



# X-ray crystal structure, infrared, Raman and density functional studies of 7-azaindole-3-carboxaldehyde



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## ABSTRACT

A single crystal X-ray analysis, FTIR and FT-Raman spectroscopic studies and the B3LYP/6-311++G (p,d) calculations were performed for 7-azaindole-3-carboxaldehyde, 1*H*-pyrrolo [2,3-*b*]pyridine-3-carbaldehyde (7AI3CA). This compound is an important building block of antibacterial, antifungal and anticancer agents. It crystallizes in the monoclinic system (space group  $P2_1/c$ ) with  $a = 3.83610$  (13),  $b = 18.0442$  (6),  $c = 9.9572$  (4) Å,  $\beta = 96.682$  (3)°,  $V = 684.55$  (4) (Å<sup>3</sup>) and  $Z = 4$ . In the crystal structure, the 7AI3CA molecules form a dimer linked by the moderately strong, dual and nearly linear N–H...N intermolecular hydrogen bonds between the pyrrole and pyridine rings. In addition, each dimer is held together with the neighboring molecules via C–H...O intermolecular interactions, which play an important role in stabilizing the crystal structure. The optimized geometry and the calculated vibrational spectra of a trimer linked by N–H...N and C–H...O intermolecular hydrogen bonds show very good agreement with the experiment. Detailed vibrational assignments of the experimental IR and Raman spectra have been made on the basis of the potential energy distribution (PED), calculated for a trimer of 7AI3CA.

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## 1. Introduction

Heterocyclic compounds with embedded nitrogen atoms are prevalent in nature. They are present in numerous natural products and pharmaceutical leads [1,2]. Among the nitrogen heterocycles, 7-azaindole derivatives are important motifs, many of them display biological activities such as potential anticancer immunomodulators [1]. Moreover, 7-azaindole-3-carboxaldehyde (7AI3CA), Scheme 1, serves as a building block in synthetic chemistry [3–5]. For example, 7AI3CA is a starting material for synthesis of anti-malarial agents [4], streptochlorin analogues of antifungal activity [6] and inhibitors of Cdc7 kinase (cell division cycle 7 kinase), which have been found to be effective in the inhibition of tumor growth in animal models [7].

The crystal structure and vibrational spectra of the title compound have not been reported up to now. It is well known that theoretical calculations assist in a deep understanding of the vibrational spectra, which can be used to identify the substances.

In this work, we have performed a combined experimental and

theoretical study on 7AI3CA by using a single crystal X-ray diffraction analysis, infrared and Raman spectroscopy and density functional (B3LYP) calculations. The theoretical vibrational spectra have been calculated for two different models of the title molecule, monomer and trimer. To make an unequivocal assignment of the experimental spectra, a rigorous normal coordinate analysis has been carried out.

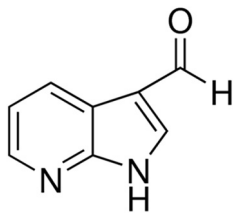
## 2. Experimental

### 2.1. Preparation of crystals of 7AI3CA

7-Azaindole-3-carboxaldehyde (7AI3CA) was purchased from Sigma-Aldrich. Single crystals suitable for the X-ray analysis were obtained by a slow evaporation of an ethanol solution of 7AI3CA. We attempted to prepare the N-deuterated species from C<sub>2</sub>H<sub>5</sub>OD solution. However, despite the repeated recrystallization from deuterated ethanol, the N-deuterated derivative of the title compound could not be obtained. This is probably due to the fact that the N–H bond in the pyrrole ring of 7AI3CA is involved in a strong electronic conjugation with the aromatic azaindole rings, therefore, a substitution of this H atom is quite difficult.

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**Scheme 1.** 7-Azaindole-3-carboxaldehyde.

### 2.1.1. X-ray diffraction analysis

The single crystal X-ray diffraction data were collected by means of a four-circle diffractometer equipped with a CCD detector and using an  $\omega$ -scan technique ( $\Delta\omega = 1^\circ$ ). The data collection and reduction along with absorption corrections were performed by the CrysAlis<sup>Pro</sup> software package [8]. The structure was solved by the SHELXS2013 and refined by the SHELXL2014 programs [9]. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located in a difference Fourier map and their coordinates and isotropic displacement parameters were refined freely. The visualization of the structure was prepared with the Ortep-3 and Mercury CSD 3.3 programs [10,11]. The details of data collection parameters, crystallographic data and final agreement parameters are gathered in Table 1.

### 2.1.2. Spectroscopic measurements

The Fourier transform mid infrared (MIR) spectrum of 7AI3CA in the region 4000–400  $\text{cm}^{-1}$  was measured at 2  $\text{cm}^{-1}$  resolution on a Nicolet-Nexus spectrometer using the KBr pellet technique. The far infrared (FIR) spectrum of 7AI3CA (in the range 600–50  $\text{cm}^{-1}$ ) were measured on a Bruker VERTEX 70V spectrometer equipped with a diamond ATR accessory and air-cooled DTGS detector. The instrument was kept under vacuum and the spectrum was recorded at a resolution of 2  $\text{cm}^{-1}$ . The ATR spectra were elaborated in the OPUS<sup>TM</sup> software to convert them from reflectance into absorbance.

