on single crystals grown from the solid-state products by seeding the corresponding methanol solutions with those obtained from the polycrystalline powder by solid-state ^1H and ^{15}N and ^{13}C spectroscopy.

For example, it has been possible to correlate the isotropic ^1H and ^{15}N chemical shift data with the $\text{N}-\text{O}$ distances of the atoms involved in the hydrogen bond interaction in a series of solid adducts of formula $[\text{N}(\text{CH}_2\text{CH}_2)_3\text{N}]-\text{H}-[\text{OOC}(\text{CH}_2)_n\text{COOH}]$ ($n = 1-7$) (Fig. 16). The ^1H MAS and ^{15}N CPMAS NMR data are in agreement with the X-ray data and allow discrimination between the proton transfers for the **1C3** and **1C5** adducts and the strong $\text{N} \cdots \text{H}-\text{O}$ interactions

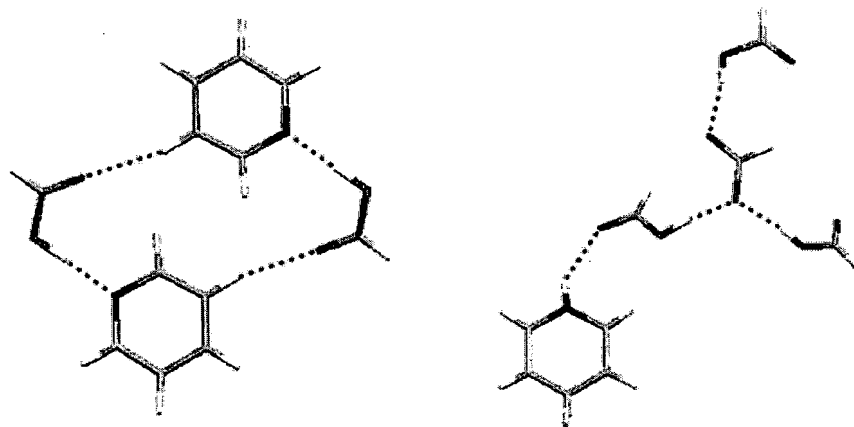


Fig. 14 The 1:1 co-crystal of pyridine and formic acid where the proton transfer does not occur (*left*) and the 1:4 co-crystal of pyridine and formic acid where the formate anion is present (*right*)

