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Intramolecular interactions, isomerization and vibrational frequencies of two paracetamol analogues: A spectroscopic and a computational approach

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ABSTRACT

The aim of this investigation was to determine the molecular properties and provide an interpretation of the vibrational mode couplings of these two paracetamol analogues: 2-bromo-2-methyl-N-(4-nitrophenyl)-propanamide and 2-bromo-2-methyl-N-p-tolyl-propanamide. E/Z isomers, keto/enol unimolecular rearrangement and prediction of the transition state structures in each mechanism were also assessed using the Density Functional Theory (DFT). The DFT estimates a high energy gap between E and Z isomers (9–11 kcal·mol^{-1}), with barrier heights ranging from 16 to 19 kcal·mol^{-1}. In contrast, the barrier energies on the keto/enol isomerization are almost 10 kcal·mol^{-1} higher than those estimated for the E/Z rearrangement. The kinetic rate constant was also determined for each reaction mechanism. Natural bond orbital analysis and the quantum theory of atoms in molecules were used to interpret the intramolecular hydrogen bonds and to understand the most important interactions that govern the stabilization of each isomer. Furthermore, an analysis of the atomic charge distribution using different population methodologies was also performed.

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1. Introduction

Paracetamol is considered to be a first-line treatment for children's pain and fever due to its analgesic and antipyretic actions [1]. Because of the different environmental [2–5] and pharmacological implications of paracetamol [6–10], several investigations have been performed to assess its spectroscopic properties [11–15] and to determine the different aspects of its crystallization [16–21]. Different paracetamol derivatives have also been shown to have antioxidant activity [22,23] as a fatty acid amide hydrolase inhibitor [24], and these derivatives are potentially safer analgesics than paracetamol itself [25–32].

The purpose of this study is to describe the electronic properties and provide an interpretation of the vibrational mode couplings in these two paracetamol analogues: 2-bromo-2-methyl-N-(4-nitrophenyl)-propanamide and 2-bromo-2-methyl-N-p-tolyl-propanamide (Fig. 1). In this investigation, we will characterize the E/Z isomers, the keto/enol unimolecular arrangement and the transition state structures in each mechanism. A natural bond orbital (NBO) analysis and a topological analysis using the quantum theory of atoms in molecules (QTAIM) [33] will also be performed. These compounds have already been synthesized and their structures were analyzed using X-ray diffraction [34,35]. However, there are few studies on their electronic properties and also little information on the details of their vibrational frequencies and their respective vibrational couplings. Therefore, a combined experimental and quantum chemical investigation on the electronic properties will provide a good understanding of these systems, as shown in previous studies [36–42].

2. Materials and methods

The compounds were synthesized using the procedure published by Moreno-Fuquen et al. [34,35]. The infrared spectrum was recorded between KBr windows from 4000 to 400 cm^{-1} on a FTIR GX1 spectrophotometer with a resolution of 1 cm^{-1} and using 64 scans.

All the calculations were carried out using the GAUSSIAN 09 program [43]. Stationary points on the potential energy surface were fully optimized, and harmonic vibration frequencies were evaluated to characterize their nature as minima. The absence of imaginary frequencies indicated that all optimized structures were the true minimum. The PBE1PBE functional [44,45] was used in the optimization procedure with the 6-31G(2df,2pd) basis set [46,47]. A tight convergence and an ultrafine grid were used in the optimization

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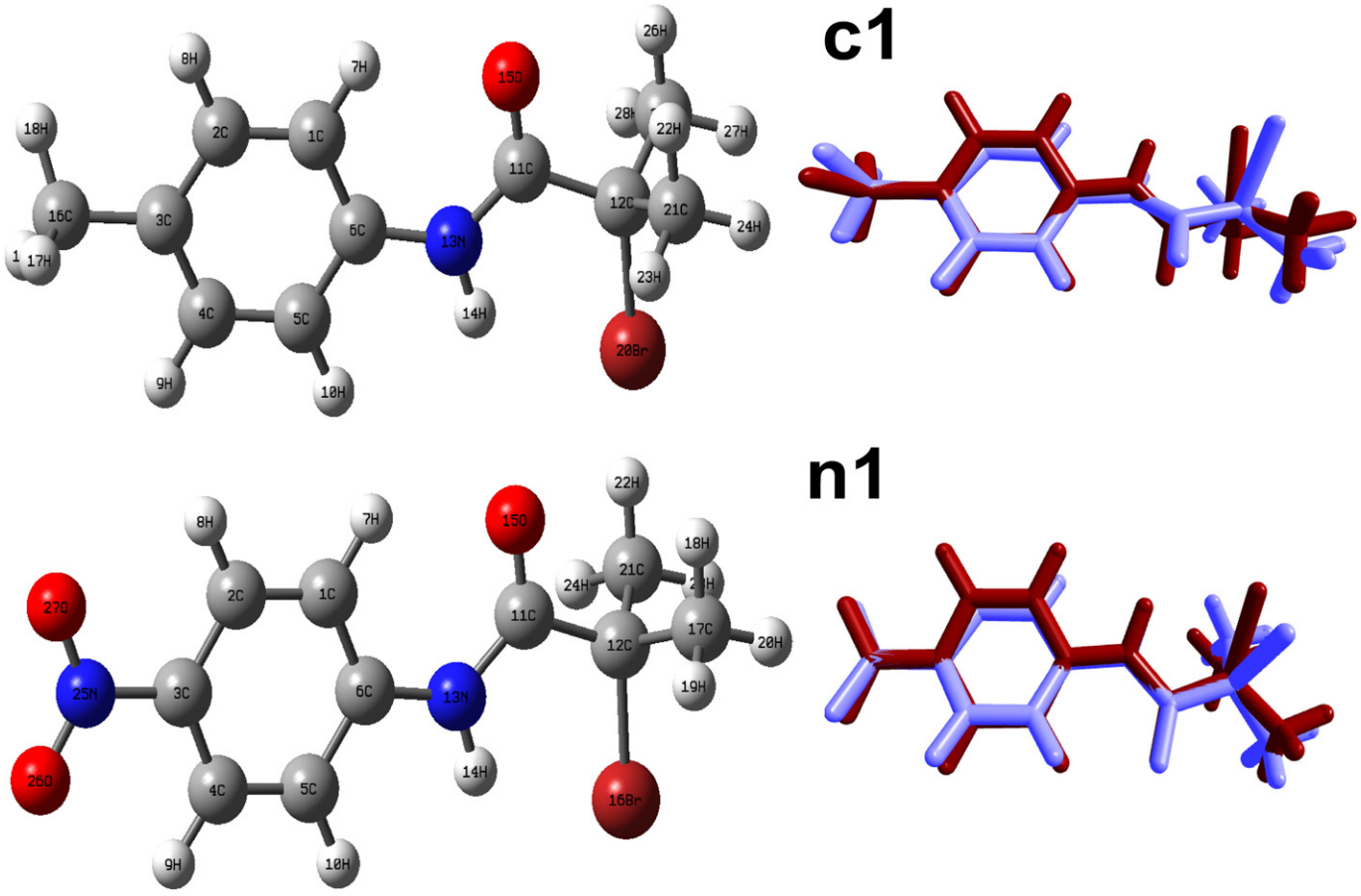

