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Synthesis, characterization and computational study on ethyl 4-(3-Furan-2yl-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate

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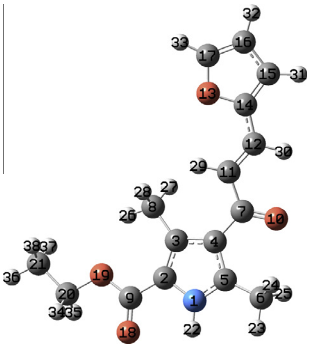
HIGHLIGHTS

- UV–visible spectrum studied using TD-DFT/6-31G(d,p) method indicates n–π^* and π–π^* transitions.
- FT-IR spectrum study indicates dimer formation.
- Vibrational analysis shows red shifts in ν_{N-H} and $\nu_{C=O}$ as result of dimer formation.
- Binding energy of dimer is calculated as 13.82 kcal/mol.
- Descriptors analyses indicate that chalcone $>C{=}C{-}C{=}O$ frame is prone to attack leading to formation of heterocyclic compounds.

GRAPHICAL ABSTRACT



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ABSTRACT

As part of study on pyrrole derivatives, we have synthesized a pyrrole chalcone derivative: ethyl 4-(3-Furan-2yl-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate (EFADPC) by aldol condensation of ethyl 3, 5-dimethyl-4-actyl-1*H*-pyrrole-2-carboxylate with furan-2-carbaldehyde in the presence of strong hydroxyl base as catalyst. The product EFADPC has been confirmed by spectroscopic (FT–IR, ^{1}H NMR, and UV–visible) analyses. Quantum chemical calculation also provides good correlation with experimental data. The molecular electrostatic potential surface (MEP), natural bond orbital interactions (NBO), electronic descriptors, quantum theory of atoms' in molecules (QTAIM) and experimental FT-IR spectrum have been used to predict the sites and nature of interactions which indicate that the dimer formation with multiple interactions through N—H···O and C—H···O. The vibrational analysis shows red shifts in ν_{N-H} and $\nu_{C=O}$ as result of dimer formation. The binding energy of dimer is calculated as 13.82, 15.24 kcal/mol using DFT, QTAIM analysis, respectively. The result of ellipticity confirms the existence of resonance assisted hydrogen bonds (RAHB) in dimer. The MEP and local reactivity descriptors analyses have been performed and the results indicate that carbonyl carbon and β-carbon of chalcone frame have been prone to nucleophilic attack and lead to large number of heterocyclic compounds such as oxirane, oxazoles, pyrazoles, pyridines, pyrimidines, and pyran.

Introduction

Chalcones are one of the major classes of natural products with widespread distribution in legumes, soy, spices, tea, beer, fruits and vegetables. Chalcones are prominent secondary metabolites precursors of flavonoids and isoflavonoids in plants. Chemically, they consist of open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α, β-unsaturated carbonyl system [1–4]. These are displaying an impressive array of pharmaceutical profiles such as antiprotozoal, anti-inflammatory, immuneomodulatory, immunosuppressive, nitric oxide and lipid per oxidation

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inhibition, antimalarial, antileishmanial, antiulcer, anticancer, antitumor, antibacterial, trypanocidal and antiviral activities [5–10,3]. They have also found numerous applications as photo protector in plastics, solar creams, as well as food additives. The α, β unsaturated ketone moiety is largely attributed for wide range of biological action of chalcones [5,11–13]. The α, β double bond has been proposed to explain the biological activity. Therefore, α, β-unsaturated ketone grouping has become a centre of interest for such compounds. The vibrational spectroscopy and NMR techniques have been widely used to study structural and dynamic aspects of molecular system. With the recent advances in computational methods, DFT [14–19] has long been recognized as a better alternative tool in the study of organic chemical systems than the *ab initio* methods used in the past because of the fact that it is computationally less demanding for inclusion of electron correlation.

Literature survey reveals that chalcones have been used as valuable compounds because of their proven biological activity and material applications. Bobarevic et al. [20], have used ethyl 3,5-dimethyl-4-acetyl-1*H*-pyrrole-2-carboxylate for synthesis of chalcones. Author has also published pyrrole chalcones and hydrazide-hydrazone derivatives [21–27] on ethyl 3,5-dimethyl-4-acetyl-1*H*-pyrrole-2-carboxylate and ethyl 3,5-dimethyl-4-formyl-1*H*-pyrrole-2-carboxylate. In this work, the synthesized ethyl 4-(3-Furan-2yl-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate) by aldol condensation of ethyl 3,5-dimethyl-4-acetyl-1*H*-pyrrole-2-carboxylate with furan-2-carbaldehyde has been characterized by various spectroscopic techniques. For accurate prediction of the geometry, FT-IR, ^{1}H NMR spectroscopy and detailed density functional theory (DFT) [14–19] calculations have been performed. This paper reports, the conformers and molecular dimeric structure of the compound through multiple interactions and the weaker interactions with the help of quantum theory of atoms' in molecules (QTAIM) [32]. Quantum chemical calculations further provide information on chemical reactivity with the help of MEP, global and local electronic descriptors. Furthermore, natural bond orbital interactions (NBO) have been also performed to determine inter-and intra molecular interaction within the monomeric unit of dimer.