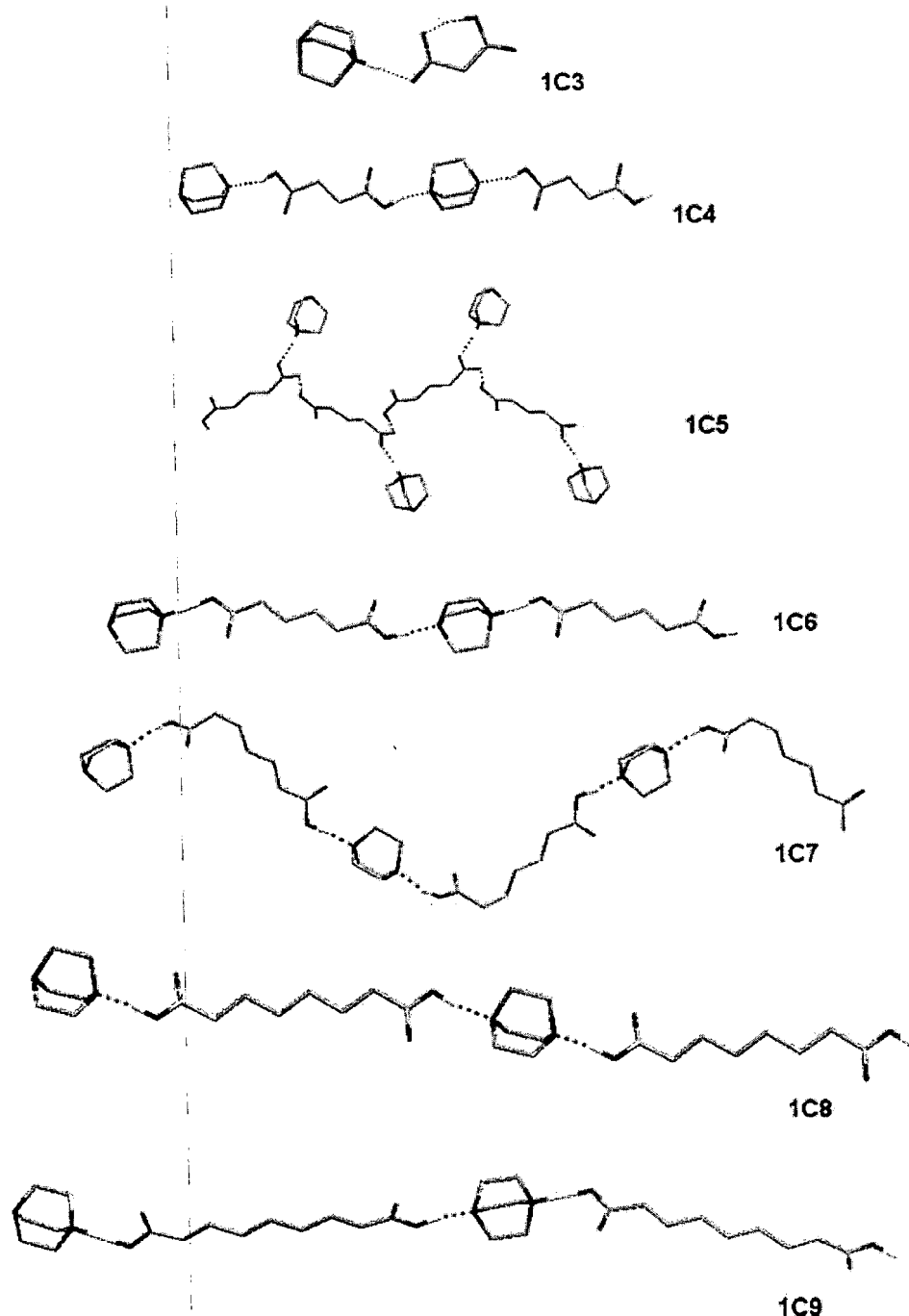


Fig. 15 Schematic representation of the packing motives in $[N(CH_2CH_2)_3N]-H-[OOC(CH_2)_nCOOH]$ ($n = 1-7$, i.e. **1C3**, **1C4**, **1C5**, **1C6**, **1C7**, **1C8**, and **1C9**)

(without proton transfer) for the **1C4**, **1C7**, **1C8** and **1C9** co-crystals. **1C6** represents an intriguing case in which one of the nitrogen atoms of dabco is intermediate between the protonated and non-protonated forms. Density functional theory, applied to explore changes upon hydrogen bonding in the ^1H and ^{15}N shielding parameters, is in agreement with the experimental values found by solid-state NMR spectroscopy [95,96].

