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Molecular docking and structural analysis of non-opioid analgesic drug acemetacin with halogen substitution: A DFT approach

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ABSTRACT

Acemetacin is a non-opioid analgesic which belongs to the class, the non-steroidal anti-inflammatory drug. The bioactive conformer was identified through potential energy surface scan studies. Spectral features of acemetacin have been probed by the techniques of Fourier transform infrared, Raman and Nuclear magnetic resonance combined with density functional theory calculations at the B3LYP level with 6-311 + G(d,p) basis set. The detailed interpretation of vibrational spectral assignments has been carried out on the basis of potential energy distribution method. Geometrical parameters reveal that the carbonyl substitution in between chlorophenyl and indole ring leads to a significant loss of planarity. The red-shifted C=O stretching wavenumber describe the conjugation between N and O atoms. The shifted C–H stretching wavenumbers of O–CH_3 and O–CH_2 groups depict the back-donation and induction effects. The substitution of halogen atoms on the title molecule influences the charge distribution and the geometrical parameters. Drug activity and binding affinity of halogen substitution in title molecule with target protein were undertaken by molecular docking study. This study enlightens the effects of bio-efficiency due to the halogen substitution in the molecule.

1. Introduction

Pain is the most recurrent reason for visiting a doctor. To prevent patient pain, the clinician may choose opioid and non-opioid analgesics. Nowadays non-opioid analgesics are among the most prescribed medicines for the treatment of pain. Because of the potential to relieve pain, they play an essential role in medicinal therapy. Despite of several available analgesics, unrelieved pain remains a major health care issues like hematological toxicities, kidney functional disorders and gastro-intestinal gashes [1,2]. Consequently, medicinal researchers recently paid more attention in developing drugs which is effective as opiates with improved safety profiles. Acemetacin (ACM) is one of the non-opioid analgesic which comes under the class, non-steroidal anti-inflammatory drug (NSAID). Nowadays, acemetacin is potentially useful in the treatment of osteoarthritis, rheumatoid, low back pain, post-operative pain, trauma pain etc. [3,4]. It has a chemical structure similar to that of indomethacin except the inclusion of acetylate group, which improve the quality of the drug. Clinical studies had indicated that acemetacin produces significantly less gastric damage than indomethacin and it shares some characteristics of acetyl salicylic acid (Aspirin) [5].

Considering these medicinal importance of acemetacin, this work is mainly focused to the detailed structural behavior of the molecule. Vibrational spectroscopic investigations aided by density functional theory (DFT) calculations have proved to be very efficient and cost effective tool for structural elucidation of bioactive molecules. Theoretical study of indomethacin, which is the parent drug of ACM, has been analysed earlier using PXRD, IR, NMR, have been reported in the literature [6–8]. M. E. Auer et al. [9] have been reported the quantitative and qualitative analyses of polymorphic forms of ACM in commercial drug rheutrop through near infrared FT-Raman spectroscopy. The structural features of the ACM have not been subject of comprehensive analysis to date. Therefore the present work aims to understand the relationship between biological activity and structural behavior of the ACM using FT-IR, FT-Raman and NMR spectroscopic techniques combined with DFT computations. Molecular geometry and charge distribution in the ACM molecule caused by the substituent F, Br and I are also analysed. Docking analysis has been performed to find out the binding affinity and drug activity of the molecule.

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2. Experimental details

The sample ACM (2-[2-[1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetyl]oxyacetic acid) was obtained from the Sigma-Aldrich Company, India with a stated purity of 99% and it was used as such without further purification to record FT-IR, FT-Raman, and NMR spectra. The FT-IR spectrum of the ACM was recorded in KBr pellet technique using Jasco FT/IR-6300 typeA spectrometer in 4000–400 cm^{-1} region with 4 cm^{-1} resolution. The FT-Raman spectrum was obtained in the range from 3500 to 50 cm^{-1} using Bruker RFS 27 spectrometer with a 1064 nm Nd:YAG laser source. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE III 500 MHz (AV 500) multi nuclei solution spectrometer using acetone as a solvent.

3. Computational details

Gaussian '09 program package [10] has been used to compute molecular geometry, vibrational wavenumbers and NMR chemical shift values using B3LYP method with the 6-311 + G (d, p) basis set [11–13]. To avoid the systematic errors caused by basis set incompleteness, negligence of electron correlation and vibrational anharmonicity a common scaling factor of 0.9688 was used to scale the computed wavenumbers [14]. The distributions of assignment of the calculated wavenumbers have been aided by means of VEDA 4 program [15]. The simulated IR and Raman spectra have been plotted with the usage of pure Lorentizian band shapes with a bandwidth of full width half-maximum (FWHM) of 10 cm^{-1}. The Raman intensities were calculated using the basic theory of Raman Scattering [16,17]. NBO 3.1 program was implemented for natural bonding orbital calculation [18].

