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A quantum chemical computational insight into the intramolecular hydrogen bond interaction in an antibacterial drug molecule-2-acetylindan-1,3-dione

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ABSTRACT

A Density Functional Theory (DFT)-based quantum chemical computational study has been carried out to characterize the intramolecular hydrogen bonding (IMHB) interaction in a potent bio-active drug molecule *viz.*, 2-acetylindan-1,3-dione (2-AID). The IMHB interaction has been explored by calculation of electron density $\rho(\mathbf{r})$ and Laplacian $\nabla^2\rho(\mathbf{r})$ at the Bond Critical Point (BCP) using Atoms-In-Molecule (AIM) theory. Topological features, energy densities provided by AIM theory are calculated with $\rho(\mathbf{r})$ for a number of intramolecular H-bond distances. The results suggest that at equilibrium geometry the IMHB interaction in the molecule develops certain characteristics typical of covalent interaction. The role of hyperconjugative charge transfer interaction in the IMHB has been critically evaluated and addressed under the provision of Natural Bond Orbital (NBO) analysis. The study also pays proper attention to an important feature of IMHB interaction, namely the directional nature, within the NBO framework in a consensus manner. Simulated IR spectra also provide reinforcing evidence for IMHB interaction on the basis of OH stretching frequency shift. The optimized geometry features, molecular electrostatic potential (MEP) map analysis are also found to produce a consensus view in relation with the formation of IMHB in 2-AID.

1. Introduction

The hydrogen bonding interaction is pervasive in nature and is, unambiguously, an inevitable conduit of the natural system to sustain and maintain life-cycle on this planet and a plethora of other events. Thus quite naturally it has formed the nucleus of many-faceted, intense research activities in many branches of natural sciences [1–6]. The directional nature of H-bond deserves a special mention as it plays an instrumental role in phenomena like crystal engineering, stabilization of the secondary structure of biomolecules like proteins and DNA [1–6]. Therefore, a thorough understanding of the interaction will pave way to delve into the critical evaluation of many effects taking place not only in the crystal state, but also in solutions and living organisms.

After nearly one century of studies on hydrogen bonds, the interest focused on this particular class of weak interaction has been radically renewed in the last couple of decades. However, despite the myriads of efforts dedicated to the subject both from theoretical and experimental standpoints, its physical nature still continues to be a matter of intense debate and hence judicially accounts for the meticulous exploration of the topic of research even to-day. One particular class of hydrogen bonding interaction is the intramolecular hydrogen bond (IMHB) which occurs within the same molecular architecture leading to the creation of the so-called quasi-ring [1–4,7]. The present work is focused on the evaluation and assessment of the IMHB interaction in a potential bio-active drug molecule 2-acetylindan-1,3-dione (2-AID). The structure of 2-AID has been studied by various techniques e.g., X-ray diffraction and Infra-Red (IR) and Nuclear Magnetic Resonance (NMR) spectroscopy [8–11]. The multi-faceted physiological functionalities of 2-AID e.g., anti-bacterial [12], anti-parasitic [13] and anti-coagulant [14] activities, have also been well documented in the literature. Additionally, being a β-diketone 2-AID exhibits good complexation properties. The metal–ligand complexes of 2-AID with Cu(II) and Zn(II) metal ions have been shown to have prospective applications as sunscreen agents [15]. The luminescence properties of 2-AID have also been investigated by Enchev et al. along with some semi-empirical (AM1) quantum chemical structural calculations [16].

In spite of such wide range of potential biological activities and applications it is rather surprising to note the little pursuance in the literature of a systematic quantum chemical investigation of

Abbreviations: 2-AID, 2-acetylindan-1,3-dione; C-form, closed form; O-form, open form; DFT, Density Functional Theory; NBO, Natural Bond Orbital; AIM, Atoms-In-Molecule; IMHB, intramolecular hydrogen bond; BCP, Bond Critical Point; MEPS, molecular electrostatic potential surface; IR, Infra-Red; ZPE, Zero Point Energy.

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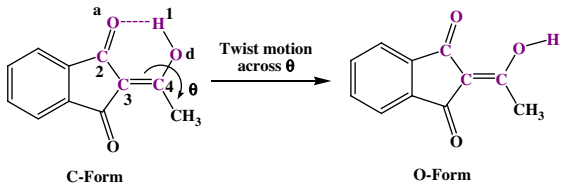

Scheme 1. Simplified paradigm showing the intramolecularly hydrogen bonded closed (C-form) and non-hydrogen bonded open (O-form) conformations of 2-AID. The numbering of atoms used throughout the study is also designated.

the structure and IMHB interaction of 2-AID which plays a crucial role in governing the overall photophysics of the drug [15–17]. The present program is designed to cast light on these particular aspects which have remained sporadically addressed in the literature till date. Particular emphasis has been rendered on the application of different quantum chemical tools for detection and evaluation of IMHB in the studied molecule 2-AID. The topological properties of IMHB interaction are assayed under the provision of Atoms-In-Molecule (AIM) [18,19] methodology, while a critical evaluation of the role of hyperconjugative charge transfer interaction is deduced from Natural Bond Orbital (NBO) population analysis [20,21]. In the present context the simulated spectroscopic (IR) method and geometrical criteria have also been employed to evaluate the IMHB interaction in 2-AID. Finally, the geometrical and quantum chemical criteria have been subject to direct comparison in a motive to provide a picture depicting the origin of and then to find reliable criteria for evaluation of H-bond strength.

