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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente N° 07-055.540

Solicitud de Patente de Invención Titulada: "SAL POTÁSICA DEL COMPUESTO N-(4-FLUOROBENCIL)-5-HIDROXI-1-METIL-2-(1-METIL-1-[(5-METIL-1,3,4-OXADIAZOL-2-IL)CARBONIL]AMINO}ETIL)-6-OXO-1,6-DIHIDROPIRIMIDIN-4-CARBOXAMIDA Y CRISTALES DEL MISMO"

Solicitante: MERCK SHARP & DOHME CORP.

Nuestra Ref.: P2007/000091

RESPUESTA AL OFICIO No. 04009, NOTIFICADO POR FIJACIÓN EN LISTA No. 76

DE FECHA 04 DE MARZO DE 2011

(PRIMER EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar la solicitud.

Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- se han combinado las Reivindicaciones 1 a 4 y 7 en la nueva Reivindicación 1;
- se han eliminado las Reivindicaciones 8 y 10;
- las antiguas reivindicaciones 5, 6 y 9 se han reenumerado como nuevas Reivindicaciones 2 a 4, respectivamente.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial, por el contrario, éstas corresponden a una franca limitación de la materia reivindicada.

2. a- El Examinador argumenta que el título de la solicitud no define apropiadamente la invención.

b- Atendiendo la observación del Examinador, el título de la solicitud ha sido modificado a:

“SAL POTÁSICA DEL COMPUESTO N-(4-FLUOROBENCIL)-5-HIDROXI-1-METIL-2-(1-METIL-1-[(5-METIL-1,3,4-OXADIAZOL-2-IL)CARBONIL]AMINO}ETIL)-6-OXO-1,6-DIHIDROPIRIMIDIN-4-CARBOXAMIDA Y CRISTALES DEL MISMO”.

3. a- El Examinador señala que la Reivindicación 10 no es patentable porque reclama un uso.

b- Considero superada la anterior objeción en tanto que se ha eliminado la Reivindicación 10 del Capítulo Reivindicatorio Modificado adjunto.

4. a- El Examinador señala que la patente WO 2003/035077 (D1), afecta el nivel inventivo de la presente invención.

El Examinador argumenta que D1 divulga un compuesto base con la misma fórmula del Compuesto A de la presente invención, y que adicionalmente, D1 sugiere una lista de sales de dicho compuesto. El Examinador argumenta además, que D1 sólo se diferencia de la presente invención en que la presente invención reclama específicamente la sal potásica del Compuesto A.

El Examinador concluye que cualquier persona medianamente versada en la materia, siguiendo las enseñanzas de D1, habría sido capaz de obtener la sal potásica aquí reclamada, y adicionalmente, que la solicitud no contiene evidencia de efectos mejorados o sorprendentes derivados de los cristales de la sal potásica del Compuesto A reclamados en las Reivindicaciones 2 a 9, cristales que encontraría obvios cualquier persona medianamente versada en la materia a la

luz de lo divulgado en D1, correspondiente a otros cristales de la misma familia de compuestos (Ejemplo 16).

b- i) En primer lugar, llamo respetuosamente la atención del Examinador al hecho que la presente invención ha sido limitada a una sal monopotásica cristalina anhidra del Compuesto A, de acuerdo con el Capítulo Reivindicatorio Modificado.

Ahora bien, respecto al arte previo citado por el Examinador, es importante señalar que D1 revela un amplio número de compuestos, entre los cuales se menciona el Compuesto A y sus usos terapéuticos, solos o en combinación con otros agentes.

Vale la pena resaltar que el Capítulo Descriptivo de esta solicitud, se reconoce la existencia de D1 como arte previo relevante en la presente invención. Sin embargo, D1 no revela, ni sugiere, la sal monopotásica anhidra del Compuesto A. De la misma forma, D1 no divulga o sugiere siquiera que la sal monopotásica anhidra del Compuesto A podría presentar formas cristalinas, y menos aún el cristal específico tal como se reclama en el Capítulo Reivindicatorio Modificado. Precisamente, los inventores de la presente solicitud reclaman específicamente una forma cristalina concreta la sal monopotásica anhidra del Compuesto A, la cual fue caracterizada por sus propiedades termodinámicas (patrones de difracción por rayos X en polvo y calorimetría diferencial de barrido).

De nuevo, el documento D1 no proporcionan ninguna referencia a las formas cristalinas de ninguno de los compuestos allí divulgados, ni mucho menos, a la forma cristalina de la sal monopotásica anhidra del Compuesto A reivindicada en la presente invención. De acuerdo con lo anterior, D1 no puede afectar el nivel inventivo de la presente invención, pues no sugiere de ninguna manera la forma cristalina específica reivindicada. Por lo tanto, la presente invención debe ser entendida como un polimorfo de la sal novedosa de un compuesto conocido, y no como un polimorfo novedoso de un compuesto conocido. El problema que se soluciona con la presente invención es proporcionar una forma alternativa del Compuesto A (raltegravir) que tiene propiedades mejoradas como su biodisponibilidad (ver Capítulo Descriptivo, página 4, líneas 4 a 25), y no solamente proporcionar un polimorfo alternativo de una sal monopotásica de raltegravir con propiedades mejoradas.

The present invention should thus be understood as a polymorph of a novel salt of a known compound as not as a novel polymorph of a known compound.

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Consequently the problem to be solved is the provision of an alternative form of raltegravir having improved properties such as bioavailability (see page 4 lines 4-14 of the present application). The problem is not the provision of an alternative polymorph of monopotassium raltegravir with improved properties.

Aparentemente, para el Examinador es fácil argumentar que el compuesto aquí reivindicado se encontraba divulgado en D1, así como sus sales, y que el técnico medio en la materia habría obtenido específicamente la sal monopotásica anhidra y su cristal mediante un proceso obvio a partir de lo divulgado en D1, olvidando sin embargo el proceso investigativo necesario para obtener el polimorfo reivindicado.

Adicionalmente, presento a continuación los resultados de un estudio de biodisponibilidad realizado en perros, a los que se les administró una dosis de 45mg/Kg de la sal ácida del Compuesto A, y la sal monopotásica cristalina anhidra de la presente invención:

	AUC ($\mu\text{M}\cdot\text{h}$)		C_{max} (μM)	
	Fenol libre	Sal potásica	Fenol libre	Sal potásica
Perro Y	9.7	108.1	4.7	63.8
Perro X	56.2	245.9	26.7	120.9
Promedio	32.9	177.0	15.7	92.3

Los resultados del estudio demostraron que la sal monopotásica cristalina anhidra del Compuesto A de esta invención, presenta menos variabilidad individuo a individuo, y una mejora considerable tanto en el parámetro AUC, como en la concentración máxima.

Teniendo en cuenta los resultados, considero respetuosamente que para la persona medianamente versada en la materia, a partir de las enseñanzas en D1, no habría podido ser obvio prever cuál compuesto alternativo a la forma ácida libre de raltegravir podría mejorar la biodisponibilidad. No existe enseñanza alguna en D1 sobre cómo este objetivo (aumentar la biodisponibilidad) podría ser alcanzado por una sal monopotásica cristalina anhidra, y de hecho, tal enseñanza tampoco existe en el estado general de la técnica.