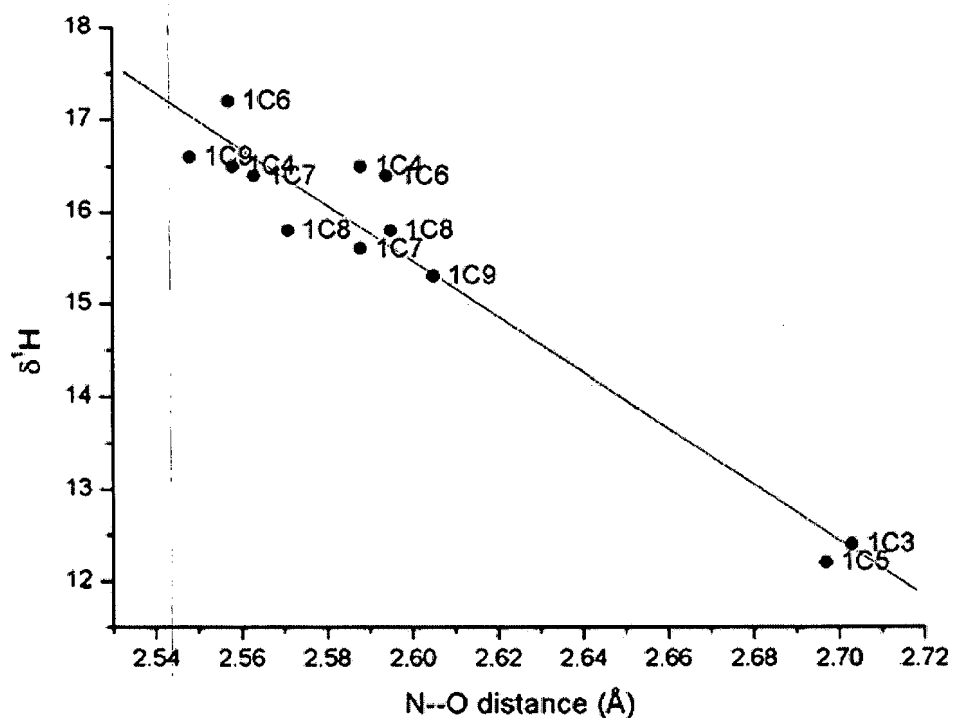


Fig. 16 Compact view of ^1H chemical shifts as a function of $\text{N} \cdots \text{O}$ distance

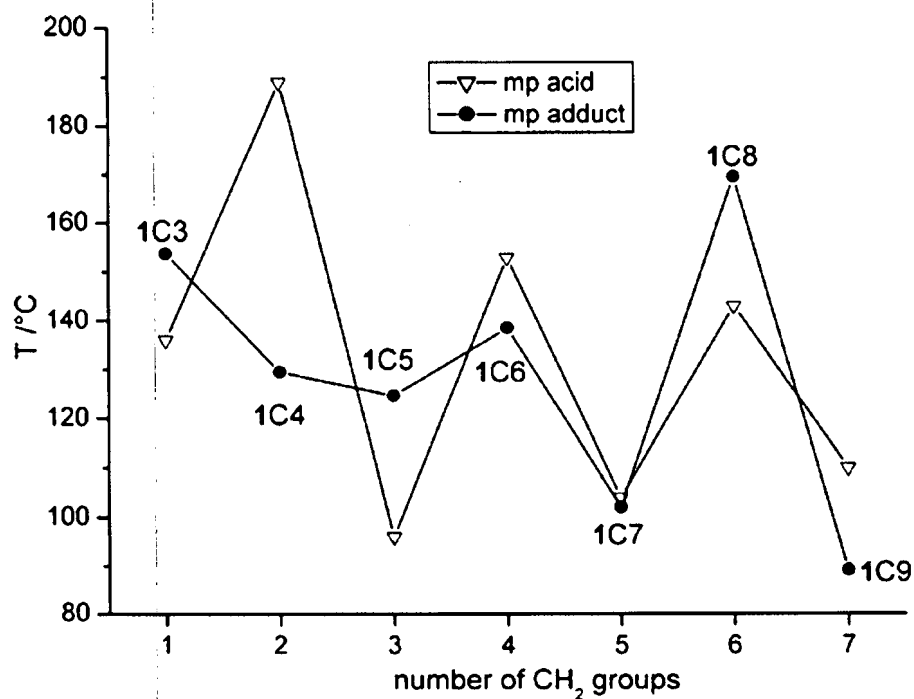


Fig. 17 Melting point alternation in neutral acids and in compounds 1C3–1C9

Comparison of melting point data of the neutral organic acids and of the co-crystals and salts discussed herein yields another interesting observation. As shown in Fig. 17, the melting points of compounds 1C3–1C9 follow a trend very similar to that of the acids, i.e. they show an alternation of melting points as a function of the even–odd carbon chain length.

