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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00.033.208
Solicitud de patente a nombre de
Syngenta Limited

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act 444 RESPUESTAREQUE Folios: 5

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad Syngenta Limited, domiciliada en Guildford, Surrey, Reino Unido de la Gran Bretaña, solicitante de la patente de la referencia, en respuesta al oficio No. 1765 notificado por fijación en lista el 16 de febrero de 2006, relacionado con el concepto técnico No. 091, me permito acompañar los siguientes documentos solicitados por el examinador:

- J. Cryst. Growth, 166(1)1996 900-903.

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3, 35 inciso 2 y 59 inciso 2 del CCA, al analizar este memorial, atentamente solicito se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,


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Ab initio prediction of polymorphs

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Abstract

The prediction of possible crystal structures from first principles, i.e. using only the molecular structure as a starting point, is still controversial. Recently, an approach to solving this crystal packing problem has been proposed. A brief outline of the methodology, the most important limitations, and several applications are presented here.

1. Introduction

Polymorphism is the ability of a compound to crystallize in more than one distinct crystal structure [1]. This polymorphic behavior of organic solids can be of fundamental importance in numerous industries, e.g. pharmaceuticals and agrochemicals [2], pigments and dyes [3], speciality chemicals [4], explosives [5], electronics, etc. In pharmaceutical and agrochemical applications, properties which may vary among polymorphs are: stability (i.e. shelf-life of drugs and vapor pressure of agrochemicals), solubility and dissolution rate (determining bioavailability), crystal shape, compressibility and density (important in formulation). A thorough study of the polymorphic behavior of a new biologically active compound is required for patenting and registration purposes. For pigments, molecular packing, crystal shape and particle size are essential parameters determining color and application properties and behavior. Since these properties vary among polymorphs, it is very important for the pigment and dye industry to study polymorphism. For explosives and propellants, solid-state density is the most significant physical property determining performance parameters such

as shock sensitivity, detonation velocity and detonation pressure.

Theoretical solid-state physics and chemistry are well recognized as predictive and explanatory tools for many solid-state properties. However, application of these theories requires a precise knowledge of crystal structure. Hence, the key to a rational design of crystalline organic materials is the ability to predict stable crystal modifications of a given molecular structure. It is still controversial whether polymorph prediction from first principles is feasible [6,7], but the problem has been addressed for molecular liquids [8], and some approaches to molecular crystals have been reported [7,9]. The basic method used in this study – and some of its applications – was described earlier [10–14]. It has been improved, extended and implemented in the Cerius² molecular modeling environment (available from Molecular Simulations Ltd.).

2. Methodology

Two items are essential for a theoretical approach towards solving the crystal packing problem: a method of pre-

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able potential energy function and an efficient and reliable search methodology to locate the lower minima of that potential function. It is assumed that these minima represent possible crystal modifications. Since lattice energy differences between different polymorphs of the same compound are very small (say, less than one kcal/mol), the potential energy function needs to be as accurate as possible. Any source of inaccuracy in the energy function causing a fluctuation of a few tenths of kcal/mol in the lattice energy differences must be eliminated. For the treatment of electrostatics, Ewald summation [15] and electrostatic potential (ESP) fitted atomic charges [16] are essential. For the other energy contributions, an established force field such as Dreiding [17], which has been parameterized against experimental sublimation energies, is used. One must bear in mind, however, that current force fields have limitations. For instance, due to the neglect of polarization effects, the results are less accurate for heavily polarized structures such as zwitter ions and salts [18]. Furthermore certain atom types, like fluorine and divalent sulphur, are currently not yet optimally parameterized. Crystal structures of these classes of compounds may be predicted, but supporting experimental data (in particular powder diffraction patterns) are needed to select the actual crystal structure from the large set of generated low-energy edge structures.

The search method employed here consists of two separate stages. First, a modified Monte Carlo simulated annealing procedure [10] is used to search the lattice energy hypersurface for low-energy structures. Due to the large number of degrees of freedom in a lattice (unit cell dimensions, translations and rotations of the molecules in the asymmetric unit), all internal degrees of freedom are currently not taken into account during this initial stage, i.e. the molecules are treated as rigid bodies (but they are allowed to relax in the final minimization stage; see below). This means that for flexible compounds, the low-energy conformation has to be considered independently. Consequently, compounds with many low-energy conformers are very computationally intensive, and pose additional problems since each conformation has its own set of atomic charges, resulting in an ambiguous comparison of the energies of polymorphs derived from different conformers.

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A related issue is the treatment of lattice symmetry. One could assume no symmetry during the Monte Carlo search (i.e. space group P1) and Z independent molecules per unit cell. Beyond Z = 2, however, the number of degrees of freedom is increased to such an extent, that a reliable search is presently not feasible [12]. Fortunately, more than 95% of the known molecular crystals belong to 17 space groups [19]. In practice, the search is therefore repeated for each of these relevant space groups. The Monte Carlo stage typically delivers tens of thousands of possible crystal structures, which are subjected to a clustering algorithm during the second stage of the polymorph prediction sequence. This algorithm compares structures on the basis of their Patterson function and removes duplicates from the Monte Carlo trajectory file. The resulting most promising and distinct crystal structures (usually a few hundred) are lattice energy minimized with respect to all degrees of freedom, including molecular conformation, during the third and final stage. The final result is a set of low-energy structures representing possible polymorphs. These structures can then be analyzed in detail, e.g. comparison to experimental powder patterns, Rietveld refinement [20], crystal dynamics simulations to assess thermal stability, prediction of solid-state properties, determination of solvent effects on the polymorphic behavior, etc.