Fig. 1. In the left side is showed the 2-bromo-2-methyl-N-(4-nitrophenyl)-propanamide (**n1**) and 2-bromo-2-methyl-N-p-tolyl-propanamide (**c1**) optimized structures with PBE1PBE/6-31G(2df,2pd). In the right side is demonstrated the structural superposition of calculated (in red) crystallographic structures (in blue from Ref. [34,35]) for each compound.

procedure. The PBE1PBE functional demonstrated a good performance in estimating the electric dipole moment and polarizability [48] as well as in the prediction of the transition state structures in organic reactions [49,50] and in unimolecular rearrangements [51]. The transition state structures (TSs) were searched using the synchronous transit-guided quasi-Newton method [52,53], where is required the reactant and product for the structure as input. The TS structures were then optimized with analytical gradients using the Berny algorithm with redundant internal coordinates until a stationary point on the potential surface was found. Finally, the transition state structures were verified by subsequent frequency calculations, which allowed us to determine the imaginary vibrational frequencies related to the reaction path. A Hessian-based predictor–corrector reaction path algorithm [54,55] was also used to confirm the reactant and the product of each TS structure. In addition, M05-2X [56] and BMK [57] functionals were also applied in the energetic profiles of the reaction pathways due to their accurate prediction of chemical reaction barrier heights for modeling kinetic rate constants [56–59]. For these both DFT functionals were employed the 6-311++G(d,p) basis sets [46,47]. All simulations were performed in gas phase.

The atomic charge analysis was performed using different methodologies: Mulliken, Lowdin, generalized atomic polar tensor (GAPT) [60], natural population analysis (NPA) [61], Chelp [62], ChelpG [63], Merz–Singh–Kollman (MK) [64,65] and the Hirschfeld method [66,67]. NBO analysis was performed using the NBO 6.0 program [68]. Topological analysis with QTAIM was performed using the AIMALL program [69]. In the charge analysis, bond indexes, NBO and QTAIM calculations were used in the PBE1PBE/6-31G(2df,2pd) method.

3. Results and discussion

3.1. Geometry and structure prediction

The structure prediction showed good agreement between the experimental and PBE1PBE/6-311G(2df,2pd) geometry, mainly when the bond lengths and angles were compared. The mean absolute error (MAE) for **c1** and **n1** were 44% and 55%, respectively. Nevertheless, the MAE values are around 6% when compared the experimental and calculated bond lengths, while these values decrease to 1% in examining the bond angles. The main reason for this difference is likely a result of the quantum chemical calculations where the molecules were simulated in vacuum. However, X-ray analysis was performed on a single-crystal sample and the crystal packing was shown to affect the structure geometry. We compared the experimental and the predicted dihedral angles. For **c1**, the C_{11}–N_{13}–C_6–C_1 torsional angle was −31.2(5)° as shown using X-ray analysis [35], while with the PBE1PBE functional is 0.2°. For **n1**, the experimental [34] and predicted C_{11}–N_{13}–C_6–C_1 angles were 12.7(4)° and 0.0°, respectively. The large value for the **c1** C_{11}–N_{13}–C_6–C_1 torsional angle occurs because this molecule is stabilized by three intermolecular interactions that are formed by each carboxyl group (a NH–O hydrogen bond and two weak CH–O bonds). In contrast, **n1** presents two intermolecular interactions for each amide group: a CH–O and a NH–O hydrogen bond [34]. Another example of a dihedral angle that is affected by the crystal packing is the Br–C_{12}–C_{11}–O_{15} angle. In **c1**, the Br–C_{12}–C_{11}–O_{15} experimental torsional angle is −100.5(3)°, while it was estimated to be 179.9° using the PBE1PBE/6-311G(2df,2pd)

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