In summary, at room temperature malonic and glutaric adducts are salts; adipic is ambiguous; succinic, pimelic, suberic and azelaic adducts are co-crystals. Diffraction data and solid-state NMR data are in agreement except in the case of compound **1C6**, which shows proton motion on the NMR time scale. Salt or co-crystals – does it matter? The melting points of compounds **1C3–1C9** do not correlate with the salt-like or co-crystal nature of the adducts, but rather with the even–odd carbon chain length in spite of the substantial differences in supramolecular arrangements in the crystals of the adducts with respect to those of the parent diacids.

On closing this discussion on co-crystal systems, it is useful to cite few examples (selected from the many available in a rapidly expanding literature) of the importance of co-crystals in the pharmaceutical field. Piracetam, (2-oxo-1-pyrrolidinyl) acetamide), has been co-crystallized by Zaworotko et al. with gentisic acid and *p*-hydroxybenzoic acid (see Fig. 18) [22].

Co-crystals of 4-hydroxybenzoic acid (4HBA) and 2,3,5,6-tetramethylpyrazine (TMP) (2:1) have been reported as a case of supramolecular synthon polymorphism in a co-crystal (see Fig. 19); in fact the two forms exhibit different hydrogen bond interactions. The co-crystal form I does not follow the hierarchy of hydrogen bonding, and converts into the stable form II, which follows the hierarchy of hydrogen bonding [97].

In yet another example, a co-crystal of caffeine and adipic acid [98] has been isolated by a co-crystallization methods based on a suspension/slurry containing both components of the co-crystal system. This approach provides an optimal environment for the putative co-crystal formation because the activity values of both