3. Application examples

For validation purposes, it is attempted to predict crystal structures which have previously been solved experimentally. The results for benzene, urea, terephthalic acid, quinaeridone and estrone are briefly discussed here (see Fig. 1 and Table 1). It is important to note that current force fields can only handle "whole" molecules, i.e. intra-molecular symmetry can not be treated. For example, the structure of urea has been solved in the P-42₁m space group [21], whereas the predicted structure belongs to the P2₁ space group. In the chemical sense, however, the two structures are identical. Due to its complex three-dimensional hydrogen bonding pattern and pronounced polarization effects, predicting the urea crystal structure is non-trivial. Table 1 shows a small deviation between experimental and predicted structures, which

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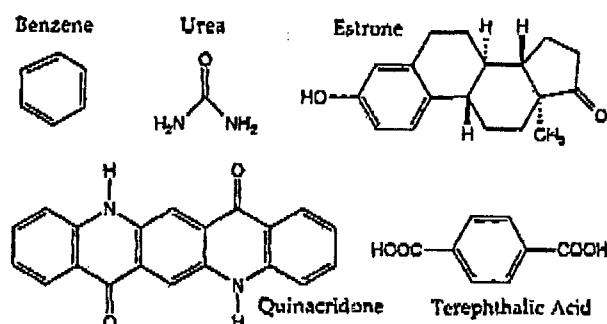


Fig. 1. Crystal structures.

can easily be rectified by means of Rietveld refinement [20].

Benzene can crystallize in two different polymorphs: a stable form with four molecules per unit cell [22] and a metastable, high pressure form with two molecules per unit cell [23]. Both forms were predicted correctly, but the unit cell lengths of the high pressure form are predicted too large since the simulation does not take pressure into account. A run in the P1 space group with four independent molecules in the unit cell was also performed and this reproduced both polymorphs, favoring the more stable form by 0.2 kcal/mol.

Terephthalic acid is an industrially important compound, used to produce PET, with an annual production of about six billion kg. Since terephthalic acid is extremely insoluble in water, it is crystallized at high pressure (30 atm) and high temperature (450 K). The two known polymorphs are very similar [24], showing a one-dimensional hydrogen bonding

pattern. The polymorph prediction method was able to distinguish between these two modifications but the predicted structure could be Rietveld refined to either of them. Interestingly, a more stable (by 0.2 kcal/mol) crystal structure with a two-dimensional hydrogen bonding network was also predicted, which may represent the polymorph which would crystallize at normal pressures and temperatures.

Quinacridone is the parent compound of one of the most important classes of pigments, in terms of tonnage produced and in terms of applications. These pigments show superior performance due to their outstanding light fastness, weather resistance and thermal stability [25]. Quinacridone is known to exhibit at least three polymorphic forms [26], each of which display different colors and application properties. Understanding and controlling the system has up to now been hampered by inadequate knowledge of the crystal structures (only the crystal structure of the most stable gamma form has been published recently [27]). Experimental powder diffraction patterns were available for the three polymorphs. The prediction sequence produced these three crystal forms in the correct stability order, and Rietveld refinement proved beyond any doubt that the previously undetermined alpha and beta forms were solved correctly [28].

Estrone, a female sex hormone, can be regarded as a prototype for the important class of steroid drugs. Steroids are known to be polymorphic, and estrone is no exception, showing at least three crystal forms. The two polymorphs with one molecule in

Table 1
Comparison of experimental versus predicted unit cell dimensions

Compound	<i>a</i> (Å)	<i>b</i> (Å)	<i>c</i> (Å)	β (°)
Benzene experimental A [23] (high pressure)	5.42	5.38	7.53	110.0
Benzene predicted A	5.58	5.63	7.94	107.4
Benzene experimental B1 [22]	7.44	9.55	6.92	90.0
Benzene experimental B2 [22]	7.39	9.42	6.81	90.0
Benzene predicted B	7.52	9.41	6.91	90.0
Urea experimental [21]	5.58	5.58	4.69	90.0
Urea predicted	5.46	5.46	4.71	90.0
Estrone experimental A [29]	12.19	16.30	7.46	90.0
Estrone predicted A	12.78	16.29	7.57	90.0
Estrone experimental B [29]	10.04	18.42	7.79	90.0
Estrone predicted B	10.24	18.94	7.96	90.0

as not symmetric unit (each in a different conformation) [29] were successfully predicted. The simulation also showed that no other polymorphs are to be expected.

Conclusions

This work opens the possibility for rational design and control of crystalline organic materials. Although the current approach is still limited with respect to size, flexibility and ionization of a molecular system, near-future developments in computer speed and force field technology will enable the polymorph prediction of any molecular crystal, including flexible systems and mixed crystals such as hydrates and salts.

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