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Synthesis, structural characterization, and computational study of novel (*E*)-N′-(1-*p*-tolylethylidene)furan-2-carbohydrazide

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HIGHLIGHTS

- Preparation and solid state study of a novel member of an interesting structural class.
- This modeling studies show that the *E*-isomer is the global minimum isomer.
- A rationale for the observed *E*-selectivity is based on strong *E*–*E* dimerization.

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ABSTRACT

An efficient synthesis of the novel (*E*)-N′-(1-*p*-tolylethylidene)furan-2-carbohydrazide is described. The molecular structural features were then confirmed by single crystal X-ray diffraction. Quantum chemical calculations including molecular geometry, intermolecular H-bonds, and vibrational frequencies were carried out for the structures to explain stability and geometry using both density functional (DFT/B3LYP) and the Hartree–Fock (HF) with 6-311+G(d,p) basis set. The calculated structural parameters are presented and compared with their experimental X-ray counterparts. The *E*-isomer is a global minimum on the potential energy surface. However, validation of the computational methods here *via* comparison with the observed X-ray data enabled computational analysis to predict that head-to-tail *E*/*E*-dimer of the observed *E*-isomer has significantly stronger intermolecular hydrogen bonding compared with the non-observed *Z*/*Z*-dimer. It was observed that the stretching mode of N—H and C=O shifted to lower frequencies, due to pairwise intermolecular N—H···O hydrogen bonds. This provides a clear rationale for the isomeric specificity obtained and provides a validation of the optimized method which could be applied to predict structures of other useful carbohydrazides. Generally, it has been concluded that the findings of B3LYP hybrid functional fit better to the observed geometrical and vibrational parameters than the results of the HF.

1. Introduction

Hydrazones possessing an azomethine —NHN=CH— proton represent a key component of organic compounds which have been used in various biological and chemical applications [1]. These compounds can be synthesized under simple reaction conditions at moderate temperature. These materials are normally generated *via* a condensation reaction between an acid hydrazide and aldehydes or ketones, either in the presence or absence of acid catalyst [2,3]. In addition to their own important properties and applications, both *N*-acyl- and *N*-arylhydrazones are vital precursors for the synthesis of a wide range of organic compounds including 1,3,4-oxadiazoles derivatives [4–7]. For example, *N*-heterocyclic hydrazones derivatives have received major interest due to their coordination properties which enable them to act as mono- or polydentate ligands towards metal ions, and several such metal complexes have been synthesized and characterized [8]. They also act as precious spectrofluorimetric reagents in metal ion determination in various environments including for Os(VIII), Cd(II), Co(II), and Hg(II) [9]. Furthermore, these compounds may exhibit pharmacological activities. In fact, there is considerable evidence to suggest that the hydrazone moiety present in many derivatives imparts a valuable pharmacophoric character for example for the inhibition of COX, treatment of tuberculosis in combination with

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other drugs, and potential inhibitory activity toward protein tyrosine phosphate from Mycobacterium Tuberculosis [10–12].

Hydrazones that possess acidic hydrogen are identified by their prototropic tautomerism. Therefore, two different geometrical structures are possibly available; *syn*-Z or *anti*-E isomers with different tautomeric forms. Inter and Intra- molecular hydrogen bonds of such compounds and their subsequent influence in generating different supramolecular arrays have been identified [13–15].

Hydrazone-containing compounds have been attracting substantial attention in computational sciences. For example, Guner et al. employed both *ab initio* and DFT methods to investigate cyanobenzaldehyde isonicotinoyl hydrazone [16]. The absorption and fluorescence energies of substituted aryl-1,8-naphthalimide hydrazones was modeled using high level DFT [17]. Also, the structural activity relationships of a series of pyrrole hydrazones were examined as new tuberculosis agents where various computed constitutional, topological, physicochemical and quantum–mechanical descriptors were correlated with their reactivity [18].

In this study, as a part of our ongoing interest in functionalized hydrazides we report the synthesis of (*E*)-N′-(1-*p*-tolylethylidene)furan-2-carbohydrazide and comparison of X-ray structural characterization with detailed computational investigations of the structures. In addition, the roles of energy and H-bonding in the subsequent stabilities of the *E*/*Z*-geometrical isomers are computationally investigated.

2. Experimental work

2.1. Syntheses and characterization

FTIR spectra was recorded using Shimadzu 8201 spectrophotometer with KBr technique in region 4000–400 cm^{-1} that was calibrated by polystyrene. ES–MS and HRMS were recorded on a Micromass LCT orthogonal acceleration time-of-flight mass spectrometer (positive ion mode). ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz on a DPX400 spectrometer. Chemical shifts are denoted in ppm (δ) relative to internal solvent standard.