Materials and methods

Method for synthesis and physical measurements

Freshly distilled furan-2-carbaldehyde with ethyl 3,5-dimethyl-4-acetyl-1*H*-pyrrole-2-carboxylate in 1:1 ratio were dissolved in ethanol at room temperature and 5% KOH was added as catalyst. The progress of the reaction was monitored by TLC. The reaction mixture was neutralized by HCl and poured into ice cold water. The yellow coloured precipitate was obtained as product. Yield: 76%. Solubility: soluble in chloroform, ethyl acetate, ethanol and methanol. The infrared spectrum of the compound was recorded on a Perkin Elmer System FT-IR spectrometer in the 4000–400 cm^{-1} region using KBR pellet technique. The ^{1}H NMR was taken in $CDCl_3$ solution on a Bruker DRX-300 MHz spectrometer (FT-NMR) and tetramethylsilane (TMS) used as internal standard. The chemical shifts was expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), q (quartet) and m (multiplet). The ultraviolet absorption spectrum of the titled compound was recorded in the range 200–800 nm at 1×10^{-5} mol L^{-1} concentration in chloroform solution.

Computational methods

Gaussian 09W [28] software package has been used for theoretical calculations. The quantum chemical calculations have been performed applying the DFT [14–19] method using B3LYP functional [14–19,29] and 6-31G(d,p) basis set. The motivation for use of B3LYP functional is due to its ability to successfully predict a wide range of molecular properties [14–19,29]. The optimized geometrical parameter has been used in the vibrational wavenumbers calculation to characterize all stationary points as minima and found all harmonic vibrational wavenumbers positive. Internal coordinate system recommended by Pulay et al. is used for the assignment of vibrational modes [30]. The ^{1}H NMR chemical shifts have been calculated by applying the GIAO method. The time dependent density functional (TD-DFT) has been carried out to find the electronic transitions. The topological parameters have been obtained by AIM 2000 software [31].

Results and discussion

Molecular structure of the studied compound

The route adopted for the synthesis of ethyl 4-(3-Furan-2yl-acryloyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylate is given in Fig. 1. Two conformers have been obtained around the dihedral angle C2—C9 as shown in Supplementary material Fig. S1, having energy value of −975.6120 a.u., (conformer I) and −975.6117 a.u., (conformer II). They have energy difference of 0.25 kcal/mol and exist in the ratio of 62.56%, 37.44%, respectively, at room temperature as per Boltzmann population distribution. The structural parameters obtained at the B3LYP/6-31G(d,p) level of theory is given in Table 1. The endocyclic angles of pyrrole and furan ring on adding result to 539.99°, 540°, respectively, show that both 5-member rings are perfectly planar. The asymmetry in N—C bond length of pyrrole moiety was observed in EFADPC N1—C2, N50—C48 (1.3882 Å), N1—C5, N50—C52 (1.3443 Å) due to the presence of electron withdrawing group (ester). This effect has been found in our quantum calculation and also reported in single crystal structure data of other pyrrole derivatives [17,19,32]. The C11—C12, C65—C66, C9—O18, C44—O49, C7—O10 and C57—O64 bond lengths indicate a typical double bond character as compared with bond lengths recommended by Pulay et al. [30]. Optimized geometry of dimer is shown in Supplementary material Fig. S2, with atom numbering. In dimer, heteronuclear intermolecular hydrogen bonding (N—H···O) between pyrrolic (N—H) and carbonyl (C=O) oxygen of ester form two hydrogen bonds. In intermolecular hydrogen bonds, N—H bond acts as proton donor, C=O bond as proton acceptor and form cyclic ten member pseudo ring denoted as $R_2^2(10)$ or more extended sixteen member pseudo ring $R_2^2(16)$. In dimer, due to intermolecular hydrogen–bond formation both proton donor (N—H bond) and proton acceptor (C=O bond) are elongated from 1.0108 to 1.0205 Å, 1.2240 to 1.2321 Å, respectively. Total energy of the monomer (conformer I) and its dimer are calculated as −975.6120, −1951.2460 a.u., respectively. The binding energy of the analyzed dimer is computed as the difference between the calculated total energy of the dimer and the energies of the two isolated monomers. The total binding energy of dimer and hydrogen bond energy of each hydrogen bond have been calculated to be as 13.8, 6.90 kcal/mol, respectively. The calculated hydrogen binding energy of dimer formation has been corrected for the basis set superposition error (BSSE) via the standard counterpoise method [17,32] and found to be 9.63 kcal/mol.

Spectroscopic analysis

IR spectrum

The FT-IR spectrum of the studied compound has been calculated at the B3LYP/6-31G(d,p) level of theory and compare the results with the experimental values. Since the calculated vibrational frequencies are known to be higher than the experimental