Investigations on 2-(4-Cyanophenylamino) acetic acid by FT-IR, FT-Raman, NMR and UV-Vis spectroscopy, DFT (NBO, HOMO-LUMO, MEP and Fukui function) and molecular docking studies

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ABSTRACT

Extensive quantum chemical calculation have been carried out to investigate the Fourier Transform Infrared(FT-IR), Fourier Transform Raman(FT-RAMAN) and Nuclear magnetic resonance(NMR), and Ultra Violet-Visible(UV-vis) spectra of 2-(4-Cyanophenylamino) acetic acid. The molecular structure, fundamental vibrational frequencies and intensities of the vibrational bands were interpreted with the aid of optimizations and normal coordinate field calculations based on density functional theory (DFT) and ab initio HF methods with 6–311+G(d,p) basis set. The theoretical vibrational wavenumbers are compared with the experimental values. The calculated HOMO-LUMO energies were found to be -6.2056 eV and -1.2901 eV which indicates the charge transfer within the molecule. Natural bond orbital analysis has been carried out to explain the charge transfer (or) delocalization of charge due to the intra molecular interactions. Molecular Electrostatic Potential (MEP), First order hyperpolarizability, and Fukui functions calculation were also performed. The thermodynamic properties of the title compound were studied for different temperatures. Molecular docking studies were made on the title compound to study the hydrogen bond interactions and the minimum binding energy was calculated.

