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Structure activity relationship, vibrational spectral investigation and molecular docking analysis of anti-neuronal drug 4-(2-Aminoethyl) morpholine

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ABSTRACT

Vibrational spectral analysis and quantum chemical computations based on density functional theory have been performed on the anti-neuronal drug 4-(2-aminoethyl) morpholine. The geometry, intermolecular hydrogen bond, and harmonic vibrational frequencies of the title molecule have been investigated with the help of B3LYP method. The calculated molecular geometry has been compared with the experimental data. The various intramolecular interactions have been exposed by natural bond orbital analysis. Analysis of SERS bands in comparison to the normal Raman spectrum indicates the chemisorption of the drug on the silver surface. The analysis of the electron density of HOMO and LUMO gives an idea of the delocalization and low value of energy gap indicates electron transport in the molecule and thereby bioactivity. Effective docking of the drug molecule with 2C6C protein also enhances its bioactive nature.

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1. Introduction

The interaction of nanoparticles with biomolecules is an imminent field of research. Within this field, an area that has been largely gaining attention is the interaction of metal nanoparticles with drugs. Noble-metal nanomaterials are ideal candidates for such interactions. Among noble metals, silver nanoparticles have received considerable attention due to their attractive physicochemical properties. Silver nanoparticles exhibit a strong optical activity due to plasmon resonance, an electrodynamic phenomenon based on the excitation of conduction electrons at specific frequencies of light. These plasmon resonances enhance the detection and tracking of Ag NPs by a number of optical imaging methods, from simple light scattering to multiphoton luminescence, surface-enhanced Raman scattering (SERS) and *in vivo* biomedical imaging modalities. Most of these cases can be considered exploratory in their use of Ag NPs, but also demonstrate their potential utility in the design of *in vitro* and *in vivo* studies that address downstream toxicological effects. Drugs containing morpholine moiety have exhibited remarkable biological properties, viz phendimetrazine as CNS stimulant [1]. Substituted morpholines display anaesthetic properties [2], and the morpholine derivative, amorolfine, finds use as an antifungal drug [3]. Morpholine is a simple heterocyclic compound of great industrial importance and has wide range of applications. It is used as an anticorrosive agent in water boiling systems, as a chemical intermediate, in textile industry, photographic developers, air conditioners, waxes and in the preservation of book paper.

Morpholine can exist as two conformers, equatorial or axial and the *ab initio* studies, predicted the equatorial conformer to be the lower energy form [4–6]. Conformational problems in morpholine have received much interest [6–13] but the structural and vibrational spectroscopic analysis of the morpholine derivative, 4- (2-aminoethyl)morpholine otherwise called AEM which has anti-neuronal properties has not been carried out. Over the years, SERS has proven to be one of the most sensitive spectroscopic techniques that provides greatly enhanced Raman signal. The SERS technique has been widely exploited in identifying biomolecules,

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drugs, and proteins as it provides information about the binding sites and the orientation over the metal surfaces. The various properties of the drug including its ability to bind to residues, its bioactivity etc. are all related to the structure, which makes a study of the structure of vital importance.

The theoretical computational studies possess indeed a large inherent potential for simulating spectra of different kinds and often show high accuracy for molecules in the gas phase. It is the approved method of comparing the calculated and experimental analysis of the materials. Currently, quantum mechanical calculations are very popular because of their efficiency and accuracy with respect to the evaluation of a number of molecular properties. The present work deals with the vibrational spectra of 4-(2-Aminoethyl) Morpholine (AEM) compound and compared with the computed result by the DFT method. The Potential Energy Distribution (PED) also calculated to enhance the detailed assignment of the vibrational spectra. Natural Bond Orbital (NBO) analysis has been used to identify the possible intra and inter molecular interaction present in the compound. The calculated HOMO–LUMO energy gap confirms the occurrence of the charge transfer interaction.

2. Computational details

By providing detailed insight into molecular properties and processes, computational methods have become a powerful and complementary approach to experiment providing better understanding of SAR (structure-activity relation). DFT computations of AEM were performed by using Gaussian'09 [14] at the B3LYP hybrid exchange–correlation three-parameter functional with standard 6–31++G (d,p) basis set to derive the complete geometry optimization. All the optimized geometry corresponding to minimum on the potential energy surface has been obtained by solving self-consistent field equation iteratively. The calculated harmonic vibrational wavenumbers have been analytically calculated by taking second order derivative of energy using the similar level of theory. The calculated wavenumbers were scaled with a single scaling factor (0.9670). The vibrational modes were assigned on the basis of PED analysis using VEDA 4 program [15]. The internal co-ordinates were optimized repeatedly to maximize the PED contributions. The Raman activities (Si) calculated with Gaussian '09 program converted to relative Raman intensities (I_i) using the following relationship derived from the intensity theory of Raman scattering [16,17] given by Eqn. (1) as:

$$I_i = \frac{f(\nu_o - \nu_i)^4 S_i}{\nu_i\left[1 - \exp\left(\frac{-hc\nu_i}{kT}\right)\right]} \quad (1)$$

where ν_0 is the exciting wavenumber, ν_i is the vibrational wavenumber of the ith normal mode, h, c, and k are universal constants, and 'f' is a suitably chosen common scaling factor for all the peak intensities. The simulated IR and Raman spectra were plotted using pure Lorentzian band shapes with a FWHM of 10 cm^{-1}.

