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Spectroscopic (FT-IR, FT-Raman, UV, NMR, NBO, NLO) investigation and molecular docking study of (R)-2-Methylamino-1-Phenylethanol (Halostachine)

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ABSTRACT

FT-IR (4000–400 cm^{-1}) and FT-Raman (4000–100 cm^{-1}) spectra of (R)-2-Methylamino-1-Phenylethanol have been recorded in solid phase, ^1H and ^{13}C NMR in deuterated chloroform ($CDCl_3$) phase and UV spectrum (200–400 nm) in solid phase and in ethanol solution. The different conformers of the compound and their minimum energies were studied by potential energy surface scan, using semi-empirical method PM6. The computed wavenumbers obtained from B3LYP and B3PW91 functionals along with 6-311++G (d, p) basis sets were scaled so as to agree with the experimental values and the scaling factors have been reported. All the fundamental modes have been assigned based on the potential energy distribution (PED) values and the structure of the molecule was analyzed in parameters like bond length, bond angle and dihedral angles through B3LYP and B3PW91 functionals along with 6-311++G(d,p) basis set. The values of dipole moment (μ), polarizability (α) and hyper polarizability (β) of the molecule were calculated using which, the non-linear optical property of the molecule has been discussed. The observed HOMO-LUMO mappings reveals the different charge transfer possibilities within the molecule. Natural Bond Orbital analysis was computed and possible transitions were correlated with the electronic transitions. Mulliken charges, electrostatic potential charges and natural charges are also predicted. The theoretical ^1H and ^{13}C NMR chemical shifts were computed using B3LYP functionals using 6-311++G (2d, p) basis sets. The temperature dependence of the thermodynamic properties; heat capacity, entropy and enthalpy for the title compound were also determined by B3LYP functionals with 6-311++G (d, p) basis set. Molecular docking study shows that the title compound might exhibit inhibitory activity against *Bacillus anthracis* (3V5O).

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1. Introduction

2-Methylamino-1-Phenylethanol (MAPE), an alkaloid, was first isolated from the Asian shrub Halostachys caspica by Syrneva [1]. Hence, it is also called as Halostachine and was found to be a levorotatory enantiomer. It appears as a colorless solid. The presence of the hydroxyl-group on the benzylic carbon of MAPE creates a chiral center, so the compound exists in the form of two enantiomers. The dextrorotatory isomer corresponds to the S-configuration, and the levorotatory isomer to the R-configuration [2,3]. The amino-group in MAPE makes it a weak base. It reacts with acids to form salts.

Butz et al., [4] studied the conformational preferences of MAPE using MP2/6-311 + G (d, p) method. The effect of solvation on 2-Amino-1-Phenylethanol was studied by Baker et al., [5]. Melandri et al., [6] observed the shape of 2-Methylamino-1-Phenylethanol by free jet microwave spectroscopy. Efficient preparation of (R) and (S) 2-Amino-1-Phenylethanol was performed by Lohse et al., [7]. Lopez et al., [8] observed the conformational study of 2-Phenylethylamine by Molecular beam Fourier transform microwave spectroscopy. Sabelli et al., [9] studied the behavioral and electrophysiological effects of 2Amino-1-Phenylethanol. Kapitan et al., [10] studied the vibrational Raman optical activity of 1-phenylethanol and 1-phenylethylamine. Urban et al., [11] analyzed the solvent effects on the intramolecular amine-aryl interactions in charged and

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neutral 2-phenylethylamines.

Though various studies have been reported, areas such as FT-IR, FT-Raman, UV, NMR studies have not been explored so far on MAPE. Hence, the present study is undertaken to carry out a thorough and systematic conformational, structural, vibrational, NBO, UV and NMR analysis of the compound. The probing was extended by the rigorous computation using DFT methods in combination with a proper basis set. The triple zeta basis set in 6-311++G (d, p) employs three basis function of each type, occupied in separate atoms. Thus, it increases the size of the basis set in an effort to get closer to the exact electronic energy. Also, it includes both polarization and diffuse functions. The polarization functions enhance the flexibility of atoms to form chemical bonds in any direction and hence improve calculated molecular structures. Diffuse functions improve the predicted properties of species with extended electronic densities such as anions or molecules forming hydrogen bonds [12,13]. In order to understand the electrical, electronic and thermal properties of the molecule, Mulliken population analysis, Electrostatic potential analysis, Natural population analysis, NLO and thermodynamic properties were also carried out for the molecule in this present study.

2. Experimental details

The compound under investigation namely (R)-2-Methylamino-1-Phenylethanol was purchased in the powder form from Sigma-Aldrich Chemicals, Chennai with 98% purity. The FT-IR spectrum of the compound was recorded using a Thermo Nicolet 6700 spectrometer in the range of 4000–400 cm^{-1}. The spectral resolution is ±2 cm^{-1}. The FT-Raman spectrum of the same compound was also recorded using the same instrument with an FRA 106 Raman module equipped with ND: YAG laser source operating at 1.064 μm line widths 200 mW power, in the range of 4000–100 cm^{-1} with a scanning speed of 30 cm^{-1} min^{-1} and spectral width 2 cm^{-1}. The frequencies of all bands are accurate to ±1 cm^{-1}. The high resolution ^{1}H NMR and ^{13}CNMR were recorded using 300 MHz and 75 MHz NMR spectrometer respectively. The UV–Vis spectra were recorded in solid phase and ethanol solution in the range 200–800 nm, with the scanning interval of 0.2 nm, using Shimadzu UV-250 spectrometer.