1. Introduction

The 2-(4-Cyanophenylamino) acetic acid (24CPA) is used as a Hypercoagulable diseases. An Extensive work has been carried out on the title compound in recent years. Based on the literature studies and Swiss Institute of Bioinformatics software, the target class have been identified for Hypercoagulable is 2-(4-Cyanophenylamino) acetic acid (24CPA) is an oxidoreductase enzyme [1, 2]. Hypercoagulable is a blood clot formation in a human body, which is very dangerous. Early identification and treatment are essential for hypercoagulability. Otherwise, an increase in the risk of severe leg pain, heart attack, stroke when the arteries not properly carried away the blood from the heart. When the blood clot in the veins carry blood to the heart causes, intestines, kidney, liver, and lung problems. There are two types of hypercoagulable states available called inherited and acquired nature in the human system. Prothrombin gene mutation, protein C, and protein S deficiencies and factor V Leiden are inherited hypercoagulable states. The inflammatory bowel syndrome, HIV, surgery, cancer medications, and birth control pills are the causes ofacquired hypercoagulable states [3, 4, 5, 6, 7]. Literaturesurvey, points out that a complete quantum mechanical calculation for the selected title compound has not yet been reported so far. Quantum chemical calculations, and molecular modeling are playing a major role for drug design and research vibrational spectroscopy [8, 9, 10, 11]. To find the structural information, functional groups, and other quantum level parameters, FT-IR, FT-Raman, NMR, UV-Visspectroscopy using density functional theory (DFT) approaches are followed. The stability of the compound 24CPA is obtained by natural bond orbital analysis (NBO). The quantitative and qualitative of the reactive are identified by molecular electrostatic potential (MEP) and Fukui function studies. The stability, energy gap, are obtained using frontier molecular orbital analysis. The electronic transition details inside the molecule 24CPA are identified using UV-Vis spectroscopy. Thermodynamic parameters entropy, enthalpy, and heat
high-resolution NMR spectrometer at 400 MHz, the NMR spectra of
range 4000
Bruker RFS 27 spectrometer the FT-Raman spectrum was recorded in the
genuine and geometric parameters such as bond length and bond angle of the title
4.1. Molecular geometry
4. Results and discussion
by Autodock 4.2.6 software [19].
using Swiss ADME tool [18]. The ligand and protein interactions are done
Drug-likeness nature and ADME properties of the derivatives are obtained
software by DFT-B3LYP method, 6
3. Computational methodology
were obtained using VEDA4 software [16] in the form of a potential
MEP were carried out by the optimized structure. Thermodynamics
numbers and other molecular properties like HOMO-LUMO,NBOand
deviation between the experimental and theoretical values may be due to
the experimental values are taken in the solid phase and computational
values are from the gas phase. From the different bond lengths, we found
that like bonds repel each other, so C-C bonds are higher than other
bonds. Due to attraction, the atoms come closer and the bond length
decreases for different atoms. Similarly, the bond angles also are close to
each other.
4.2. Vibrational spectroscopic analysis
The molecule 24CPA consists of 21 atoms and 57 normal modes of vibration. The simulated and experimental vibrational wavenumbers along with their assignments, infrared vibrational frequencies and intensities, Raman vibrational wavenumbers and intensities of the title compound are given in Table 2. And the comparison graph is shown in Figure 2 and Figure 3. A small scaling factor 0.961 introduced to obtained scaled values for the 6-311++G(d,p) basis set.
4.2.1. N-H vibrations
The stretching vibrations of amino group N-H should be 3400-
3500cm⁻¹ [21,22]. In this study, a weak band isoccurring in the
FT-IRspectrum at 3453 cm⁻¹. The correlated scaled frequency is
observed at 3493 cm⁻¹with a PED contribution of 100%.
4.2.2. C-H vibrations
The aromatic C-H vibrations should be descried at2800-3100 cm⁻¹
[23]. For this compound stretching vibrations occurred at 3097,3045,
3070, 3048, and 2848, 3031 cm⁻¹ in the FT-IR spectrum, and FT-Raman
spectrum. The scaled values are at 3097, 3050, 3084, 3068, 2912, 3121
and 2895 cm⁻¹with PED contribution more than 90%.
4.2.3. Nitriles vibrations
The C triple bond N (Nitriles) vibrations should be observed normally
at 2240-2260 cm⁻¹. For24CPA, Nitriles vibrations is detected at
2219cm⁻¹ in the FT-IR spectrum, In the FT-Raman spectrum at2217cm⁻¹
and thescaling value is noted at 2246 cm⁻¹ with PED contribution 90%.
The mixed vibrations are observed at 1145, 1148, and 1117 cm⁻¹. In FT
IRthe stretching vibrations of NC, bending vibrations of HCC, and HNC
are observed at 1345, 1348, and 1341 cm⁻¹. Due to stretching vibrations of NC, stretching vibrations of OC, bending vibrations of HO and HNC a strong peak is
observed at 1145 cm⁻¹ [24].
4.2.4. C-C vibrations
In FT-IR, FT-Raman the stretching vibrations of C-C bond are
observed at 735, 736, and 724 cm⁻¹scaled values respectively with PED
contribution 43% [25]. The mixed vibrations, stretching-C-C, and bending vibrations HCC are observed in the title compound at 1605, 1609, and
1601 cm⁻¹and 1410 cm⁻¹and 1407 cm⁻¹ respectively. The FT-IR,
FT-Raman, and scaled values of symmetricCC, bendingHNC and
torsional vibrations of HCCO are observed at 1221, 1224, and 1239
cm⁻¹. The stretching vibrations of CC, NC, and bending vibrations of
CNC is observed at 829 cm⁻¹.
Figure 1. 24CPA optimized molecular structure with numbering system.

