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Drug Discovery—Development Interface

## The Crystal Structure and Behavior of Fenamic Acid-Acridine Complex Under High Pressure

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## ABSTRACT

The crystal structure of fenamic acid-acridine complex is determined by X-ray diffraction. The strong OHN hydrogen bond linking the complex components and other interactions responsible for packing of the molecules into a crystal are investigated within the Quantum Theory of Atom in Molecule theory. The crystal structure is compared with the structure optimized at B3LYP/6-311++G\*\* level and with the theoretical structures optimized under systematically changed pressure. Analysis of the lattice constants, hydrogen bond lengths, and angles of the inter- and intramolecular hydrogen bond under compression is performed. The structural transformation observed at 5 GPa is connected with a change in the intermolecular OHN hydrogen bond. The proton shifts to acceptor and a new interaction in the crystal appears.

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## Introduction

Pharmaceutical solids are important materials which have a practical application. In addition to their molecular structure, the physical and dosage properties are also important for this group of compounds and could be predictable.<sup>1</sup> Cocrystals of small organic molecules deserve great interest as they have properties that can easily be modified. The design of pharmaceutical cocrystals became a stimulus to identify and explain the molecular and physical properties and, as a consequence, the interactions responsible for packing the molecules in crystal.<sup>2</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large group of compounds that can be classified according to their chemical structure. The main groups of NSAIDs are the following: derivatives of salicylic acid, arylalkanoic acids, 2-arylpropionic acids, enolic acid and coxibs, pyrazolone, oxicams, sulphonamides, benzoxazocine, and *N*-arylanthranilic acids (fenamic acids). Compounds of the last group (mefenamic, tolfenamic, flufenamic, meclofenamic acid) are used as popular drugs. For a long time these drugs have been used for the treatment of inflammation, pain, and fever. Recently, the neuroprotective<sup>3</sup> and antitumor<sup>4</sup> properties of NSAIDs have also been

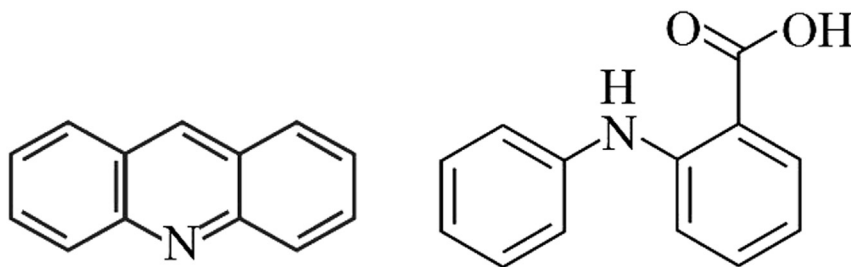
revealed. The therapeutic potential and growing popularity of these agents have led to a search for new, more effective drugs. Fenamic acid is not used in therapy because of its unfavorable properties but it can be used as a precursor in drug design.

In this article, the crystal structure of fenamic acid-acridine complex is described. The investigated compound is an example of a typical complex formed by intermolecular OHN hydrogen bond; therefore the results obtained for this compound are common for all OHN hydrogen bonded complexes. It can also be expected that other molecular interactions responsible for packing the molecules in crystals are typical for molecular crystals. One of the most useful tools to characterize weak intermolecular interactions is the Quantum Theory of Atom in Molecule (QTAIM) method.<sup>5</sup> The presence of critical points of electron density between the molecules in crystal proves the existence of an intermolecular interaction. The electron density parameters can be used as a measure of the interaction strength and character.

For drug compounds, the influence of pressure is important for practical reasons, and it is expected that the hydrogen bond and weak interaction would be pressure sensitive. For the investigated crystal, experimental investigation of the pressure influence is not possible. Melting of the complex is connected with its decomposition and evaporation of acridine. For this reason, we decided to perform the calculation of pressure influence instead of experimental measurement. QTAIM analysis performed for crystal structures at changed pressure allows the detection of changes to

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**Scheme 1.** Structural formula for acridine and fenamic acid.

the strong OHN hydrogen bonds and other interactions associated with packing of the molecules in crystal.

## Experimental

### Crystal Preparation

The fenamic acid-acridine complex crystals were obtained by crystallization in acetonitrile equimolar reagent solutions. Structural formulae for the 2 molecules in the complex are presented in Scheme 1. The crystals were recrystallized 3 times in ethanolic solution. The solvent evaporation occurred at room temperature under atmospheric pressure.