The applicant considers that it would not be obvious to the skilled person from D1 what alternative to the free acid form of raltegravir would improve bioavailability. There is no teaching in D1 that this will be achieved by the anhydrous crystalline monopotassium salt, nor any general teaching in the art to this effect.

ii) En este sentido, es importante resaltar que el polimorfismo es un problema vigente en particular para las industrias farmacéutica y de alimentos, ya que solamente algunos

polimorfos tienen propiedades deseables (p.ej. estabilidad, propiedades de flujo mejoradas, biodisponibilidad, disolución, etc), por lo que la patentabilidad de éstos se basa en las propiedades ventajosas logradas con nuevas formas cristalinas.¹

No puede olvidarse que la búsqueda de polimorfos no es predecible, por lo que siempre los científicos investigadores deben explotar intensamente su conocimiento y creatividad con el fin de desarrollar nuevas formas cristalinas. De hecho, no hay un método general para la predicción de estructuras cristalinas a partir de una fórmula molecular; el diseño de sólidos orgánicos que respondan a propiedades deseadas previamente continúa siendo un sueño.²

Teniendo en cuenta lo anterior, es importante resaltar que además de no ser posible garantizar *a priori* la obtención de formas cristalinas, tampoco es posible predecir cuántas formas son posibles y qué propiedades presentará cierta forma particular. Es decir, algunos compuestos son polimórficos y otros no los son, y no hay un método conocido que permita predecir cuales compuestos podrían proveer formas cristalinas adicionales. Igualmente es virtualmente imposible anticipar, con aceptable grado de certeza, cuál será su estructura tridimensional, cuáles sus propiedades fisicoquímicas (tales como tasa de disolución, higroscopicidad, solubilidad, biodisponibilidad, etc.) y cuál será su estabilidad. Ni siquiera un conocimiento profundo de la teoría de cristales o una amplia experiencia específica en el área, permitirían a una persona medianamente versada en la materia anticipar inequívocamente los anteriores hechos, basándose en la divulgación general del compuesto de D1 y la teoría de cristales sólidos, pues solamente con la invención de la presente solicitud se logró la obtención de las formas cristalinas reivindicadas, sin seguir ningún tipo de indicación o enseñanza del arte previo.

Evidencia de lo anterior se puede encontrar en el artículo "An experiment in crystal structure prediction by popular vote" de Graeme et al, adjunto al presente memorial como "Anexo 1", publicado y disponible en el momento en el que se radicó la presente solicitud, en donde se evidencia la no predictibilidad de una forma cristalina de un compuesto dado. En este estudio, se evalúa la habilidad de diferentes experimentadores cristalógrafos expertos para predecir estructuras cristalinas correctas a partir de una lista de estructuras cristalinas diferentes para un compuesto dado. La metodología del estudio involucra dos compuestos específicos (5-fluoro-2-oxindol y 3-quinoclidinol racémico) con estructuras rígidas, que no se encontraban publicadas en la base de datos de Cambridge (Cambridge Structural Database -CSD-), para las cuales se generaron diferentes estructuras cristalinas por métodos computacionales, en las que se buscaba

¹ University of Minnesota. <http://www.chem.umn.edu/groups/siepmann/research/phasc.php>

² G.R. Desiraju, Nature Materials, 1, 77-79 (2002)

el menor empaquetamiento energético posible, de las cuales se escogieron 5 estructuras para ser incluidas en el test. Posteriormente, se realizó una competencia de predicción de la estructura cristalina en el Centro de Datos Cristalográficos de Cambridge (CCDC por sus siglas en inglés), donde los participantes del concurso, con diferentes años de experiencia en cristalografía (ver Figura 5, página 1988, desde profesionales recién graduados y cristalógrafos con más de 30 años de experiencia) debían determinar cuál de las estructuras era más probable que fuera la real forma cristalina, a partir de cierta información para cada estructura (densidades calculadas, grupos espaciales y condiciones de crecimiento del cristal) y acceso a la visualización de las estructuras a través de un computador.

Los resultados demostraron que la estructura de la forma cristalina real del compuesto I (5-fluoro-2-oxindol) fue la menos popular entre dichos expertos por un margen significativo (página 1989, párrafo de conclusiones, línea 7-9). Para la segunda molécula, que resultaba ser más difícil de analizar (sólo se recibieron 38 análisis, mientras que para la molécula I, se recibieron 50), ya que las diferentes estructuras cristalinas se podían distinguir menos, no se pudo establecer una marcada diferencia entre la popularidad de las diferentes estructuras cristalinas, sin embargo, la estructura cristalina obtenida experimentalmente fue de nuevo la menos popular.

De lo anterior se puede concluir que el estudio de las diferentes formas cristalinas de una molécula específica no es tarea fácil, requiere experiencia y experticia, así como no es posible predecir a partir de técnicas rutinarias (como lo señala el Examinador) y tampoco mediante técnicas computacionales a disposición de los expertos.

De la misma forma, adjunto al presente memorial se encuentra el artículo “Materials Engineering of Solid-State Dosage Forms” en donde se establece que:

“A pesar de la investigación rigurosa, nuestro conocimiento sobre nucleación y cristalización se encuentra lejos de ser completo: nuestras habilidades para predecir y controlar la morfología cristalina y el polimorfismo son decepcionantemente limitadas” (mi traducción).

Dado el esfuerzo involucrado en el desarrollo de estas mejoras, y dado que éstas proporcionan ventajas comerciales competitivas, y se derivan directamente de la investigación y creatividad humanas, el sistema de patentes *debe* garantizar su protección. El Examinador no puede basarse en apreciaciones subjetivas para privar al inventor de la protección merecida para su desarrollo novedoso y no sugerido por el estado de la técnica. En el mundo entero las formas cristalinas

específicas son consideradas no-obvias y por ende, materia patentable. Si bien en los medicamentos actuales, o las moléculas candidatas a ser medicamentos, es posible encontrar múltiples formas sólidas, algunas similares, algunas drásticamente diferentes en sus características técnicas, estas formas, son todas candidatas para obtener protección vía patentes de manera individual.³ Así las cosas, la investigación de las diferentes formas sólidas de un medicamento puede conducir al desarrollo de nuevos productos con propiedades mejoradas, tales como mayor estabilidad, que resultan ventajosos y deseables en operaciones de procesamiento farmacéutico a gran escala.

El Examinador debe tener en cuenta que el análisis de nivel inventivo no puede estar basado en si es o no posible obtener la invención reclamada, pues claramente era posible, toda vez que las formas polimórficas reivindicadas existen. Esta aproximación conllevaría a que ninguna invención sería patentable, volviendo así inoperante el sistema de patentes. En este caso, el hecho que pudiera existir eventualmente una mínima motivación general para llevar a cabo trabajo experimental para determinar si hay otras formas físicas (monohidrato y formas cristalinas), no hace el resultado positivo obtenido (es decir la invención) obvio o evidente; si así fuera, el trabajo experimental sería innecesario. **El que sea obvio intentar, no necesariamente hace obvia la invención.**

Adicionalmente, como también lo ha determinado el Tribunal Andino de Justicia, “lo obvio es aquello que salta a la vista de manera clara y directa; lo “que se encuentra o pone delante de los ojos, muy claro o que no tiene dificultad”. Lo evidente consiste en la “certeza clara y manifiesta de la que no se puede dudar, cierto, claro, patente y sin la menor duda”. Continúa el Tribunal diciendo que “una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado.”⁴

Así las cosas, durante el análisis de una solicitud de patente, el Despacho debe poder citar anterioridades que específicamente motiven a una persona versada en el arte a combinar los elementos del estado de la técnica y a intentar las opciones específicas para llegar a la solución inventiva reclamada. No es suficiente alegar que la persona versada podría llegar a la invención, puesto que, como se ha dicho, este criterio desdibujaría por completo el sistema de patentes,

³ Sherry L. Morissette, et. Al., “High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids”. Advanced Drug Delivery Reviews 56 (2004) 275– 300.

⁴ Proceso 10-IP-2009, página 12, párrafos 5 y 6.

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elevando el requisito de nivel inventivo a tal punto que nada sería patentable e indicaría que en todos los casos no hubo creatividad inventiva en el desarrollo de nuevas invenciones, porque éstas siempre serían vistas cómo logros apuntados por el estado de la técnica.

De hecho, quiero anotar que el desconocimiento de las estructuras cristalinas polimórficas específicamente reivindicadas en la presente solicitud constituye innegablemente la evidencia de que se está frente a una “estructura cristalina inesperada”, con lo cual cumpliría el requisito de patentabilidad de nivel inventivo, como bien lo señala el Examinador al establecer que dichas formas son novedosas, y además, como lo demuestran los resultados del estudio de biodisponibilidad realizado en perros, una mejor actividad. El Examinador parece rechazar el principio establecido por el Manual Andino de Patentes que establece que un compuesto tiene nivel inventivo cuando (i) el compuesto tiene estructura inesperada, o (ii) cuando el compuesto exhibe un uso o un efecto sorprendente.⁵

En conclusión, el documento citado no proporcionan ninguna referencia a las formas cristalinas de ninguno de los compuestos allí divulgados, ni mucho menos, a la forma cristalina de la sal monopotásica cristalina anhidra del Compuesto A reivindicada en la presente invención.

5. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 473 han sido resueltas y por consiguiente solicito respetuosamente que el Despacho tenga por cumplidos los requisitos de patentabilidad y proceda con la concesión de la patente.

Atentamente,



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⁵ Manual Andino de Patentes. OMPI, EPO, Secretaría de la Comunidad Andina, 2004. Sección 10.8.1.

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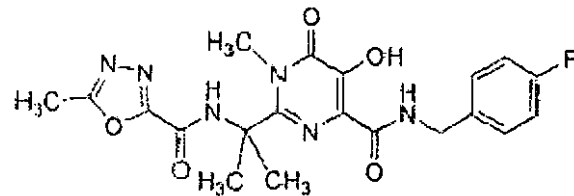
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Anexo:

- Capítulo Reivindicatorio Modificado.
- Anexo 1: Graeme, D., et al “An experiment in crystal structure prediction by popular vote”. Crystal Growth & Design. Vol. 6, No. 9. Pages 1985-1990. 2006.
- Anexo 2: Editorial “Materials Engineering of Solid-State Dosage Forms” Pharmaceutical Research Vol. 25, No. 4, April 2008. Pages 949-952.

CAPITULO REIVINDICATORIO MODIFICADO
(Primer Examen de Fondo)

1. Una sal monopotásica cristalina anhidra del Compuesto A, que se caracteriza por un patrón de difracción de rayos X, obtenido usando radiación de cobre $K\alpha$, que comprende valores en grados 2θ de 5.9, 20.0 y 20,6, en donde el Compuesto A tiene la fórmula:



2. La sal potásica cristalina anhidra del Compuesto A de acuerdo con las Reivindicación 1, que se encuentra caracterizada por un patrón de rayos X que comprende valores en grados 2θ de 5.9, 12.5, 20.0, 20.6 y 25.6.

3. La sal potásica cristalina anhidra del Compuesto A de acuerdo con las Reivindicación 1, que además se caracteriza porque muestra una curva de calorimetría diferencial de barrido, obtenida a una velocidad de calentamiento de $10^{\circ}\text{C}/\text{min}$ en una campana cerrada en atmósfera de nitrógeno, que muestra un solo un único proceso endotérmico con una temperatura pico de aproximadamente 279°C .

4. Una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de la sal monopotásica del compuesto A como se ha reclamado en cualquiera de las Reivindicaciones 1 a 3, y un vehículo farmacéuticamente aceptable.

Perspective

An Experiment in Crystal Structure Prediction by Popular Vote

Graeme M. Day^{*,†} and W. D. Sam Motherwell[‡]

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK, CB2 1EW, and
The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK, CB2 1EZ

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Ⓜ This paper contains enhanced objects available on the Internet at <http://pubs.acs.org/crystal>.

ABSTRACT: The ability to identify the crystal structures of small molecules by visual inspection, given a list of computer-generated low-energy possibilities, has been tested in an experiment conducted at an international crystallographic conference. The surprising result of the test was that the experimentally observed crystal structures were the least popular of five choices for the two molecules included in the test, casting doubt on the reliability of crystallographic intuition as a complement to computational methods in crystal structure prediction.

Introduction

Crystal structure prediction (CSP), a developing area of computational materials chemistry, has progressed to the point that the best methods can usually produce, at least for small rigid molecules, a short list of computer-generated crystal structures that we can be confident will contain the observable structures, starting from no more than the molecular diagram.¹ The calculated ordering of energies is almost always used to choose the most likely crystal structure from the list of calculated possibilities, and the energies of the potential structures are often very close, so that the calculated order of stability is very sensitive to small errors in the model used to evaluate lattice energies. Furthermore, which of these computer-generated crystal structures results from a particular crystallization experiment is influenced by inadequately understood kinetic influences during nucleation and growth. The goal of crystal structure prediction therefore prompts the question: what can we use to distinguish those crystal structures that will be observed from the many unobservable but energetically competitive alternatives? Energy calculations can, of course, always be improved, through parametrization of atom–atom model potentials² or the development of more sophisticated approaches to calculating lattice energies.³ Furthermore, dynamics simulations give access to free energies, to account for temperature and pressure effects,⁴ and sophisticated simulations of crystal nucleation might provide insight into kinetic factors.⁵ What has been relatively

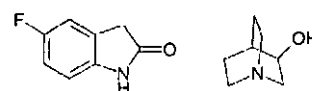


Figure 1. Molecular diagrams of 5-fluoro-2-oxindole, molecule I (left) and 3-quinuclidinol, molecule II (right).

Table 1. Crystal Data for 5-Fluoro-2-oxindole (I) and 3-Quinuclidinol (II)^a

	I	II
chemical formula	C ₈ H ₆ FNO	C ₇ H ₁₃ NO
fw	151.14	127.18
crystal system, space group	monoclinic, <i>P</i> 2 ₁	monoclinic, <i>P</i> 2 ₁ / <i>n</i>
temperature/K	180(2)	120(2)
<i>a</i> , Å	4.3901(3)	6.4549(3)
<i>b</i> , Å	7.1531(5)	10.4034(4)
<i>c</i> , Å	11.0189(8)	10.1283(5)
β , deg	92.880(3)	92.9420(10)
<i>V</i> , Å ³	345.59(4)	679.25(5)
<i>Z</i>	2	4
<i>D</i> (calcd), g cm ⁻³	1.452	1.244
μ (Mo K α), mm ⁻¹	0.115	0.083
<i>R</i> ₁	0.0329	0.0597
<i>wR</i> ₂	0.0822	0.1513

^a CIFs of both structures are deposited as Supporting Information.

unexplored to date is the usefulness of crystallographic intuition or experience. Through working with and analyzing crystal structures as part of daily research, does the crystallographer develop experience that can be used to visually distinguish between “good” and “bad” crystal structures, to pick out from a small set which structure is most likely to be observed? If such an ability could be established, it would supplement the usefulness of current computational methods whereby calculations provide a “short list” of likely crystal structures from which

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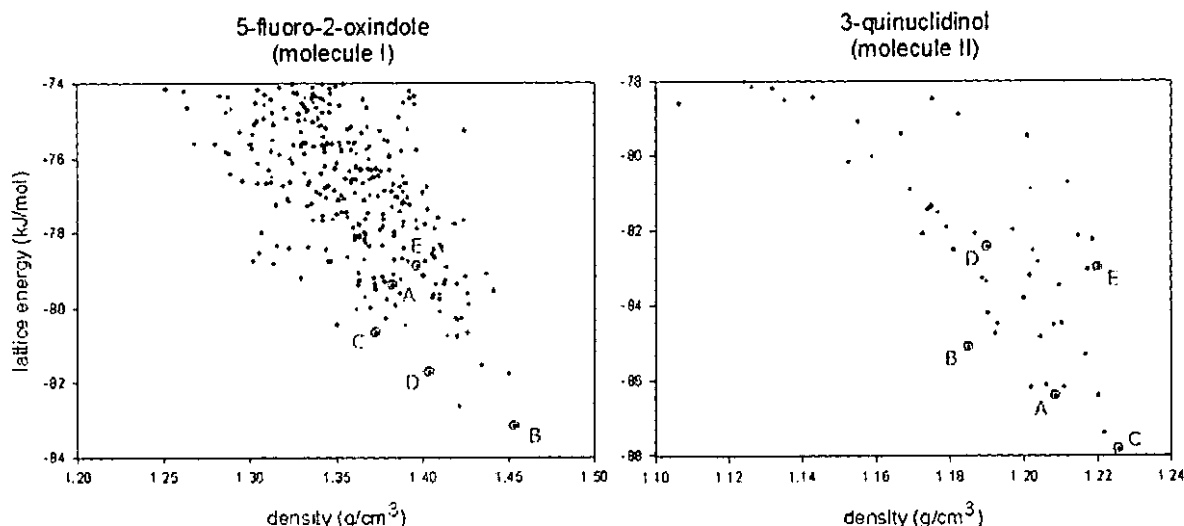


Figure 2. Calculated lattice energy vs density plots for 5-fluoro-2-oxindole (left) and 3-quinuclidinol (right). Each point is a distinct crystal structure and the structures included in the test are highlighted in red.

an experienced crystallographer could choose the most likely. Furthermore, an exploration of the criteria used in making such judgments could guide the future development of modeling methodologies.