Furic acid hydrazide (0.0158 mol) and 1-*p*-tolylethanone (0.0158 mol) were heated under reflux in ethanol (20 ml) for 30 min until a solid precipitate was formed. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure. The solid was washed successively with cold ethanol, filtered and then recrystallized from cold ethanol to give the pure product in 89% yield and Mp 169–170 °C. IR (KBr) ν cm^{-1}: 3178 (NH str.), 1151 (N—N), 1658 (C═O), 1507 (C═C), 1561 (N═C), 1134 (C—O). MS (ESI) *m*/*z*: [M+Na]$^+$, 265.0], ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.6 (s, 1H, N**H**), 7.9 (d, *J* = 0.9 Hz, 1H, OC**H**CH, furan ring), 7.8 (d, *J* = 7.7 Hz, 2H, aromatic ring), 7.7 (d, *J* = 8.7 Hz, 2H, aromatic ring), 7.4 (d, *J* = 3.3 Hz, 1H, OCHC**H,** furan ring), 6.7 (dd, *J* = 3.5, 1.7 Hz, 1H, CHC**H**CH, furan ring), 2.4 (s, 3H, **C**$\mathbf{H_3}$), 2.3 (s, 3H, **C**$\mathbf{H_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (**C**═O), 154.3 (**C**═N), 147.2 (O**C**HCH, furan ring), 144.3 (O**C**CH, furan ring), 140.1, 135.0, 129.3, 126.7 (aromatic ring), 115.9 (OC**C**H, furan ring), 112.6 (OCH**C**H, furan ring), 21.4 (**C**H_3), 13.2 (**C**H_3).

2.2. Crystallographic analysis

X-ray single crystal data were collected at 230 K using graphite monochromated Mo Kα λ = 0.7107 Å radiation on a Bruker SMART APEX CCD diffractometer. Data reduction was carried out using SAINT [19] and the structure was solved using SHELXS-97 [20] and showed that there are two molecules of the title compound in the form of a dimer in the asymmetric unit. Full matrix refinement on F^2 was performed with SHELXL-97 [20] and all calculations were carried out using the SHELXTL package [20]. The non-H atoms were refined anisotropically and H atoms were included in calculated positions, except for those bonded to N, which were found by Difference Fourier Methods and refined isotropically. It was necessary to collect the data at 230 K, since flash freezing to 100 K caused the crystal to break up. The crystal data are summarized in Table 1.

3. Computational work

The molecular structures of compounds involved in the study were constructed using Hyperchem 7 [21] and initially optimized at the Semiempirical PM7 Sparkel level of theory implemented in MOPAC09 [22]. Then, using Gaussian 09 package [23], the initially optimized structures were fully optimized at their ground state in the gaseous phase at the DFT/B3LYP and HF level of theories with 6-311+G(d,p) basis set [24,25]. The stationary natures of the fully optimized structures were analytically examined by calculating the harmonic vibrational frequencies at the same level of theories and then zero point energies were estimated. To generate the correct frequencies, the computed vibrational frequencies were scaled by 0.9613 and 0.905 for B3LYP and HF subsequently as reported in literature [26,27]. Electrical Energies of ground state isomers, dimers and rotational states were estimated using single point energy calculations at a higher level of theory; B3LYP/6-311++G(2df,pd)//B3LYB/6-311+G(d,p). Predicted energies were corrected for zero-point vibrational energies. Intermolecular hydrogen bondings and chemical potentials extrema (maximum and minimum) were evaluated at the same level of theories. Atomic charges were calculated using natural population analysis [28]. GaussView and Gapedit programs were used for visualization of structures [29,30].

Table 1
Crystal data and structure refinement of (*E*)-N′-(1-*p*-tolylethylidene)furan-2-carbohydrazide.

Parameter	Value
Empirical formula	$C_{14}H_{14}N_2O_2$
Formula weight	242.27
Crystal color	Colorless
Crystal size (mm^3)	0.5 × 0.5 × 0.5
Crystal system	Triclinic
Space group	*P* − 1
Unit cell dimensions	10.311(7)
a (Å)	11.633(8)
b (Å)	12.480(8)
c (Å)	67.050(12)
α (deg)	74.755(13)
β (deg)	64.172(11)
γ (deg)	1232.8(14)
Z	4
$D_{calculated}$ (g cm^{-3})	1.305
F(000)	512
μ Mo Kα (mm^{-1})	0.089
T (K)	230(2)
λ (Å)	0.71073
Absorption coefficient (mm^{-1})	0.089
Absorption correction	None
Range of *h*, *k*, *l*	−7/12, −13/14, −11/15
θ min/max (deg)	2.05/26.42
R (int)	0.0403
Completeness to theta = 26.42	96.5%
Reflections collected/unique/	7164/4907
Data/restraints/parameters	4907/0/337
GOF on F^2	0.902
Final *R* indices [$I > 2\sigma(I)$]R_1, wR_2	0.0466, 0.1131
R indices (all data) R_1, wR_2	0.0732, 0.1210
$\Delta\rho_{min}$, $\Delta\rho_{max}$, $\Delta\rho_{rms}$	−0.241 eÅ^{-3}, 0.211 eÅ^{-3}, 0.05
Refinement number of parameters	337
Refinement number of reflections	4907