Crystal Structure of Carnidazole Form II from Synchrotron X-ray Powder Diffraction: Structural Comparison with Form I, the Hydrated Form and the Low Energy Conformations *In Vacuo*

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ABSTRACT: The crystal structure of carnidazole form II, *O*-methyl [2-(2-methyl-5-nitro-1*H*-imidazole-1-yl)ethyl]thiocarbamate, has been determined using synchrotron X-ray powder diffraction in combination with simulated annealing and whole profile pattern matching, and refined by the Rietveld method. For structure solution, 12 degrees of freedom were defined: one motion group and six torsions. Form II crystallizes in space group $P2_1/n$, $Z = 4$, with *unit cell* parameters after Rietveld refinement: $a = 13.915(4)$, $b = 8.095(2)$, $c = 10.649(3)$ Å, $\beta = 110.83(1)^\circ$, and $V = 1121.1(5)$ Å^3. The two polymorphic forms, as well as the hydrate, crystallize in the monoclinic space group $P2_1/n$ having four molecules in the cell. In form II, the molecules are held together by forming two infinite zig-zag chains *via* hydrogen bonds of the type N−H . . . N, the same pattern as in form I. A conformational study of carnidazole, at semiempirical PM3 level, was performed using stochastic approaches based on modification of the flexible torsion angles. The values of the torsion angles for the molecules of the two polymorphic forms and the hydrate of carnidazole are compared to those obtained from the conformational search. Form I and form II are enantiotropic polymorphic pairs this agrees with the fact that the two forms are conformational polymorphs. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:2123–2136, 2006

Keywords: crystal structure; X-ray powder diffractometry; carnidazole; crystallography; polymorphism; molecular modeling; conformational search; differential scanning calorimetry (DSC)

INTRODUCTION

Polymorphism denotes the existence of more than one crystal structure of a substance, and it is of great theoretical and practical interest for the chemical and pharmaceutical industries. There is an intimate relationship between the structure and properties of materials which means that different polymorphic structures of a material can have different physical, chemical biological, or

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pharmaceutical properties. Molecules used by the pharmaceutical industry tend to form polymorphs; these are typically distinguished by different techniques such as X-ray powder diffraction (XRPD), thermal analysis, FTIR, FT-Raman, etc. Each crystalline form shows a different spatial arrangement of the molecules within the crystal lattice (different intermolecular interactions and hence different molecular packing). Different polymorphs have, in general, different solubility and different rates of uptake in the body, leading to lower or higher biological activity than desired. A very large number of pharmaceuticals exhibit the phenomenon of polymorphism, where nearly one-third forms the so-called true polymorphs.[1,2] The nature of this polymorphism is in most cases conformational,[3] where the molecule has different conformations in its different crystal structures. To understand the formation of different polymorphs, the relationship among them and their thermodynamic properties, it is crucial to have an accurate knowledge of the structural aspect of these compounds in the solid state: their crystal structure.

The problems of considering the huge range of possible crystal structures, and modeling the intermolecular forces involved, are very challenging. In this matter, the field of computational crystal structure prediction has tended to concentrate on rigid molecules. The majority of the crystal structure predictions are based on computationally demanding methods like searching for the global minimum in the lattice energy.[4] However, such searches often find more hypothetical crystal structures within the small energy range of possible polymorphism than known polymorphs. Crystal structure prediction can be particularly sensitive to whether the balance between the intermolecular forces and the intramolecular forces produces the correct molecular conformation and thus the relative total energy used in the calculations. The success of these approaches depends on how close the molecular conformation in the solid state is to the gas phase conformation and also how sensitive the lattice energy search is to these packing induced differences. The degree of conformational change induced by packing forces is very dependent on the strength of the torsional potential about the most flexible single bonds relative to the packing forces.[5]

Conformational and structural analysis of complex organic molecules can be performed using molecular modeling *in vacuo* to determine conformations of a molecular system that are low in potential energy, and particularly the values of torsion angles that could lead to stable conformations of a molecule. Besides determining the global minimum of the potential energy surface, it is important to determine all minima that will be thermally populated and will therefore influence macroscopically observable properties of the system. For small molecular systems having few conformational degrees of freedom, a search by systematic variation of all conformational parameters is possible. However, the number of combinations to be systematically explored grows exponentially with the number of degrees of freedom. Since molecular flexibility is usually due to rotation of unhindered bond dihedral or torsion angles, with little change in bond lengths or bond angles, a frequent choice is to only consider the variation of bond torsion angles.[6]

Single crystal X-ray diffraction has been the traditional technique for determining the three-dimensional structure of organic compounds in the solid state. Unfortunately, the necessary prerequisite to obtaining crystals suitable for X-ray diffraction analysis is not always met for all compounds. In recent years, a considerable progress has been made in the techniques for solving crystal structures of relatively complex organic molecular structures from XRPD data by modeling the structure in direct space (global optimization) using, among others, Monte Carlo simulated annealing.[7,8] The majority of variants on the basic global optimization strategy exploit the known connectivity of the structure under study, making this method ideal for solving unknown packing of molecules whose internal structures are largely predictable.[9] Thus the structural variables are position, orientation, and intramolecular geometry: the position is defined by coordinates (x, y, z) of the center of mass or a selected atom, orientation is defined by rotation angles (θ, φ, ψ) and the intramolecular geometry is specified by a set of variable torsion angles $(\tau_1, \tau_2, \ldots, \tau_n)$ that define the molecular conformation.[10] When the difference between the calculated and the observed patterns is minimum, that is, the hypersurface of the multivariable parameters $(x, y, z, \theta, \varphi, \psi, \tau_1, \tau_2 \ldots \tau_n)$ is minimum, and the stacking of the cell is reasonable, the initial structural model is obtained and further refined using the Rietveld method.[11]

Nitroimidazoles are very often associated with antimicrobial activity, whereas imidazolines are often present in drugs acting as adrenergic agents. Carnidazole (Spartrix®), ($C_8H_{12}N_4O_3S$, IUPAC name: *O*-methyl [2-(2-methyl-5-nitro-1*H*-imida-

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