2. Computational procedures

All calculations have been performed with the Gaussian 03W suite of programs [22] using Density Functional Theoretical (DFT) method [23]. Theoretical calculations were performed with the hybrid B3LYP functional, i.e., a combination of the Becke's three-parameter (B3) exchange functional [24] and Lee–Yang–Parr (LYP) nonlocal correlation functional [25]. In our calculation particular emphasis is delivered on the 6-311++G(d,p) basis set because this basis set is of triple-ζ quality [22,26] for valence electrons with diffuse functions which are useful in calculations for anions and structures with lone pair electrons [26,27]. We have exploited the 6-311++G(d,p) basis set for calculation considering the necessity of diffuse functions for full characterization of the hydrogen bond interaction [22–28]. The geometrical constraints were not imposed in equilibrium geometry optimizations. Vibrational frequency calculations were carried out for the optimized structures in order to assess the nature of stationary points and to obtain Zero Point Energy (ZPE) corrections. The characteristic of local minimum was verified by establishing that matrices of energy second derivatives (Hessian) have no imaginary frequency [22,27,29,30].

The Natural Bond Orbital (NBO) analysis has been employed to evaluate the direction and magnitude of donor–acceptor interactions. The contour plot for visualization of the results is generated on NBO View (Version 1.1) suite of programs [20,21] using the standard keywords implemented therein. All necessary computations for AIM and NBO analyses have been performed on Gaussian 03W software package [22,27].

3. Results and discussion

3.1. Optimized geometry parameters and calculation of the IMHB energy (E_{IMHB})

The initial insights into the presence of IMHB interaction in the studied molecular system 2-AID are assessed from comparison of the optimized geometrical parameters of the closed conformer (i.e., C-form) with those in the open counterpart (O-form) (Scheme 1). Since the open form of the molecule is devoid of the IMHB interaction a comparison of its optimized geometry parameters with those of the closed form will reflect the modulations in optimized geometry parameters as imparted by the presence of IMHB. As seen in Table 1, the shortening of the proton donating bond length (H_1—O_d distance) in the open form compared to the closed form is in line with the occurrence of IMHB interaction in 2-AID [29–37]. Apart from this, the data compiled in Table 1 also reveals some detectable modulations in geometry parameters surrounding the entire IMHB framework in the studied molecule, e.g., shortening of C_2=O_a and C_3=C_4 bonds along with lengthening of C_2=C_3 and O_d=C_4 distances. The changes in the optimized geometry parameters in these directions upon moving from the C-form (which accompanies the formation of the IMHB) to the O-form can be corroborated to the presence of some degree of π-electron delocalization within the IMHB framework in 2-AID.

Table 1
Optimized geometry parameters surrounding the IMHB site in the C-form and O-form of 2-AID.

Parameters (Å)	C-form	O-form	$\Delta_{(C\text{-form}-O\text{-form})}$ (Å)
O_d—H_1	0.995	0.965	0.03
O_a=C_2	1.235	1.214	0.021
C_2—C_3	1.461	1.492	−0.031
C_3=C_4	1.375	1.362	0.013
C_4—O_d	1.325	1.343	−0.018

Now, as the presence of the IMHB in the studied molecule (2-AID) is indicated from perusal of the optimized geometry parameters, herein we endeavor to theoretically estimate the strength of the IMHB present in the studied molecular system. The IMHB energy (E_{IMHB}) has been estimated by computing the difference in optimized energies between the closed and the open conformations [29–37] and the results obtained using different basis sets are as follows: E_{IMHB} (kcal mol^{-1}) = 12.68 at 6-311++G(d,p), 13.03 at 6-31+G(d,p), 13.01 at 6-31+G(d) and 13.85 at 6-31G(d,p). A representative plot of variation of energy as a function of the twist angle θ leading to the formation of the nonhydrogen-bonded O-form from hydrogen-bonded C-form is depicted in Fig. 1. The effect of basis set on the computed IMHB energy (E_{IMHB}) is a relevant and important issue in the present context. The use of basis sets of inadequate size is often invoked to account for the inaccurate prediction of H-bond energies [31–35,38,39]. Thus in order to cast light on the issue in our present calculations, the effect of basis set on the computed IMHB energy value has been investigated by systematically decreasing the size of the basis set and the results are compiled above. It is, however, imperative to emphasize at this stage that estimation of the IMHB energy as to the energy difference between the C-form and the O-form produced by rotation of the twist angle θ reserves the assumption of no other geometry effects as a result of the rotation. It is perhaps the inadequacy of the assumption that the process raises the energy more than what can simply be attributed to this intramolecular hydrogen bond cleavage. This point in turn advocates for an important aspect of the present work which endeavors to implicate an argument on the issue of inadequacy of simple geometry criteria compared to quantum chemical criteria for assessment of the interaction.

3.2. Analyzing the presence and strength of IMHB in 2-AID from spectroscopic method: Simulated Infra-Red (IR) spectra

The IR spectroscopy has long been recognized as an effective tool for characterizing the presence and assessing the strength of H-bond in a molecule. Herein, we endeavor to exploit the strategy