To test the idea, an experiment was designed with some similarities to a weight-judging competition described in a 1907 letter by Francis Galton,⁶ where visitors to a cattle show were challenged to correctly guess the weight of an ox. His results (the distribution of guesses was found to have value in accurately estimating the animal's weight) were presented as an "investigation into the trustworthiness and peculiarities of popular judgments". Indeed, intuitions and hunches do play a role in guiding almost all forms of research, so investigations into their reliability are both interesting and valuable. A century since Galton's investigation, we present the curious results of our similar experiment, with the challenge changed to the prediction of crystal structures by visual inspection; the recent congress of the International Union of Crystallography (IUCr) (Florence, August 2005) was chosen as a venue.

Ⓜ Readers are invited to take the crystal structure prediction test before reading the results of this paper.

Methods

We selected a small set of rigid molecules available from Aldrich but not published in the Cambridge Structural Database (CSD). We then determined the crystal structures of two of these (Figure 1) in our own laboratory⁷ (Table 1): 5-fluoro-2-oxindole (which we will refer to as molecule I) and racemic 3-quinuclidinol (molecule II).

Crystal structures were generated by computational methods of searching for low-energy packing possibilities for both molecules. CSP calculations were performed in the same way as in our previous studies of similar molecules.⁸ The computational details are unimportant to the test but are available as Supporting Information. What is important is that crystal structures were computer-generated in a way that the low-energy packing possibilities of each molecule were explored reasonably completely (nine of the most common space groups were searched, which cover about 90% of known molecular crystal structures) and that a high-quality energy model was used to energy minimize the resulting crystal structures (using a rigid molecular geometry throughout, fixed from isolated molecule quantum mechanical calculations). Once the set of low-energy crystal structures had been generated, a subset was chosen to be included in the test. For both molecules, five of the calculated crystal structures were chosen as follows:

- (1) the calculated global minimum in lattice energy

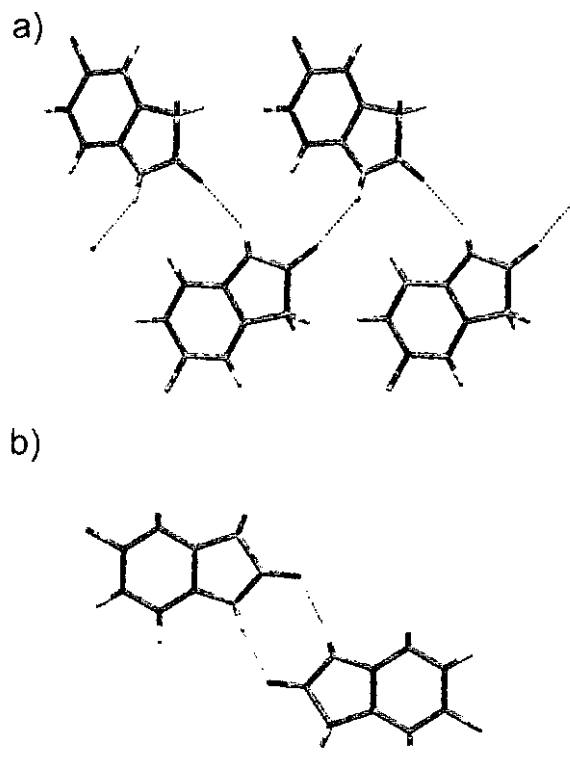


Figure 3. Hydrogen bond (a) chains and (b) dimers found in the low energy crystal structures of 5-fluoro-2-oxindole (molecule I). Grey = carbon, blue = nitrogen, red = oxygen, yellow = fluorine, white = hydrogen. Packing diagrams of all five structures are available as Supporting Information.

- (2) the lattice energy minimum corresponding to the observed crystal structure for each molecule⁹ (in neither case did the global minimum correspond to the observed crystal structure)

- (3) three additional targets chosen as a representative sample of the low-energy computer-generated crystal structures

The five structures for each molecule were randomly labeled A–E; these are highlighted on plots of the lattice energies and densities of all low-energy computer-generated crystal structures (Figure 2).

For molecule I, both dimer and catemer hydrogen-bond motifs (Figure 3) appear in the set of low-energy crystal structures, so examples were chosen of each (two dimer structures with clearly different packing

Table 2: Space Group, Energies, and Hydrogen Bonding Information on the Five Putative Crystal Structures of 5-Fluoro-2-oxindole (Molecule I)

structure	space group ^a	packing and hydrogen bonding	<i>d</i> (N···O) (Å)	calculated density (g/cm ³)	lattice energy (kJ/mol)
A ^b	<i>P2₁</i>	buckled sheets of hydrogen-bond chains	2.988	1.382	−79.38
B ^c	<i>P1</i>	stepped sheets of hydrogen-bond dimers	2.942	1.453	−83.17
C	<i>P2₁/c</i>	planar sheets of hydrogen-bond chains	2.904	1.373	−80.67
D	<i>P2₁/n</i>	buckled sheets of hydrogen-bond dimers	2.972	1.404	−81.72
E	<i>P2₁/n</i>	helical hydrogen bond chains	2.922	1.396	−78.87

^a In the setting as presented in the test. ^b Observed structure. ^c Global minimum in lattice energy.

Table 3: Space Group, Energies, and Hydrogen Bonding Information on the Five Putative Crystal Structures of Racemic 3-Quinuclidinol (Molecule II)

structure	space group ^a	hydrogen bonding	<i>d</i> (N···O) (Å)	calculated density (g/cm ³)	lattice energy (kJ/mol)
A	<i>P2₁/n</i>	homochiral chains along b, neighboring chains in the a and c directions are antiparallel and parallel, respectively	2.492	1.208	−86.42
B	<i>Pbca</i>	racemic chains along c, neighboring chains in the a and b directions are antiparallel and parallel, respectively	2.465	1.185	−85.11
C ^b	<i>P2₁/n</i>	racemic chains along [101], neighboring chains along b are antiparallel aligned and all chains in the (ac) plane are parallel	2.483	1.226	−87.85
D	<i>P2₁/a</i>	racemic chains along a, neighboring chains in the b and c directions are parallel and antiparallel, respectively	2.518	1.190	−82.44
E ^c	<i>P2₁/n</i>	racemic chains along [101], neighboring chains along b are antiparallel aligned and all chains in the (ac) plane are parallel	2.596	1.220	−83.00

^a In the setting as presented in the test. ^b Global minimum in lattice energy. ^c Observed structure.

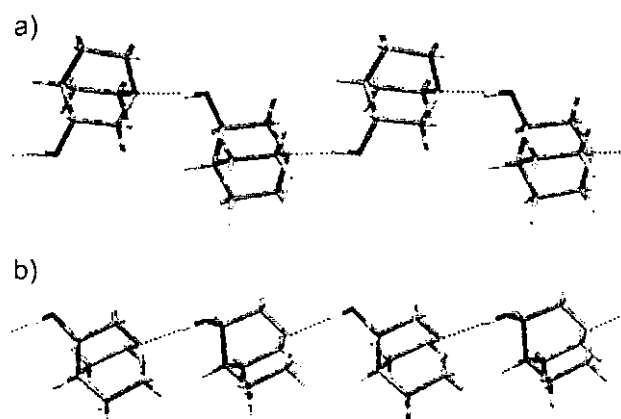


Figure 4. Hydrogen-bond chains in two of the low energy crystal structures of 3-quinuclidinol (molecule II): (a) structure A and (b) structure E. Packing diagrams of all five structures are available as Supporting Information.

of the dimer units and three chain structures, with varying chain geometry and alignment of chains). Some details of the five structures are presented in Table 2.