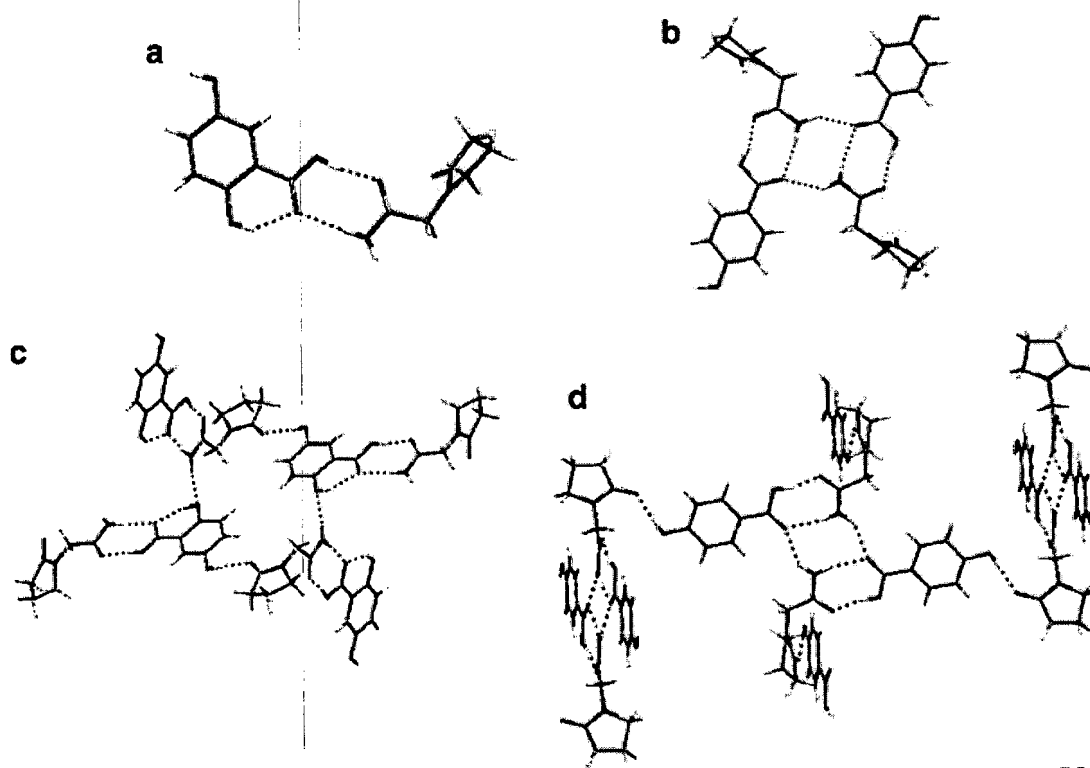


Fig. 18 Co-crystals of piracetam, (2-oxo-1-pyrrolidinyl) acetamide with gentisic **a** and **c**, and *p*-hydroxybenzoic acids **b** and **d**

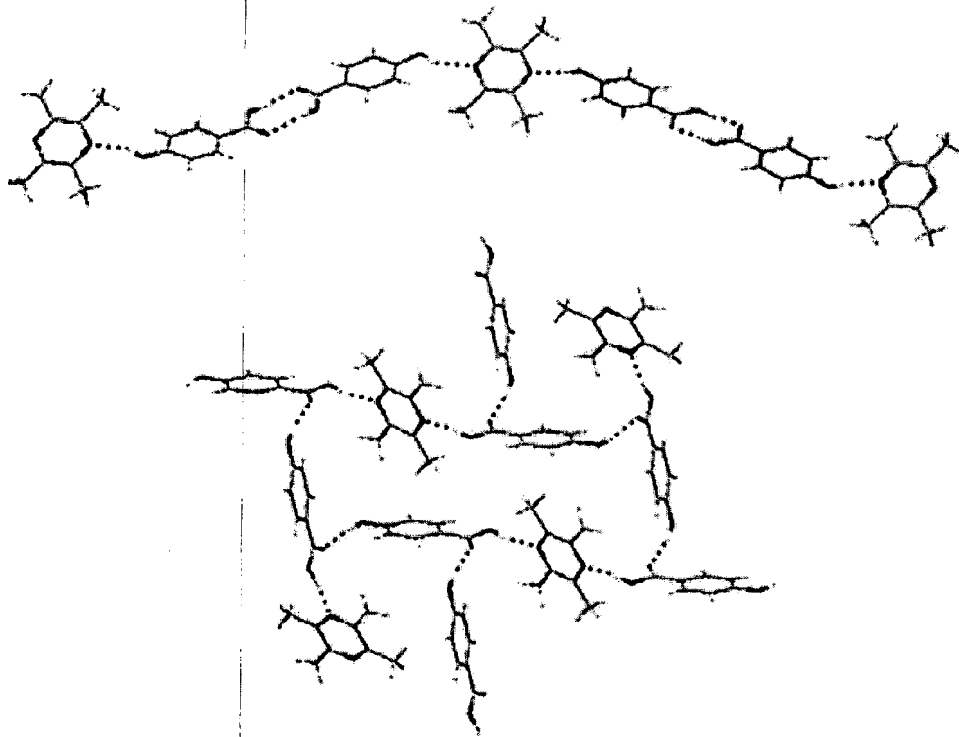


Fig. 19 Linear chain formed through carboxylic acid dimer and hydroxyl O-H...N hydrogen bonds in form I (*top*). Herringbone network in form II (*bottom*)