3. Experimental details

Liquid AEM sample was purchased from Sigma–Aldrich Chemical Company with a stated purity of greater than 98% and was used as such without further purification to record the spectra. The FT-IR spectrum was recorded between 4000 cm^{-1} and 400 cm^{-1} on a Jasco, LOCALE 1033 spectrometer by NaCl crystal method. The FT-Raman spectrum of the sample was recorded between 3500 and 50 cm^{-1} region on a FT RAMAN BRUKER RFS100/S instrument using 1064 nm excitation from a Nd:YAG laser and a standard InGaAs detector. Raman laser power is 350 mW, resolution is 4 cm^{-1}, no of scans is 50 and temperature of measurement is 22 °C. Silver hydrosol for recording the SERS spectrum was prepared by the chemical reduction of $AgNO_3$, with $NaBH_4$ using Lee and Meisel method [18]. In brief, 10 ml $AgNO_3$ [10^{-3} M] solution was added drop wise to 30 ml of 2×10^{-3} M ice-cold $NaBH_4$ with slow stirring. The silver hydrosol was yellow in color and was stable at room temperature for several weeks. The pH of the silver hydrosol was 9. AEM was added to the silver hydrosol and characterized using UV–vis absorption (0.1 M) and Raman (10^{-2} M and 10^{-3} M) techniques. The UV–vis absorption spectra were recorded using a Jasco V-650 spectrophotometer. For the Raman measurements, the sample solution as well as silver hydrosol was taken in a standard 1 cm × 1 cm cuvette and the Raman scattered light was collected at 90° scattering geometry and detected using a CCD (Synapse, Horiba Jobin Yvon) based, monochromator (Triax550, Horiba Jobin Yvon, France) together with a notch filter, covering a spectral range of 200–1700 cm^{-1}.

4. Molecular geometry

The structural parameters of AEM monomer and dimer namely the bond lengths, bond angles and dihedral angles as calculated using DFT theory at B3LYP/6–311++G** level by Gaussian '09 [14] program package and presented in Table 1 in accordance with the atom numbering scheme for the compound given in Fig. 1 and 2 depicts the molecular geometry of AEM dimer. From Table 1, it is observed that the various ring C–C, C–O, and C–H bond lengths vary from their experimental values by about 0.047, 0.005 and 0.128 Å, respectively. Appreciable variation (0.128 Å) shown by C–H bonds of the morpholine ring is due to charge transfer interaction between the morpholine ring and the aminoethyl moiety. Also, the C–N bond distances (C_1–N_{21}, C_4–N_{21} and C_{12}–N_{21}) are significantly shorter than the normal C–N single bond of about 1.48 Å. The shortening of these C–N bonds confirms the well-known effect of resonance in this part of the molecule.

The morpholine ring has basically a chair conformation [19,20] with the atoms C_1, C_2, O_{20}, C_3, C_4 and N_{21} alternate between two parallel planes, one with C_1, O_{20} and C_4, the other with C_2, C_3, and N_{21}. The molecule has a symmetry axis perpendicular to these two planes, and is congruent to itself after a rotation of 120° about that axis. All bonds are tilted relative to the mean plane, but opposite bonds are parallel to each other. The increase (instead of 109°) in bond angles O_{20}–C_2–C_1, O_{20}–C_3–C_4, N_{21}–C_1–C_2, N_{21}–C_4–C_3, C_4–N_{21}–C_1 and C_3–O_{20}–C_2 as given in Table 1, makes the chair conformation slightly flattened so that the dihedral angles O_{20}–C_2–C_1–N_{21} and O_{20}–C_3–C_4–N_{21} are 36.83° and 37.63° respectively instead of 60° between adjacent bonds which are not exactly parallel to the C_3 axis but lean towards from it.

As a consequence of ring warping, four of the eight carbon-hydrogen bonds (C_1–H_9, C_2–H_6, C_3–H_7 and C_4–H_{11}) end up almost perpendicular to the mean plane and almost parallel to the symmetry axis, with alternating directions, and are said to be "axial". The other four C–H bonds (C_1–H_5, C_2–H_{22}, C_3–H_8 and C_4–H_{10}) lie almost parallel to the mean plane, and are said to be "equatorial". The precise angles are such that the two C–H bonds in each carbon, one axial and one equatorial, point in opposite senses relative to the symmetry axis. Thus, in a chair conformation, there are three C–H bonds of each kind — axial "up", axial "down", equatorial "up", and equatorial "down"; and each carbon has one "up" and one "down", and one axial and one equatorial. The hydrogens in successive carbons are thus staggered so that there is little torsional strain. The conversion from one chair shape to the other is referred to as ring flipping or chair-flipping in which carbon-hydrogen bonds that is axial in one configuration become equatorial in the other, and vice-versa; but their "up" or "down" character remains the same.

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