The low-energy crystal structures of molecule II are much more similar. The hydrogen bonding is the same in all of the structures — chains of O—H···N hydrogen-bond chains (Table 3). Most of the crystal structures contain chains with alternating R and S enantiomers (e.g., Figure 4b), while some contain homochiral chains (e.g., Figure 4a). The differences between structures are much more subtle than for molecule I, and so we considered this a more difficult test.

The procedure for the test was as follows: a poster advertising the crystal structure prediction competition was displayed at the Cambridge Crystallographic Data Centre (CCDC) exhibition stand at the IUCr conference, and a monetary prize was offered to increase the popularity of the experiment.¹⁰ Participants were allowed to enter guesses for either or both molecules and, to keep conditions as controlled as possible, were asked to work alone, could not take the structures away from the

stand, and were allowed a maximum of 15 min for each molecule. Three views of each crystal structure were supplied in paper form, along with the calculated densities, space groups, and conditions of crystal growth (the forms used in the test are provided in Supporting Information), and a computer was available to visualize and analyze all of the structures, using the Mercury crystal structure analysis program.¹¹ Participants were asked to choose their three favorite structures and rank these as 1 (judged as most likely to be the real crystal structure), 2, and 3. The entry forms also included questions regarding the length and type of crystallographic experience of the entrant and for comments on the criteria used to judge the structures.

Results and Discussion

We received 50 entries for molecule I and, as might be expected, fewer people tried their luck with the seemingly more difficult molecule II: only 38 entries were received for this molecule. There was a mix of experience among the participants, ranging from graduate students to lifelong crystallographers with over 30 years of experience. The distributions of guesses, categorized by the participants' experience, are presented in Figure 5. (Note that not all entries listed second and third choices: 49 and 44 of the 50 gave second and third choice guesses for molecule I, respectively, while 37 gave second and third choices for molecule II.)

We first tested the data against the hypothesis that the guesses were random, in which case each crystal structure should have received the same number of guesses. A χ^2 test against this hypothesis shows that, for molecule I, the observed deviation from such an even distribution is significant at a level greater than 0.005 (> 99.5% confidence that the observed trend is significant); there were real preferences expressed for certain structures over others. The second choices were also unevenly distributed. However, within the third choices, the five structures were equally popular. The differences in popularity of the five crystal structures of molecule II were less pronounced, and

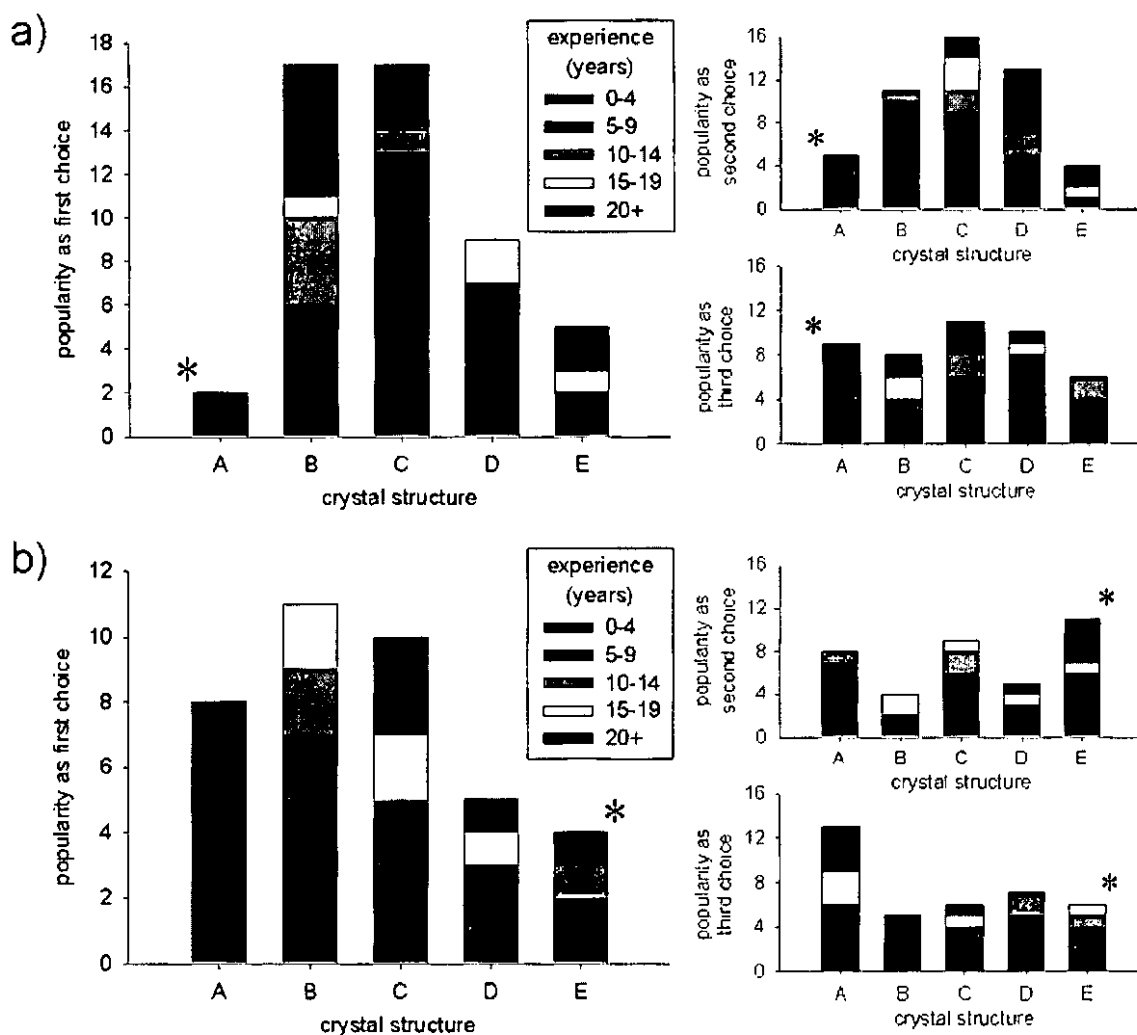


Figure 5. Distribution of first guesses among the proposed crystal structures of (a) molecule I (5-fluoro-2-oxindole) and (b) molecule II (3-quinuclidinol). The bar charts are colored by the number of years crystallographic experience of the participants. The experimentally observed structures are indicated by an asterisk.

statistical tests show that the data do not differ significantly from the case in which all structures were equi-popular (the observed deviations are only significant at a 0.25 confidence level). Either there were no features of the low-energy crystal structures of molecule II that lead to consistent preferences or the sample size of 38 was not large enough to confirm such preferences.

It is clear from Figure 5a that structures B and C were preferred for molecule I, while structure A—the true crystal structure of 5-fluoro-2-oxindole—was the least favorite, collecting only 2 of 50 votes. In fact, of the 44 participants who assigned first, second, and third structures, only 16 (36%) had the correct structure among these three; there was a clear aversion to this crystal structure. While there is a low confidence in the significance of the molecule II results, it is interesting to note that the observed crystal structure of 3-quinuclidinol was also the least popular among the five options—in total, of 88 entries for the two molecules, only six (7%) gave one of the observed crystal structures as first preference. While the distribution of guesses does vary with the length of crystallographic experience (Figure 5), there is no indication that longer experience leads to improved ranking of the correct crystal structures.