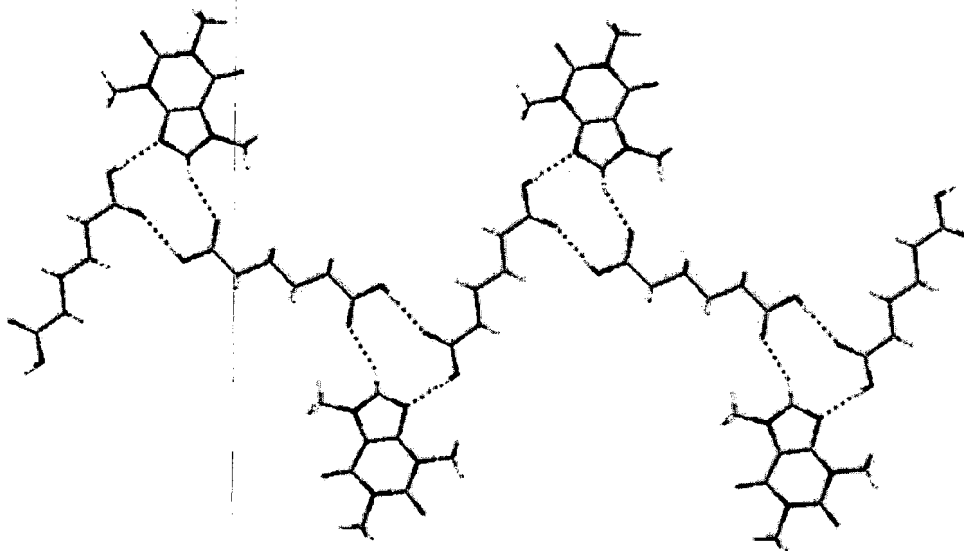


Fig. 20 View of caffeine-adipic acid trimers along the crystallographic plane (1 -2 0). The trimers are linked via hydrogen-bonded adipic acid molecules into molecular tapes

components are held at one. This method was applied to 16 pharmaceutically related co-crystal systems and was found to be 100% successful [99]. In the case of the co-crystal caffeine/adipic acid, a suspension of caffeine and adipic acid (1:1 molar ratio) in acetonitrile was prepared and equilibrated overnight at ambient temperature. The powder X-ray diffraction pattern of the solid after equilibration indicated formation of a new solid phase, which was then characterized as shown in Fig. 20.