3. Computational details

All the quantum chemical computations, of the compound (R)-2-Methylamino-1-Phenylethanol was carried out with the Gaussian 09W program [14]. The conformational analysis was carried out using semiemprical method PM6. B3LYP density functional provides better bond length results than the other density functionals [12]. Hence, the structural parameters were computed for the optimized geometry of the most stable conformer using B3LYP and B3PW91 functionals using 6-311++G (d, p) basis sets for comparison purpose. The wavenumbers for vibrational modes were calculated using the same methods. The unscaled wavenumbers from 3530 cm^{-1} to 2939 cm^{-1} were scaled by scaling factor 0.957 and wavenumbers from 1642 cm^{-1} to 22 cm^{-1} were scaled using 0.99 for B3LYP method. Similarly, in B3PW91 method, unscaled wavenumbers from 3536 cm^{-1} to 2951 cm^{-1} and 1656 cm^{-1} to 27 cm^{-1} were scaled using 0.957 and 0.99 scaling factors respectively [15]. The assignments of the calculated normal modes have been made on the basis of the corresponding Potential energy distribution (PEDs). The PEDs are computed from quantum chemically calculated vibrational frequencies using VEDA program [16]. Gauss view program [17] has been considered to get visual animation and for the verification of the normal modes assignment. The electronic absorption spectra for optimized molecule were calculated using time dependent self-consistent field (TD-SCF) theory at B3LYP/6-311++G(d,p) level in gas and solvent phases. This calculation, based on DFT computational method, is found to be successful in supporting the analysis of the experimental data [18]. It obtains the wave functions of Molecular Orbitals that oscillate between ground state and the first excited states. The number of excited states and the type of transition to be calculated, can be selected, for example TD = Nstates = 3, TD = singlet. The thermodynamic functions such as the heat capacity, entropy and enthalpy were calculated for different temperatures from the vibrational frequencies calculated using the same method and basis set. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) chemical shifts of the molecule were calculated by the gauge independent atomic orbital (GIAO) theory in combination with B3LYP/6-311++G(2d,p) and compared with experimental results. Parameters such as dipole moment (μ), polarizability (α), anisotropy (Δα) and the first order hyper polarizability (β) are determined to study the non-linear optical property of MAPE using B3LYP functional with 6-311++G(d,p) basis sets [19]. The β components of Gaussian output are reported in atomic units and therefore the calculated values are converted into e.s.u units (for α: 1 a.u. = 0.1482×10^{-24}e.s.u, for β; 1 a.u. = 8.6393×10^{-33}e.s.u).

4. Results and discussion

4.1. Potential energy surface (PES) scan for conformational analysis

Goncalves et al., [20] observed that the energy profiles obtained through semi-empirical method PM6 were similar to the one obtained by DFT. At the same time, it is much less time consuming when compared with DFT. Hence, conformational analysis in our work, was carried out by means of potential energy scan using semi empirical method PM6. Gamez-Garcia et al. [21] observed that, dipole moment is affected by molecular shape in a similar compound.

Five different dihedral angles, H20-N15-C13-H18, H24-C12-C3-C4, H18-C13-C12-O16, C3-C12-O16-H17 and H20-N15-C14-H21 were chosen for conformational analysis.

During the scan, all the geometrical parameters were simultaneously relaxed; while the dihedral angle was allowed to vary in steps of 10° with a total 36. Plots describing the variation in ground state energy (in Kcal/mol) with the dihedral angle are depicted in Fig. 2a–e. From Fig. 2a, we observe that, conformer (B) has a maximum energy value of 4.76 kcal/mol and the minimum energy is at 0.36 kcal/mol (C). From Fig. 2b, we understand that, the minimum energy is obtained at 0.36 kcal/mol (B) and the maximum value corresponds to 4.04 kcal/mol (A). Thus, it is inferred that the minimum energy value and the corresponding conformer is identical along the dihedral angles H20-N15-C13-H18 and H24-C12-C3-C4. In Fig. 2c, the minimum energy is observed at

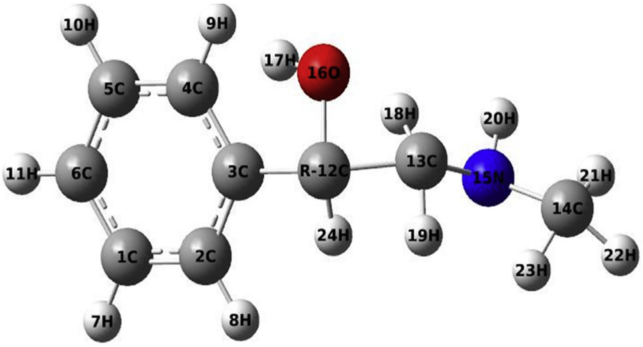

Fig. 1. Molecular structure of (R)-2-Methylamino-1-Phenylethanol (MAPE).

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