

# Molecular structure of 4-benzoyl-3-ethylcarboxylate 1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole: A combined experimental and theoretical study

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## ABSTRACT

The title molecule, 4-benzoyl-3-ethylcarboxylate 1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole, (C<sub>26</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>), was synthesized and characterized by IR–NMR spectroscopy and single-crystal X-ray diffraction. In addition to the molecular geometry from X-ray experiment, the molecular geometry, vibrational frequencies and gauge-independent atomic orbital (GIAO) <sup>1</sup>H and <sup>13</sup>C NMR chemical shift values of the title compound in the ground state have been calculated using the spin-restricted Hartree–Fock (HF) and density functional theory (DFT/B3LYP) method with the 6-31G (d, p) basis set, and compared with the experimental data. To determine conformational flexibility, molecular energy profile of the title compound was obtained by semi-empirical (AM1) with respect to selected degree of torsional freedom, which was varied from –180° to +180° in steps 10°. Besides, molecular electrostatic potential (MEP) distribution, frontier molecular orbitals (FMOs) and thermodynamic properties of the title molecule were investigated by theoretical calculations at the B3LYP/6-31G (d, p) level.

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## 1. Introduction

Pyrazoles have occupied a unique position in the design and synthesis of novel biologically active agents that exert remarkable anti-cancer activities. In fact, pyrazoles have been studied for over a century as an important class of heterocyclic compounds and still continue to attract considerable attention due to the broad range of biological activities they possess. Among these, *N*-Arylpyrazoles are an interesting class of heterocycles with remarkable pharmacological activities such as antibacterial-antifungal, tumor-necrosis inhibitor, antimicrobial, hypoglycemic, hypolipidemic and anti-inflammatory [1–5]. Pyrazole-3-carboxylate derivative was obtained from Fischer esterification reaction of 4-benzoyl-5-phenyl-1-(4-methoxyphenyl)-1*H*-pyrazole-3-carboxylic acid or -acid chloride with ethanol. The possible properties of the pyrazole derivatives make it attractive to study these compounds [5–8].

In this study, we present results of a detailed investigation of the synthesis and structure characterization of 4-benzoyl-3-ethylcarboxylate 1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrazole using single crystal X-ray, IR, NMR and quantum chemical methods, besides elemental analysis. Vibrational spectroscopy (IR, Raman) and NMR techniques are widely used to study structural and dynamical aspects of molecular systems. With the recent advances

in computational methods and common access to large-scale powerful computers and software, it is possible to describe molecular properties of relatively small molecules [9] with near chemical accuracy using theoretical methods.

The combination of HF and DFT calculations of chemical shifts and harmonic vibrations with nuclear magnetic resonance (NMR) and IR experimental parameters, respectively, has become an accepted technique to gather insight into the molecular structure. The aim of the present work was to describe and characterize the molecular structure, vibrational properties and chemical shifts of the title compound, both experimentally and theoretically. A comparison of the experimental and theoretical spectra can be very useful in making correct assignments and understanding the basic chemical shift-molecular structure relationship. And so, these calculations are valuable for providing insight into molecular analysis. Therefore, we also make comparisons between experimental and calculated values.

## 2. Materials and methods

### 2.1. General remarks

Melting points were measured on an Electro thermal 9200 apparatus and are uncorrected. Microanalysis was performed using a Leco-932 CHNS-O elemental analyzer. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured with a Bruker Avance III 400 MHz

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spectrometer and the chemical shifts are expressed in ppm relatively to TMS. IR spectra of the compound were recorded in the range of 400–4000  $\text{cm}^{-1}$  region with a Shimadzu FT-IR 8400 spectrophotometer. Solvents were dried by refluxing with the appropriate drying agents and distilled before use. All other reagents were purchased from Merck, Fluka, Aldrich and used without further purification. The starting material was prepared according to the literature procedure that described by Ziegler and co-workers [10] and by Akçamur and co-workers [11,12].

## 2.2. Synthesis

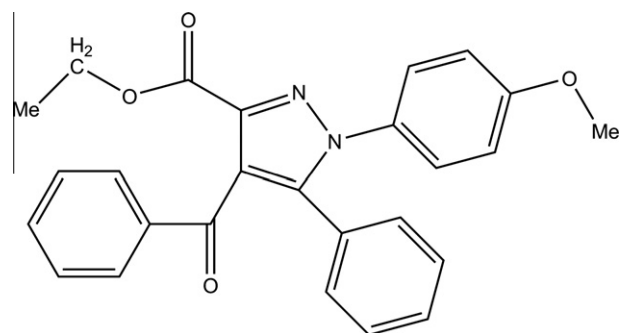
To the cold solution of 4-benzoyl-5-phenyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylic acid (0.40 g, 1 mmol) in sulfuric acid was added a large excess of methanol with stirring. Then the reaction mixture was refluxed on a steam bath for 5 h with stirring. After cooling's to 5 °C, the precipitate formed was filtered off and recrystallized from the same alcohol to give 0.275 g (64%), mp 152 °C; FT-IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3059 (aromatic C–H), 2964 (aliph. C–H), 1730 (O=C=O), 1657  $\text{cm}^{-1}$  (Ph–C=O);  $^1\text{H}$  NMR (400 MHz, Chloroform,  $\text{CDCl}_3$ ):  $\delta$  7.87–6.83 (m, 14H,  $\text{H}_{\text{arom}}$ ); 4.16 (q, 2H,  $\text{CH}_2$ ); 3.80 (s, 3H,  $\text{OCH}_3$ ), 1.03 ppm (t, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  191.32 Ph–C=O, 161.33 (C=O, ester), 159.49 (C-23), 143.62, 142.12, 138.21, 133.25, 131.91, 129.84, 129.19, 128.50, 128.46, 127.88, 126.95, 122.83, 114.09 (C–Ph), 61.32 ( $\text{CH}_2$ ), 55.49 ( $\text{OCH}_3$ ), 13.73 ppm ( $\text{CH}_3$ ) (Scheme 1).