The unexpected outcome raises the question of how the participants made their choices, and it is noteworthy that the global minimum energy structure was one of the most popular for both molecules (the global minimum was one of the two most popular for molecule I and the second most popular for molecule II). Not being supplied with the calculated lattice energies, the two obvious criteria for those thinking in terms of packing energy are the crystal density—the most dense having the greater van der Waals contribution to the lattice energy—and quality of specific interactions, such as hydrogen bonds. Some stated that the density was a part of their criteria, but the distribution of guesses does not show this as an overall determinant of the predictions: for both molecules, the least dense of the five structures (C for molecule I, B for molecule II) was the most popular first choice, with the most dense either equally popular (B for molecule I) or second most popular (C for molecule II). Hydrogen-bond geometries also might have played a role. The N...O hydrogen-bond distances were ordered $C < E < B < D < A$ for molecule I and $B < C < A < D < E$ for molecule II, and shorter donor–acceptor distances are normally thought to give stronger hydrogen bonds. Although only 9 of 50 (molecule I) and 5 of 38 (molecule II) people mentioned hydrogen-bond geometry in their criteria, the most

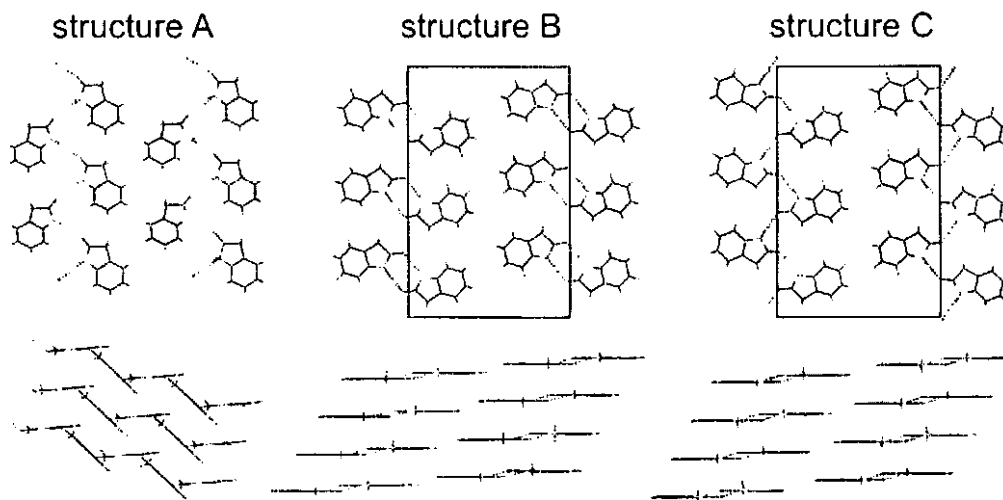


Figure 6. Hydrogen bonding (top) and stacking (bottom) in structures A, B, and C for 5-fluoro-2-oxindole. Grey boxes are included to highlight the areas of similar packing between structures B and C.

popular structure for each molecule had the shortest hydrogen bonds and the least popular structure had the longest hydrogen bonds.¹²

The most popular crystal structures for molecule I (B and C) show the most planar packing of molecules (Figure 6) and, despite the differing hydrogen bonding, have remarkably similar molecular arrangements; non-hydrogen-bonded molecules (highlighted by gray boxes in Figure 6) are arranged in almost exactly the same way. That B and C received the same number of first votes shows that there was no consistent preference for chain or dimer hydrogen bonding, and it was the overall packing of molecules in these two structures that was attractive. Some participants expressed a belief that the C—H...F and F...F interactions between dimers (B) and chains (C) seemed favorable, although these contacts are longer than the sum of van der Waals radii.

Conclusions

A first controlled test of crystallographers' ability to visually select the correct crystal structure from a short list generated by crystal structure prediction calculations has been performed. We anticipated at worst an even distribution of guesses, showing no discriminatory ability in visual assessment of crystal structures, and expected to find a preference among the guesses for the real, experimentally obtained structures. Instead, we found that, for one of the molecules (I), the "correct" crystal structure was least popular by a significant margin. For the other (molecule II) whose crystal structures were less easily distinguished, there was only weak evidence for a consistent preference being given to some structures over others, although again the experimentally observed structure was least popular as first choice. The results of this experiment cast doubts on our initial hunches or intuition when it comes to the "goodness" of a proposed crystal structure. Undoubtedly, with no time constraint and access to everyday research tools—be they databases, molecular modeling, or visualization software—the results might have been different.¹³ Testing crystallographers' abilities to judge computer-generated crystal structures with his or her normal tools at hand would be an interesting further investigation but beyond the scope of this study.

Acknowledgment. The authors thank Andrew Trask and Delia Haynes for discussions while organizing the test, Tomislav

Frišđić for growing crystals of molecule II, and Frank Allen, Gary Battle, James Chisholm, Owen Johnson, Elna Pidcock, Susan Robertson, and Steve Salisbury of the Cambridge Crystallographic Data Centre for help in running the experiment. We thank Dr. J. E. Davies for X-ray data collection and structure determination.

Supporting Information Available: (1) Details of the small manual screen for crystal structures of molecules I and II. (2) Computational details of the lattice energy search. (3) Forms used in the test, including the packing diagrams and crystal information for the five calculated structures of both molecules. (4) CIFs of the experimentally determined crystal structures of 5-fluoro-2-oxindole and 3-quinuclidinol. (5) CIFs of the 10 calculated structures (five for each molecule). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Day, G. M.; Shan, N.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2004**, *4*, 1327–1340.
- (2) Price, S. L. *CrystEngComm* **2004**, *6*, 344–353.
- (3) Gavezzotti, A. *CrystEngComm* **2003**, *5*, 429–438.
- (4) Day, G. M.; Price, S. L.; Leslie, M. *J. Phys. Chem. B* **2003**, *107*, 10919–10933.
- (5) Hamad, S.; Moon, C.; Catlow, C. R. A.; Hulme, A. T.; Price, S. L. *J. Phys. Chem. B* **2006**, *110*, 3323–3329.
- (6) Galton, F. *Nature* **1907**, *75*, 450–451.
- (7) Both molecules were subjected to a small manual screen of crystallization conditions, more details of which are provided as Supporting Information. The crystal structure of molecule I was solved from a crystal grown by slow evaporation from a 1:1 acetone/water solution. The crystal structure of molecule II was originally solved from a crystal grown from a toluene solution at high supersaturation. After the test, a higher-quality crystal structure of molecule II was determined from a crystal grown from acetonitrile.
- (8) Day, G. M.; Motherwell, W. D. S.; Jones, W. *Cryst. Growth Des.* **2005**, *5*, 1023–1033.
- (9) The energy minimized version of the experimentally observed crystal structures were used in the test instead of the X-ray determined structures because this is the situation in true crystal structure prediction studies, where predictions are made based on the calculated structures before a structure is determined by experimental methods.
- (10) The prize was generously donated by the Cambridge Crystallographic Data Centre, and any participants correctly guessing a crystal structure were entered in a draw.
- (11) Macrae, C. F.; Edgington, P. R.; McCabe, P.; Pidcock, E.; Shields, G. P.; Taylor, R.; Towler, M.; van de Streek, J. *J. Appl. Crystallogr.* **2006**, *39*, 453–457.
- (12) Most participants (37 of 50 for molecule I and 27 of 38 for molecule II) indicated that they analyzed the structures in Mercury, so they could measure the geometries of intermolecular contacts, such as

hydrogen bonds. The sample size of people who only used the printed packing diagrams, which had no intermolecular distances shown, are too small to assess whether the lack of such information significantly affected the choice of structures.

- (13) In the case of 5-fluoro-2-oxindole, an analysis of the Cambridge Structural Database (CSD) of all published molecular crystal structures might have been misleading. The non-fluorinated 2-oxin-

dole has one reported crystal structure (CSD refcode ZOYL11), with hydrogen-bond dimers instead of the chains seen in 3-fluoro-2-oxindole. A wider search of the CSD shows a nearly equal distribution of dimers and chains in molecules containing the same $\text{NH}-\text{C}=\text{O}$ fragment in a planar five-membered ring.