### X-Ray Diffraction

Crystals of fenamic acid-acridine complex CCDC 1436986 were measured with a KUMA KM4 4-circle diffractometer equipped with a CCD area detector and a graphite monochromator using Cu K $\alpha$  ( $\lambda = 0.7173 \text{ \AA}$ ) radiation. All data were corrected for Lorentz, polarization, and absorption effects. The structure was solved by direct methods and refined by the full-matrix least squares method using SHELXTL software.<sup>6</sup> The crystal structure was solved for orthorhombic and monoclinic system. Crystal data and structure refinement for monoclinic and orthorhombic refinement of the investigated compound are presented in Table 1. Both refinements included in Table 1 illustrate this same structure of the investigated crystal. It is well known that the monoclinic phase is not, strictly speaking, a superstructure but should be considered as a polymorph of the orthorhombic structure.

### Computational Details

The investigated molecule was optimized using Gaussian 09 package<sup>7</sup> at DFT B3LYP/6-311++G\*\* level<sup>8,9</sup> taking the crystal geometry as a starting model.

The pressure influence on the crystal structure was investigated based on the density functional theory (DFT)<sup>10,11</sup> using the Cambridge Serial Total Energy Package plane wave code<sup>12</sup> using Materials Studio 7.0 software. Calculations were performed using the generalized gradient approximation (GGA), which is known to provide a very accurate description of the structural and electronic properties of hydrogen bonded systems,<sup>12</sup> in the form of Perdew-Burke-Ernzerhof (PBE) exchange correlation potential.<sup>13,14</sup> These results are compared with those obtained for GGA-PW91 functional.<sup>15</sup> Norm-conserving pseudopotentials with a basis set cutoff energy of 260 eV were used. Criteria of optimization of the atomic positions were as follows: total energy convergence  $5 \times 10^{-6}$  eV/atom, maximum force on atom 0.01 eV/Å, and atomic displacement  $5 \times 10^{-4}$  Å.

The wave function evaluated for the X-ray crystal structure and the optimized molecules was used as the input to the AIMALL program.<sup>16</sup>

## Results and Discussion

### The Structure of Fenamic Acid-Acridine Complex

The molecular structure of the investigated compound is shown in Figure 1.

Fenamic acid-acridine complex is a typical benzoic acid—a tertiary amine cocrystal with an OHN hydrogen bond. The main interaction responsible for forming this cocrystal is the intermolecular OHN hydrogen bond. The relatively short O...N distance of 2.609(2) Å between the hydrogen bond donor (O) and acceptor (N) suggests the presence of moderately strong hydrogen. The lengths of the bonds of the proton to the oxygen of the carboxylic group and the proton acceptor—the acridine nitrogen—are 1.06(2) and 1.55(2) Å, respectively. The OH and NH bond lengths confirm the molecular character of the OHN hydrogen bond with

**Table 1**  
Crystallographic Data and Refinement Parameters for Fenamic Acid-Acridine Complex

Variable	C <sub>13</sub> H <sub>10</sub> NO <sub>2</sub> ·C <sub>6</sub> H <sub>13</sub> N <sub>2</sub>	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub> ·C <sub>13</sub> H <sub>9</sub> N
<i>M<sub>r</sub></i>	325.40	392.44
	Orthorhombic, Pbc <sub>a</sub>	Monoclinic, P2 <sub>1</sub> /c
<i>a</i> (Å)	9.256(3)	9.184(3)
<i>b</i> (Å)	12.931(4)	17.224(3)
<i>c</i> (Å)	27.055(3)	13.116(4)
$\alpha$ (°)	90	90
$\beta$ (°)	90	106.08(2)
$\gamma$ (°)	90	90
<i>V</i>	3238.2(15)	1993.6(10)
<i>Z</i>	8	4
<i>F</i> (000)	1392	824
<i>D<sub>c</sub></i> (mg/m <sup>3</sup> )	1.335	1.308
$\mu$ (mm)	0.09	0.08
<i>T</i> (K)	100	100
Measured reflections	19,850	24,855
Independent reflections	3513	3905
Reflections with $I > 2\sigma(I)$	2386	2622
<i>R<sub>in</sub></i>	0.080	0.071
$\theta_{\max}$ (°)	27.0	26.0
<i>h</i>	$h = -11 \rightarrow 11$	$-11 \rightarrow 11$
<i>k</i>	$k = -16 \rightarrow 15$	$-21 \rightarrow 21$
<i>l</i>	$l = -34 \rightarrow 34$	$-14 \rightarrow 16$
$R[F^2 > 2\sigma(F^2)]$	0.055	0.040
$wR(F^2)$	0.141	0.100
<i>S</i>	1.00	0.87
Parameters	225	279
( $\Delta/\sigma$ ) <sub>max</sub>	0.001	0.001
$\Delta\rho_{\max}$ (e/Å <sup>3</sup> )	0.36	0.25
$\Delta\rho_{\min}$ (-0.20 e/Å <sup>3</sup> )	-0.23	-0.20

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