The FT-Raman spectrum (FT-R) of 7AI3CA (in the range 3500–50  $\text{cm}^{-1}$ ) was measured on a Bruker MultiRAM spectrometer equipped with a liquid nitrogen cooled germanium detector and a Nd:YAG laser (emitting radiation at a wavelength of 1064 nm). The

spectrum was recorded at a resolution of 2  $\text{cm}^{-1}$  with co-addition of 256 scans.

### 2.1.3. Theoretical methods

The computations were performed with the Gaussian 09 set of programs [12]. Full geometry optimizations were performed for the two models of 7AI3CA: monomer and a trimer connected by intermolecular N–H $\cdots$ N and C–H $\cdots$ O hydrogen bonds. The harmonic frequencies, infrared intensities and Raman scattering activities were calculated for monomer and trimer (consisting of 51 atoms). In the calculations we used the Becke three-parameter hybrid functional, B3LYP [13–15] combined with the 6-311++G (d,p) basis set [16,17]. The theoretical Raman intensities (which simulate the measured Raman spectrum) were calculated according to the formulas reported earlier [18]. The deficiencies of the applied harmonic approximation were corrected by using the scale factors for the calculated frequencies, similarly as in our earlier studies [19–21]. The rigorous normal coordinate analysis for 7AI3CA monomer was carried out, and the potential energy distribution (PED) was calculated using the BALGA program [22]. For 7AI3CA trimer, PED was calculated by the FCART06 program [23,24]. In addition, the Gauss-View program [12] was employed for the graphic visualization of the normal modes.

## 3. Results and discussion

### 3.1. Crystal and molecular structure of 7AI3CA

The structure of 7AI3CA is monoclinic of the space group  $P2_1/c$  with  $Z = 4$ . The overall view of 7AI3CA molecule with the atom labeling is shown in Fig. 1.

The full optimization of geometry has been performed for two possible 7AI3CA conformers (1 and 2), which differ in the orientation of the C8=O1 bond relative to the C3–C8 bond in the carboxaldehyde group, as shown in Fig. 1S (Supplementary data). Both conformers are planar ( $C_s$  symmetry). Conformer 2 is slightly higher in energy than 1, by about 1.6 kcal mol<sup>-1</sup>. In 2, the CHO group is rotated (by 180°) in comparison to 1. The subsequent calculations of vibrational frequencies have revealed that both 1 and 2 conformers are stable in a gas phase. The single crystal X-ray diffraction study indicates the presence of conformer 1 in a crystal.

We have also performed the geometry optimization of a trimer ( $C_1$  symmetry), where the monomeric units a, b and c are linked by intermolecular N–H $\cdots$ N and C–H $\cdots$ O hydrogen bonds (Fig. 2).

Table 2 lists the selected experimental bond lengths and angles along with the corresponding theoretical values calculated for monomer (conformer 1) and for trimer of 7AI3CA. The average relative deviation (ARD) between the experimental and theoretical bond lengths is equal to 3.74% in conformer 1. The ARDs values for the trimer are equal to: 3.84% in unit a, 3.82% in unit b and 3.75% in unit c. The ARD values for the bond angles are: 0.64% (conformer 1), 0.51% in unit a, 0.59% in unit b and 0.62% in unit c. The average relative deviation (ARD) of bond lengths in 7AI3CA (omitting the C–H and N–H bond lengths) is equal to: 0.60% (conformer 1), 0.49% (unit a), 0.48% (unit b) and 0.61% (unit c). The ARD values for the bond angles (neglecting those involving the H atoms) are: 0.38% (conformer 1), 0.31% in unit a, 0.29% in unit b and 0.38% in unit c of the trimer.

According to the X-ray results, the conjugated six-membered pyridine and five-membered pyrrole rings of the 7-azindole part are nearly coplanar, for example, the C3–C3A–C7A–N7 torsion angle is 179.56 (12)° and the N1–C2–C3–C3A torsion angle is nearly zero (–0.22 (16)°). The carboxaldehyde group of 7AI3CA shows only a small distortion from the molecular plane: the O1–C8–C3–C3A and O1–C8–C3–C2 torsion angles are 3.8 (2)°

**Table 1**  
Crystal data and structure refinement details for 7AI3CA.

Empirical formula	C <sub>8</sub> H <sub>6</sub> N <sub>2</sub> O
Formula weight	146.15
Temperature (K)	299 (2)
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions (Å, °)	a = 3.83610 (13) b = 18.0442 (6) c = 9.9572 (4) $\beta = 96.682$ (3)
Volume (Å <sup>3</sup> )	684.55 (4)
Z (molecules/cell)	4
Density calculated (Mg m <sup>-3</sup> )	1.418
Crystal size (mm)	0.15 × 0.25 × 0.50
Absorption coefficient (mm <sup>-1</sup> )	0.098
F (000)	304
$\theta$ range for data collection (°)	2.26 to 26.00
Reflections collected	2324
Independent reflections (all)	1351
Independent reflections [ $I > 2\sigma(I)$ ]	1171
Data/restraints/parameters	1351/0/125
Goodness-of-fit on $F^2$	1.066
R (int)	0.011
Final R indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0361$ , $wR_2 = 0.0918$
$\Delta\rho_{\max}$ and $\Delta\rho_{\min}$ (eÅ <sup>-3</sup> )	0.217, –0.151

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