4. Results and discussion

4.1. Conformational analysis

The most appropriate method of revealing conformational stability of an ACM is in terms of potential energy surface (PES) scan study. Minimum energy conformation is obtained by PES scan analysis by choosing the dihedral angles D_1 (C_5–C_6–O_{15}–C_{16}), D_2 (C_{19}–C_{18}–C_{17}–N_1), D_3 (C_{18}–C_{17}–N_1–C_2), D_4 (C_{26}–O_{13}–C_{10}–C_{11}), D_5 (O_{13}–C_{10}–C_{11}–C_3) and D_6 (C_{27}–C_{26}–O_{13}–C_{10}). The selected dihedral angles varied from 0° to 360° rotations by a step of 10°. The PES energy curves for the rotations of the dihedrals are presented Fig. 1. Fig. 1(a) the torsional barrier of the methoxy group around the bond C_6–O_{15}, (b) indole ring around the bond C_{17}–N_1 (c) chlorophenyl ring around the bond C_{18}–C_{17}, (d) around the bond O_{13}–C_{10}, (e) around the bond C_{10}–C_{11} and (f) around the bond C_{26}–O_{13} by varying the torsional perturbation have been performed. The PES scan of the ACM is very intricate and numerous similar structures have been identified with different geometries. The result shows that the internal rotation of bond C_{18}–C_{17} (D_3) yielded more stable (low-energy) conformer located at angles 150° and 210° with the energy −1777.8086 Hartree. This minimum energy conformer is used for further investigations.

4.2. Molecular geometry

The molecular geometry of ACM was theoretically predicted using Gaussian 09 software package. The minimum energy conformer (D_3) was further re-optimized by substituted by fluorine, bromine and iodine. The ACMX (X = F, Br, I) geometry is defined in Table 1, following the atom numbering of Fig. 2. The computed results are compared with the already reported experimental data [4]. The values are slightly different with crystallographic data [4]. These discrepancies arise due to the fact that theoretical results belong to gaseous phase (isolated molecule) whereas the experimental results belong to solid phase. A statistical treatment of gaseous and solid phase bond lengths is shown in Fig. 3. The optimized molecular structure of title molecule exposes that the substituted methoxy group is co planar with the plane of the indole ring. The C_{16}–O_{15} bond length of the methoxy group is found to be larger than the ring attached C_6–O_{15} bond length. This is due to the effective overlapping of lone pair electrons of oxygen atom with the π electron system of the indole ring [4]. The C_{17}–C_{18} and N_1–C_{17} bond lengths are longer than the typical C–C and N–C single bond lengths, these bonds causes charge transfer between indole and chlorophenyl moieties. Carbonyl group bridge ($C_{17} = O_{24}$) increases its single bond character by 0.0095 Å from the other carbonyl group in this molecule. The methyl substituent at C_{14} of the indole ring prevents the carbonyl group $C_{17} = O_{24}$ from being coplanar with the indole ring, the corresponding torsion angle is C_2–N_1–C_{17}–$O_{24} = -29.104°$. A similar steric strain, involving ortho hydrogens of two rings (H_{44}& H_{32}), prevents the chlorophenyl ring from being coplanar with the carbonyl group; the torsion angle C_{19}–C_{18}–C_{17}–$O_{24} = -31.814°$. The bond lengths of C_{11}–C_{10} and C_{26}–C_{27} are 1.5285 and 1.52 Å, respectively. These values are good agreement with solid phase values.

Substituent effects: Replacing chlorine by fluorine, bromine and iodine causes dramatic changes in molecular structural parameters. The bond lengths of C–F, C–Cl, C–Br and C–I are 1.351, 1.7541, 1.9133 and 2.139 Å, respectively. The DFT calculation shows that the bond length difference increases on the order of F<Cl<Br<I. The bond length of C_{21} with its adjacent carbon atom C_{20} and C_{22} in the chlorophenyl ring increases with the change in halogen substitution from F to I, which is illustrated in Table 1. It shows that the bond length of C_{21}–C_{20} and C_{21}–C_{22} are shorten in the fluorine substitution. The endocyclic angle C_{20}–C_{21}–C_{22} of carbon atom attached to the fluorine, chlorine, bromine and iodine atoms are 122.614, 121.369 121.355 and 120.72 respectively, decreases in the order of F>Cl>Br > I. These geometrical changes depend on the electron-withdrawing inductive effect of the substituent [19], and it decreases from fluorine to Iodine.

4.3. Natural bond orbital analysis

4.3.1. Donor-accepter interactions

The Donor-acceptor interactions are considered by analysing viable interactions between filled lewis and empty non lewis NBOs, after estimating their energies through second-order perturbation concept. These lively interactions are termed to as 'delocalization' corrections to the zeroth-order natural Lewis structure. The potency of these delocalization interactions, $E^{(2)}$, are proportional to the NBO interacting intensities and energies which give essential facts on the interactions among various parts of the molecules [20–22]. Some significant orbital interactions and corresponding second order perturbation energies derived from the NBO computation are listed in Table 2, which shows the most significant interactions between Lewis and non-Lewis orbital with N and O lone pairs. The very important interaction among them was the electron donation of N_1 and O_{24} lone pair orbitals to the neighbouring anti-bonding orbitals of the indole ring, bridge carbonyl group and chlorophenyl ring [$n1(N_1) \rightarrow \pi^*C_4$–$C_9$, $\pi^*C_{17} = O_{24}$and $n2(O_{24}) \rightarrow \sigma^*C_{17}$–$C_{18}$]. NBO analysis shows the magnitude of charge transferred from indole moiety to the chlorophenyl moiety through the carbonyl group, which clearly manifests the evidences for the elongation and weakening of the bond $C_{17} = O_{24}$. Also an exchange interaction happens among the bonding and anti-bonding π-orbitals of C_4–C_9 and C_5–C_6 leads to stabilization energy 30.61 and 12.63 kcal/mol, respectively. π-orbitals of C_4–C_9 further stabilized