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ORIGINAL ARTICLE

Evaluation of non-covalent interactions of chlorambucil (monomer and dimer) and its interaction with biological targets: Vibrational frequency shift, electron density topological and automated docking analysis

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Abstract Chlorambucil is a well-known chemotherapy drug that is being used to treat chronic myelogenous leukemia. As it contains ten flexible rotational bonds, the possible spatial conformations have been identified theoretically. The spectral signatures of monomer and dimer structures of chlorambucil and the frequency shifts due to non-covalent interactions (NCIs) have been illustrated using FT-IR and FT-Raman spectra. The bond correlation between carbon and hydrogen nuclei of chlorambucil has been obtained using 2D-HSQC NMR spectrum. The assignments of harmonic normal modes have been done in order to find the vibrational contributions of each functional group. Besides the spectroscopic studies, the electron density based quantum topological atoms in molecule analysis have been performed to explore the possible interactions between the non-bonded atoms. The reduced density gradient and isosurface plots have been used in this study to understand the strength of NCIs. The charge delocalization patterns of monomer and dimer structures were explained so as to investigate the chemical stability profile. The active sites for the electrophilic and nucleophilic attack on the monomer conformers have been determined by applying Hirshfeld charges and atomic spin densities into Fukui and Parr functions, respectively. From the automated docking analysis, it is found that chlorambucil interacts with the aldo-keto reductase family 1 (AKR1B1, AKR1B10, AKR1B15) and FAD-linked sulfhydryl oxidase ALR proteins through strong hydrogen bonds and shows a potential inhibition. In order to take into account the interactions ranging from short to long range, the modern density functionals viz. M06-2X,

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wB97XD, B97D which includes dispersion-corrected repulsion terms have been employed and the theoretical results were found coincide with the experimental observations.

1. Introduction

The study of non-covalent interactions (NCIs) plays a key role to unlock the possibility of rational drug design. In the recent years, the utilization of spectroscopic and theoretical topological tools for exploring the NCIs was increased considerably due to its ease and accuracy (Karthick et al., 2017a, 2017b; Srivastava et al., 2016). The fundamental spectral features such as IR and Raman allow us to know the occurrence of those interactions in particular molecular systems in terms of vibrational frequency shift (δ). Since the value of δ depends on the strength of NCIs present, sometimes it is very difficult to obtain the information concerning long-range interactions. Hence, the modern density functionals which incorporate long-range dispersion-corrected repulsion terms have been used to calculate the optimized structural properties, vibrational frequencies and stabilization energies due to charge delocalization within the molecule. Moreover, in the present study, quantum topological atoms in molecule (QTAIM) analysis have been performed to explore the interactions ranging from short to long range which occurs between the non-bonded atoms. The reduced density gradient and isodensity surface plots have been used to distinguish the interactions taking place within the molecule.

Chlorambucil is a well-known nitrogen mustard alkylating agent that is being used for treating chronic myelogenous leukemia (CML) (Kufe et al., 2003). The electronic structure of chlorambucil and its tentative vibrational assignments have been investigated (Gunasekaran et al., 2008a, 2008b). Also, the important functional group ($-CH_2CH_2COOH$) which is expected to be involved in the formation of dimer was considered as a single mass point group and its assignments were not proposed. In the same year, tentative vibrational assignments of all the functional groups of chlorambucil were also proposed (Gunasekaran et al., 2008a, 2008b). Unfortunately, the proposed tentative assignments were not supported by the experimental especially the modes of ─COOH group. Hence, there were lots of discrepancies between the experimental and theoretical results assignments proposed by Gunasekaran et al. (Gunasekaran et al., 2008a, 2008b). This clearly indicates the dimer form of chlorambucil through ─COOH group.

Charak et al. studied the interactions of chlorambucil with DNA with the help of spectroscopic and molecular docking approaches (Charak et al., 2012). The non-covalent interactions of chlorambucil with calf thymus DNA have been investigated by multi-spectroscopic techniques and molecular docking study (Rehman et al., 2015).

However, the spatial conformations along the flexible bonds, dimer structure and the details of NCIs of chlorambucil were not yet revealed. As it has nine flexible bonds, there are numerous conformers possibly to exist at the room temperature. Hence, an attempt has been made to find the feasibly existing stable conformers of chlorambucil along the flexible bonds without any steric hindrance. The expected vibrational frequency shifts due to the existence of NCIs have been explained with the detailed potential energy distribution (PED) results. Since the molecule that contains carboxylic acid group exhibit as dimer form in the solid state (Balachandran et al., 2011; Balachandran et al., 2012; Karthick et al., 2015), the electronic structure of chlorambucil dimer has been proposed and the spectral features of dimer has been compared with the experimental spectra. In addition to NCIs, the interaction energies due to charge delocalization between the donor and acceptor species are also taking part in the chemical stability of a molecule. Hence, the natural population and second order perturbation theory analysis have been carried out to find the donor-acceptor species which are more predominant to the chemical stability.

2. Experimental

A pure sample of chlorambucil was purchased from Sigma Aldrich chemicals Ltd. For FT-IR measurement, the mixer of chlorambucil and potassium bromide in the ratio 100:1 was used to make pellet which readily usable for recording the spectra. The FT-IR spectrum of chlorambucil was recorded in a mid-IR region on a Bruker Tensor 27 spectrophotometer which outfitted with mid-IR source (4000 to 400 cm^{-1}), a KBr beam splitter and a room temperature DTGS detector. The multi-tasking OPUS software was used for the observed peak averaging, peak enhancement, baseline correction and other spectral manipulations. A spectral resolution of 1.0 cm^{-1} was used and the source was allowed to incident on the pellet surfaces for about 32 scans during the measurement. The FT-Raman spectrum of chlorambucil was recorded in the region 3500–100 cm^{-1} on Bruker RFS multi RAM standalone spectrophotometer. The spectral resolution of 2 cm^{-1} bandwidth of 1.5 nm was fixed and a couple of silicon diode detectors are used to record the spectrum during the process. The Nd:YAG laser of 1064 nm wavelength is used as excitation source. 2D-HSQC NMR spectrum of chlorambucil has been performed using Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution NMR Spectrometer.

3. Computational details

Initially, a careful attempt has been made to find the stable conformers of chlorambucil. Since chlorambucil has a large number of flexible bonds, the high-performance conformational analysis tool "CONFLEX" (Goto et al., 2012; Goto and Osawa, 1989,1993) has been used. From the list of 1420 conformers, only three conformers are taken from the lowest energy order for discussion. The list of conformers and their energy profile along with the percentage of population is depicted in Table S1. The conformers obtained from CONFLEX are further optimized by dispersion corrected modern density functional B97D, wB97XD and M06-2X (plus D3 empirical dispersion function) with 6-311++G(d,p) basis set

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