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Editorial

Materials Engineering of Solid-State Dosage Forms

Published online November 6, 2007

Organic crystalline materials play a central role in the pharmaceutical industry as well as in fine chemicals. Physico-chemical properties not only affect formulation and production, but also the performance and stability of products. Because the majority of pharmaceutical materials are solid and most of the solid are crystalline, controlling crystal growth and consequent materials properties of drug substances and excipients has become one of essential tasks in the industry, demanding a considerable amount of investment and posing significant challenges for scientists. Crystal size and shape are known to have a great influence on formulation and unit operations including flow, blending, granulation and compaction. Uncontrolled and unpredictable properties may lead to product failure such as content inconsistency (e.g., sub- and super-potency) of solid dosage forms, cited as one of the main reasons for product recall by the FDA, which are often caused by segregation and poor flowability. Furthermore, being unable to identify or select a suitable polymorphic form of a drug makes its products susceptible to phase transformation, and consequently difficult to meet dissolution and bioavailability requirements, likely putting patients' life in jeopardy and throwing a company into a market crisis.

Understanding of crystal growth is critically needed in order to control particulate properties. In spite of vigorous research, our knowledge of nucleation and crystallization is far from being complete; our abilities to predict and control crystal morphology and polymorphism are disappointingly limited. It is widely recognized that solvents or additives can significantly affect crystal growth including growth morphology (habit) and polymorphism of organic crystals. For instance, co-solvents have been utilized to control crystal morphology (1). Uncovering the mechanistic role played by solvent in enhancing or inhibiting crystal growth has been evolved in two general thoughts. In one theory, it is suggested that solvent-surface interactions result in the change of interfacial tension, causing so-called surface roughening and variations in growth rate of crystal faces (2). Alternatively, it is proposed that solvent molecules act in a similar way to additives, preferentially adsorbed on specific faces, posing an additional energy

barrier for solute molecules to attach to solid surfaces (3). The effect of additives on growth morphology has been extensively examined by Lahav, Leiserowitz and co-workers (4). They demonstrated using "tailor-made" or structurally similar additives to alter crystal morphology. It is postulated that additive molecules adsorb and replace host molecules on crystal surfaces due to similar molecular geometries. Depending on the structural difference between the host and additive molecules, attachment of solute molecules to specific faces may be hindered, leading to a different morphology. Interestingly, one of our earlier studies showed the appearance of a new face of acetaminophen single crystals by using a tailor-made additive, which may not be solely due to the geometry hindrance (5). Nonetheless, the theoretical models that are available for crystal growth morphology prediction are incapable of modeling the solvent or additive effect; a systematic approach considering different growth environments remains being discovered.

Because of the significance of polymorphism in the drug development, a huge amount of experimental observations have been made, stimulating vast interests and discussions about properties, analysis, preparation and manufacture of polymorphic systems of drug crystals. Polymorph screening of a new drug becomes routine, not only because of the requirement by the FDA, but also due to the fact that a different polymorph may give a company an extra edge to extend the patent life and protect the market of a high-profit drug. It is not surprising to see high-throughput crystallization (HTC) developed in the last few years. In fact, a new form of acetaminophen was reported by one HTC company (6). It appears supportive to the often-quoted McCrone's argument that the number of forms discovered is up to the time and resources spent on them (7). Growing different polymorphs of organic crystals in solvents has been widely reported. Few attempts, however, can be found in the literature illustrating the use of additives in nucleation of different forms. Additives do show the potential to stabilize one form over others in a solvent (8). Collective effects by solvent and additive make it difficult to elucidate and design additives to control poly-

morphs. Fueled by recent interests in nanotechnology and supra-molecular chemistry, crystal engineering is attracting tremendous attentions from various fields. It is still embryonic, demanding much more fundamental studies. The current approach based on designing synthons for a specific architecture lies in molecular shape and stereochemistry. Co-crystallization of drug compounds has recently attracted lots of attention due to the potential for improving solubility as well as for extending intellectual properties of drug products (9). In addition, many novel approaches for controlling crystal forms have been reported, including epitaxy (10), self-assembled monolayer (SAM) (11), polymers (12), capillary (13) and even laser (14). A recent study of seeding one form by another is intriguing (15). The paper by Lee, Lee and Myerson in this theme section highlights their recent effort in using SAMs to produce polymorphs of two model drug compounds, mefenamic acid and sulfathiazole. By applying microfabrication techniques, they formed alternating micropatterns on glass substrate with two SAMs of different lyophilic properties on which uniform droplets of drug solutions were formed. Upon evaporation, crystalline particles were developed from the droplets; more interestingly, different polymorphs could appear on the same substrate concomitantly.

The mechanistic understanding of polymorphic formation of organic crystals, however, remains to be a great challenge. Polymorphs of an organic crystal have different energies and thermal stabilities. Theoretical studies have been focused on thermodynamics and kinetics of crystal growth regarding polymorph formation, resulting in development of several widely adopted phenomenological and thermodynamic rules (Ostwald rule, phase rule, density rule, etc.). The role of a solvent has been thought as a kinetic factor that may trap a metastable form of a crystal due to its higher solubility in the solvent. However, why a unique crystal structure is formed in a specific solvent remains unanswered. Furthermore, to predict polymorphic structures is even more challenging. Most of current approaches (16), which try to search the global energy space and identify low-energy crystal structures, face a monumental hurdle in tackling this problem, because the intermolecular interactions in organic crystals are weak and the energy difference between a stable form and a metastable form can be as small as a few kilojoules/mol, or even smaller, beyond the certainty of suitable energy calculation methods. Due to the limitation of energy models such as force field to calculate molecular interactions, limited success has been achieved. Using quantum mechanical methods is out of question at present because computation of the whole energy space is overwhelming. In lieu of searching endless combinations of molecules in the crystalline state, the electronic structure of crystal needs to be studied and the intrinsic electronic property of molecule may provide further insights on the intermolecular interactions and molecular packing in solid state, likely inspiring the development of new prediction methods. The paper by our group in this theme section discusses two polymorphs of indomethacin by electronic calculations and conformational analysis. The unique electronic structure of the molecule as unveiled by density functional theory concepts is likely to account for the conformational flexibility and subsequent polymorphic formation.

Despite crystalline materials being dominant in drug development and manufacturing, amorphous substances are

also playing a key role for two reasons. First, the amorphous state may provide desirable properties such as higher dissolution rate than the crystalline counterpart particularly when handling poorly water soluble drugs (17). Compared with crystals, the amorphous state has higher internal energy and higher apparent solubility due to the lacking of the long-range order. Second, unintended amorphous particles may be produced during the manufacturing process, such as milling, resulting in the variation in the manufacturability and subsequent concerns of product quality. Because the amorphous state is thermodynamically unstable, it can transform into a more stable crystalline form. To prevent the phase transformation, amorphous drugs are typically dispersed into a polymer matrix forming a solid solution, called solid dispersion. Mobility of drug molecules is reduced by the interaction between drug molecules and polymers, minimizing the chance of recrystallization of amorphous drugs. Nonetheless, solid dispersion systems may still face stability challenges and, over time, drug molecules may aggregate and crystallize with or without help of temperature oscillation, moisture adsorption, or other conditions under which polymer chains fail to prevent the nucleation and crystal growth. To maintain the amorphous state in solid dispersions has been a huge task. Therefore, understanding the interaction between drug molecules and polymers in solid state requires considerable attentions and investigations. The paper by Komro and Taylor in this theme section offers a fresh glimpse on stabilizing solid dispersions of a drug compound, felodipine, stored at different relative humidities. By measuring the nucleation rate and collecting infrared spectra along with thermal and moisture sorption analyses, it was found that although polymers in the solid dispersions enhanced the water uptake, they were still capable of reducing the nucleation of the amorphous drug.