## 2.3. X-ray analysis

The single-crystal X-ray data were collected on a STOE IPDS II image plate diffractometer at 296 K. Graphite-monochromated  $\text{MoK}\alpha$  radiation ( $\lambda = 0.71073$  Å) and the  $w$ -scan technique were used. The structure was solved by direct methods using SHELXS-97 [13] and refined through the full-matrix least-squares method using SHELXL-97 [14], implemented in the WinGX [15] program suite. Non-hydrogen atoms were refined with anisotropic displacement parameters. All H atoms were located in a difference Fourier map and were refined isotropically. Data collection: Stoe X-AREA [16], cell refinement: Stoe X-AREA [16], data reduction: Stoe X-RED [16]. The general-purpose crystallographic tool PLATON [17] was used for the structure analysis and presentation of the results.

## 2.4. Computational details

The molecular structure of the title compound in the ground state (*in vacuo*) was optimized using the spin-restricted HF (HF) and DFT (B3LYP) [18,19] methods with the 6-31G (d,p) basis set. For modeling, the initial guess of the compound was first obtained from the X-ray coordinates. Then, vibrational frequencies for the optimized molecular structures were calculated with these methods and then scaled by 0.9260 and 0.9608 [20,21], respectively. The geometry of the compound, together with that of tetramethylsilane (TMS), is fully optimized.  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts were calculated within GIAO approach [22,23] applying the same methods and the basis set as used for geometry optimization. The predicted  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts were derived from the equation  $\delta = \Sigma_0 - \Sigma$ , where  $\delta$  is the chemical shift,  $\Sigma$  is the absolute shielding and  $\Sigma_0$  is the absolute shielding of the standard (TMS), whose values are 32.33 and 203.44 ppm for HF, and 31.74 and 192.06 ppm for B3LYP methods with the 6-31G (d,p) basis set, respectively. All the calculations were performed without specifying any symmetry for the title molecule by using Gauss View molecular visualization program [24] and Gaussian 03 program package [25]. The effect of solvent on the theoretical NMR parameters was included using the default model Integral-Equation-Formalism Polarizable Continuum Model (IEF-PCM) [26] provided by Gaussian 03. Chloroform was



Scheme 1. The formation of the title compound.

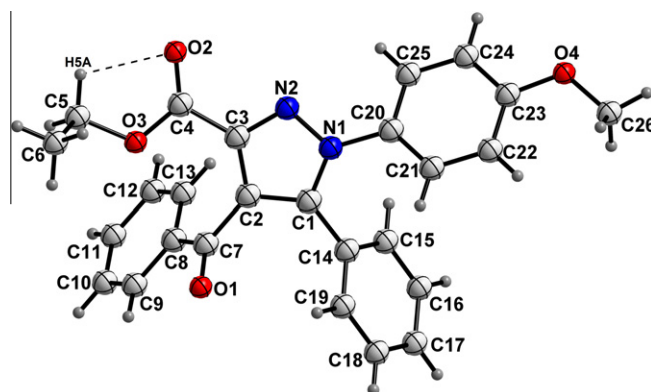


Fig. 1. A view of the title compound showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level. Hydrogen bonds are indicated by broken lines.

Table 1  
Crystal data and structure refinement parameters for the title compound.

CCDC deposition no.	834,135
Color/shape	Colorless/Prism
Chemical formula	$\text{C}_{26}\text{H}_{22}\text{N}_2\text{O}_4$
Formula weight	426.46
Temperature (K)	296
Wavelength (Å)	0.71073 MoK $\alpha$
Crystal system	Monoclinic
Space group	$P 2_1/c$
<i>Unit cell parameters</i>	
<i>a</i> , <i>b</i> , <i>c</i> (Å)	10.6321 (4), 16.4877 (5), 12.7247 (4)
$\alpha$ , $\beta$ , $\gamma$ (°)	90, 103.673 (3), 90
Volume (Å <sup>3</sup> )	2167.41 (12)
<i>Z</i>	4
$D_{\text{calc}}$ (g/cm <sup>3</sup> )	1.307
$\mu$ (mm <sup>-1</sup> )	0.09
<i>F</i> (000)	896
Crystal size (mm <sup>3</sup> )	0.78 × 0.49 × 0.29
Diffractometer/measurement method	STOE IPDS 2/ $\omega$ scan
Index ranges	$-13 \leq h \leq 13$ , $-20 \leq k \leq 20$ , $-15 \leq l \leq 15$
$\theta$ Range for data collection (°)	$2.0 \leq \theta \leq 26.0$
Reflections collected	28,826
Independent/observed reflections	4529/3687
$R_{\text{int}}$	0.023
Refinement method	Full-matrix least-squares on $F^2$
Data/restraints/parameters	4529/0/290
Goodness-of-fit on $F^2$	1.05
<i>R</i> indices [ $I > 2\sigma(I)$ ]	$R_1 = 0.0406$ , $wR_2 = 0.1056$
<i>R</i> indices (all data)	$R_1 = 0.0527$ , $wR_2 = 0.1002$
$\Delta\rho_{\text{max}}$ , $\Delta\rho_{\text{min}}$ (e/Å <sup>3</sup> )	0.14, -0.17

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