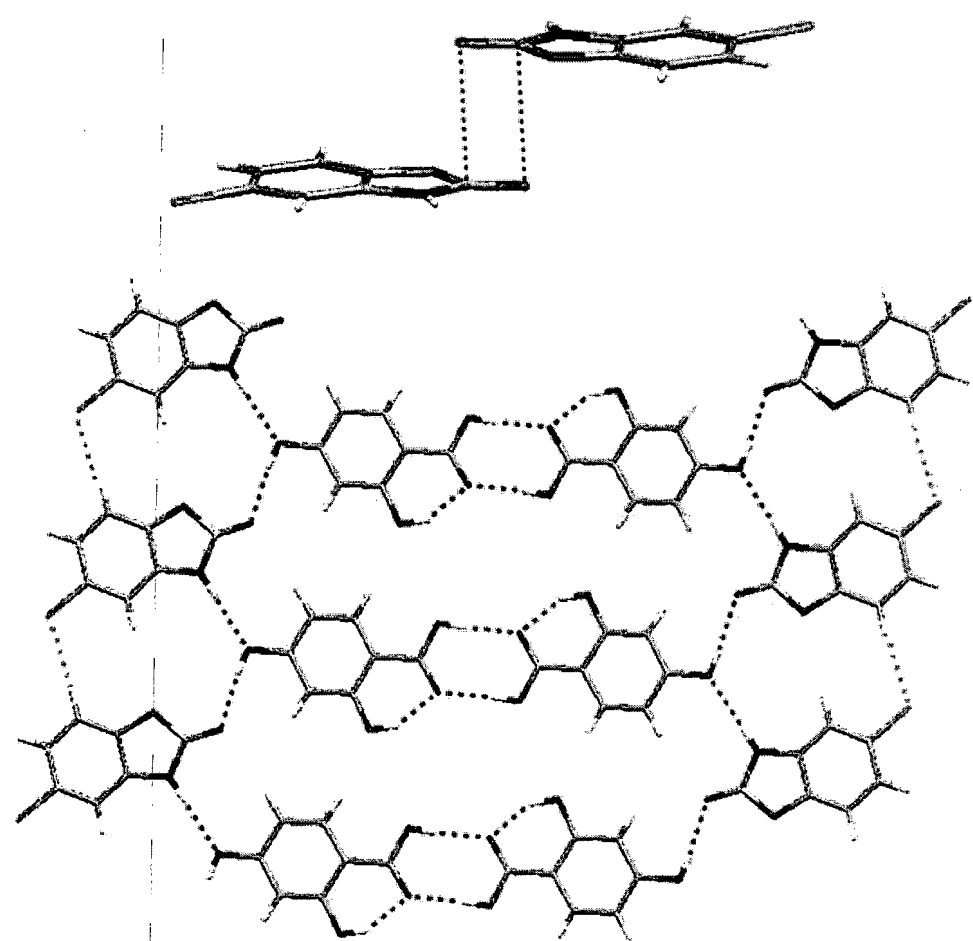


Fig. 21 Anti-parallel centrosymmetric carbonyl-carbonyl interaction between two molecules (*top*) and the packing motif (*bottom*) of chlorzoxazone in co-crystal form 1. Repulsive C-H...Cl-C interactions are in *light grey*

Evaporative crystallization experiments containing equimolar ratios of the API and guest has been instead used to obtain co-crystals of chlorzoxazone with carboxylic acids [100]. Two polymorphs of a chlorzoxazone:2,4-dihydroxybenzoic acid co-crystal and one form of a chlorzoxazone:4-hydroxybenzoic acid co-crystal have been characterized and the crystal structure of chlorzoxazone:2,4-dihydroxybenzoic acid (form 1) reported and analyzed, revealing an uncommon carbonyl-carbonyl interaction and a destabilizing C-H...Cl-C interaction (see Fig. 21).

9 Conclusions

The scope of this review has not been that of providing the reader with a comprehensive coverage of the topic of crystal forms, rather we have aimed at an introductory view of the phenomena of multiple crystals forms in general, and polymorphism in particular. For reasons of space, many problems have not been addressed (e.g. theo-

retical methods to study polymorphism), in particular the computational exploration of the possible crystalline structures of a given molecule. The interested reader will find in the necessarily limited number of references a good starting point for further reading.

The question on whether a crystalline material contains only molecules A in different arrangements (e.g. polymorphs), or molecules A *and* molecules B, and whether this latter association ought to be considered a co-crystal or a solvate is somewhat semantic. It is unquestionable, however, that crystals of different composition not only have different crystal structures but also may possess different physical properties, such as solubility, thermal behaviour, resistance to mechanical stress, gas-absorption/release capacity, colour, melting point etc. These differences may be relevant, and carry economical and practical implications, when considering, for instance, the bio-availability of a drug or the thermal stability of a pigment.

Reproducibility and predictability are paradigms in the exact sciences. This is why, beside all the utilitarian reasons associated with the marketing of solid state materials, we would like to learn how to *make* polymorphs, or, which is the same, how to effectively *prevent* polymorph formation. If seeds of a polymorphic modification can be obtained from non-solution methods (i.e. mechanical, thermodynamical, perhaps solid state reactions) these can be used in the seeding process, which may allow growth of less kinetically favoured crystal forms. Seeding may be valuable not only to obtain the desired crystalline form, but also to prevent crystallization of undesired forms. One could argue that polymorphism, with its high degree of serendipity, could be the *nemesis* of crystal engineering because polymorphism is in logical contrast with a discipline that aims to control and reproduce univocally a given crystal structure. This is not true (rather the investigation of crystal forms) of the way a molecule recognizes another molecule, whether the same or a different one, and links to form stable or metastable supramolecular arrays, it is rather a way *to tune* synthetic and assembly strategies to obtain the desired crystal structure, which is the paradigm of crystal engineering.

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