REFERENCES

1. Y. Kawashima, M. Okumura, and H. Takenaka. Spherical crystallization-direct spherical agglomeration of salicylic acid crystals during crystallization. *Science*, **216**:1127-1128 (1982).
2. E. Van Veenendaal, P. J. C. M. Van Hoof, J. Van Suchtelen, W. J. P. Van Eickevort, and P. Bennema. Kinetic roughening of the kossel (100) surface: Comparison of classical criteria with Monte Carlo results. *Surf. Sci.* **417**:121-138 (1998).
3. I. Weissbuch, L. Addadi, M. Lahav, and L. Leiserowitz. Molecular recognition at crystal interfaces. *Science*, **253**:637-643 (1991).
4. I. Weissbuch, R. Popovitz-Biro, M. Lahav, and L. Leiserowitz. Understanding and control of nucleation, growth, habit, dissolution and structure of two- and three-dimensional crystals using 'tailor-made' auxiliaries. *Acta Crystallogr. B*, **51**:315-348 (1995).
5. T. Li, K. Park, and K. R. Morris. Understanding the formation of etching patterns using a refined Monte Carlo simulation model. *Cryst. Growth Des.* **2**:177-184 (2002).
6. M. L. Petersen, S. L. Marisette, C. McNulty, A. Goldsweig, P. Shaw, M. LeQuesne, J. Monagle, N. Encina, J. Marchionna, A. Johnston, J. Gonzalez-Zagasti, A. V. Lemmo, S. J. Ellis, M. J. Cima, and O. Almarsson. Iterative high-throughput polymorphism studies on acetaminophen and an experimentally derived structure for form III. *J. Am. Chem. Soc.* **124**:10958-10959 (2002).
7. W. C. McCrone. Polymorphism. In D. Fox, M. M. Labes, and A. Weissberger, D. Fox, M. M. Labes, A. Weissberger (eds.), *Physics and chemistry of the organic solid state*, Vol. 2, Wiley Interscience, New York, 1965, pp. 725-767.

8. C. H. Gu, K. Chatterjee, V. Young, and D. J. W. Grant. Stabilization of a metastable polymorph of sulfamocazine by structurally related additives. *J. Cryst. Growth*, **235**:471-481 (2002).
9. A. M. Thayer. Form and function. *Chem. Eng. News*, **85**:17-30 (2007).
10. C. A. Mitchell, L. Yu, and M. D. Ward. Selective nucleation and discovery of organic polymorphs through epitaxy with single crystal substrates. *J. Am. Chem. Soc.*, **123**:10830-10839 (2001).
11. A. Y. Lee, A. Ulman, and A. S. Myerson. Crystallization of amino acids on self-assembled monolayers of rigid thiols on gold. *Langmuir*, **18**:5886-5898 (2002).
12. M. D. Lang, A. L. Grzesiak, and A. J. Matzger. The use of polymer heteronuclei for crystalline polymorph selection. *J. Am. Chem. Soc.*, **124**:14834-14835 (2002).
13. J. L. Hilden, C. E. Reyes, M. J. Kelm, J. S. Tan, J. G. Stowell, and K. R. Morris. Capillary precipitation of a highly polymorphic organic compound. *Cryst. Growth Des.*, **3**:921-926 (2003).
14. B. A. Garez, J. Matz, and A. S. Myerson. Polarization switching of crystal structure in the nonphotochemical light-induced nucleation of supersaturated aqueous glycine solutions. *Phys. Rev. Lett.*, **89**:2002.
15. L. Yu. Nucleation of one polymorph by another. *J. Am. Chem. Soc.*, **125**:6386-6381 (2003).
16. G. M. Day, W. D. S. Motherwell, H. L. Atwood, S. X. M. Boerigter, R. G. D. Valle, E. Venuti, A. Dzyabchenko, J. D. Donitz, B. Schweizer, B. P. van Eijck, P. Erk, J. C. Facelli, V. E. Bazzerra, M. B. Ferraro, D. W. M. Hofmann, F. J. J. Leusen, C. Liang, C. C. Pantelides, P. G. Karametranis, S. L. Price, T. C. Lewis, H. Nowell, A. Torrisi, H. A. Scheraga, Y. A. Armutova, M. U. Schmidt, and P. Verwer. A third blind test of crystal structure prediction. *Acta Crystallogr. B*, **61**:511-527 (2005).
17. B. C. Hancock, and G. Zografi. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.*, **86**:1-12 (1997).
3. What was the turning point in your career?
- Beginning as an independent researcher when trying to establish a niche of its own.
4. Who are the individuals who most influenced your research career?
- Kinam Park, Ken Morris, Steve Byrn, and George Zografi.
5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the *Pharmaceutical Research*?
- Pharmaceutical Research is still and will be the flagship journal in pharmaceutical sciences, so I believe it will and should disseminate any significant work that is interesting to the whole pharmaceutical field, be it biomedical or fundamental.
6. Where is the field of materials engineering of solid dosage forms going, and how do the articles in the theme section fill the gap?
- The field is facing pressures from the industry, regulatory agencies and consumers for the drug products to be of high quality and accountability. It will become the reality that every manufacturing step needs to be thoroughly studied and understood. Therefore, particle engineering is playing a more and more important role in the materials engineering of solid dosage forms, requiring comprehensive understanding and control of particle properties. For this purpose, more and more microscopic and molecular techniques will be employed. The three articles in the theme section offer a glimpse of fundamental studies of pharmaceutical solid-state materials, including understanding and control of crystal structure and investigation of molecular interactions of the amorphous state.
7. What are the challenges for materials engineering of solid dosage forms and how can they be overcome?
- A vast amount of literature exists focusing on the large-scale, phenomenological, and empirical aspects of that solid dosage form development. What is lacking and requires tremendous efforts is the fundamental understanding and control of particle properties. Such efforts can address not only the solubility, dissolution, and bioavailability issues, but the handling and processing difficulties during formulation and manufacturing of solid dosage forms as well.
8. What is the key to developing successful collaborative relationships?
- Specialty and commitment. Not only is your contribution unique, but you also need to be willing to take a lead at the infant stage and sometimes to put in significant efforts on minor issues like scheduling a meeting and following up on a memo.
9. What is your philosophy of educating graduate students?
- My advising philosophy is to give students the freedom to explore, allow them to make mistakes, and stimulate their research interests. I value their motivation, creativeness, attention to details and honesty to the greatest.
10. What are the challenges facing the pharmaceutical sciences?
- Pharmaceutical sciences have always been at the merging point between materials engineering and biomedical research. The balance of the two facets is determined by the funding trend (or lack of funding); for the last decade, more focus has been shifted to biological and clinical studies.

TONGLEI LI, PH.D.

He joined the University of Kentucky as assistant professor in July 2002. He obtained his doctoral degree in pharmaceutical sciences in 1999 under Prof. Kinam Park at Purdue University, IN. He then became a visiting assistant professor at the Department of Industrial and Physical Pharmacy at Purdue University, working closely with Profs. Ken Morris and Steve Byrn before his current post. He has published more than 30 peer-reviewed papers and served on the editorial boards of *Pharmaceutical Research* and *Journal of Controlled Release*. He has received the AAPS New Investigator Award, the PhRMA Research Starter Award, the AACP New Investigator Award, and the NSF CAREER Award. His research group is working on the area of solid-state organic chemistry with focus on crystal growth, surface characterization, and electronic structure calculations.

Interview Questions for Dr. Tonglei Li

1. What do you think holds the key to your success as a pharmaceutical scientist?
- Understanding of fundamental sciences as well as what the pharmaceutical industry needs.
2. What do you consider to be your key research accomplishments?
- Exploring molecular packing and intermolecular interaction of organic crystals with computational tools and atomic force microscopy.

while the pharmaceutical materials science and engineering remain significantly underfunded. As a result, there is an enlarging gap in the graduate education between what the industry needs and what the university can provide. How to fill the gap, I believe, is the biggest challenge facing the pharmaceutical sciences.

11. What is the place for collaboration with industry in academia?

— First of all, there should be more conversations between the industry and academia. Such efforts remain sporadic

and unsystematic. Second, the graduate education needs a great participation by the industry. As fewer and fewer faculty members come from industry, many education programs become isolated from the real world. Third, there should be more funding support from the industry. A few consortia currently support some academic research, but the scale of support is limited and a general, systematic mechanism is needed. Finally, a closer working relationship would be greatly beneficial between the industry's inhouse scientists and academic researchers.

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