capacity are analyzed at different temperatures. Drug-likeness,ligand, and suitable protein interactions are done by molecular docking to
know the biological activity of the compound [12].
2. Experimental method
2-(4-Cyanophenylamino) acetic acid was purchased from Sigma-
Aldrich company with 99% purity and used as such without further
processing [13]. By using PERKIN ELMER FTIR spectrometer the FT-IR
spectrum recorded in the range 400-450 cm⁻¹ was taken in evacuation
mode by KBr pellet method with resolution 1.0 cm⁻¹. By using
Bruker RFS 27 spectrometer the FT-Raman spectrum was recorded in the
range 4000-100 cm⁻¹ of an Nd:YAG laser with 200 mW powers. The spectral width is 2 cm⁻¹ with a scanning speed of 30 cm⁻¹. ByBruker
high-resolution NMR spectrometer at 400 MHz, the NMR spectra of
Carbon(13C) and Proton (1H) were taken using DMSO as a solvent with
TMS as an internal standard. The UV-1700 spectrometer was used to take
the UV-Visiblespectrum of 24CPA with the frequency range of 200-700
nm.
3. Computational methodology
The optimized structure of 24CPA was arrived from Gaussian 09
software by DFT-B3LYP method, 6-311 + +G(d,p) higher-order basis set
[14,15]. The potential energy distribution and vibrational assignments
were obtained using VEDA4 software [16] in the form of a potential
energy distribution. The geometrical parameters, vibrational waven-
umbers and other molecular properties like HOMO-LUMO,NBOand
MEP were carried out by the optimized structure. Thermodynamics
properties like entropy, enthalpy, and heat capacity values are obtained
by THERMO. PL script [17] with the Gaussian output file. The
drug-likeness nature and ADME properties of the derivatives are obtained
using Swiss ADME tool [18]. The ligand and protein interactions are done
by Autodock 4.2.6 software [19].
4. Results and discussion
4.1. Molecular geometry
The optimized molecular structure along with numbering of atoms
and geometric parameters such as bond length and bond angle of the title
compound is obtained using Gaussian09 and Gaussian5 software as
shown in Figure 1. The experimental values are taken from similar
structure [20]. From the XRD data show that the structure of 24CPA is an
Orthorhombiccrystal system, intercepts a = 18.4827 (12) Å; b = 9.8467
(6) Å; c = 22.0681 (15) Åand symmetry Z = 8. The bond length and bond
angle parameter are shown in Table 1. The experimental bond length of
O1–C12 is 1.328 Å and corresponding theoretical valuesare 1.346 Å. The experimental bond lengths of O1–H21, O2–C12, N3–C5, N3–C6,
N3–H14, N4–C13, C5–C7, C5–C8, and C6–C12 are 0.980, 1.205, 1.376,
1.456, 0.860, 1.138, 1.393 and 1.476 Å respectively. Similarly,
the equivalent bond lengths of the DFT in the same order are 0.970,
1.205, 1.371, 1.436, 1.010, 1.157, 1.409, 1.412, and 1.514 Å. The slight
deviation between the experimental and theoretical values may be due to
the experimental values are taken in the solid phase and computational
values are from the gas phase. From the different bond lengths, we found
that like bonds repel each other, so C-C bonds are higher than other
bonds. Due to attraction, the atoms come closer and the bond length
decreases for different atoms. Similarly, the bond angles also are close to
each other.
4.2.5. C=O vibrations

The C=O vibrations noted at 1733 cm$^{-1}$ in FT-IR, 1732 cm$^{-1}$ in FT-Raman, and 1761 cm$^{-1}$ respectively with a PED contribution of 85%. At 1343 cm$^{-1}$ in the FT-IR spectrum the mixed vibrations, stretching of OC, stretching vibrations of CC and torsional vibrations of HCCO were observed.

4.3. NBO analysis

Natural bond orbital analysis provides an efficient method for studying intra and intermolecular bonding interaction among bonds, and provides a convenient basis for investigation charge transfer or conjugative in molecular systems. The stabilization energy $E_2$ is obtained based on second-order perturbation [26, 27, 28].

$$E_2 = \Delta E_2 = q_i F(i,j)^2$$

where $q_i$ is the donor orbital occupancy, $E_i$ and $E_j$ are diagonal elements and $F(i,j)$ is the Fock matrix elements. NBO analysis has performed on the molecule at the DFT (B3LYP)/6-311++G(d,p) level in order to elucidate the intra-molecular, rehybridization and delocalization of electron density within the molecule. The energy values for the interaction between the filled $i$ and vacant $j$, calculated for the title compound have been tabulated in Table 3. The strong stabilization energy is from LP2 (O1) to $\pi^*(O2-C2)$ with a value of 44.63 kcal/mol. The lone pair electrons of LP1 (N3) to $\pi^*(C5-C7)$ with stabilization energy of 38.27 kcal/mol. The important transition for the high stability of 24CPA is LP2(O2), $\pi(C5-C7)$ and $\pi(C9-C11)$ donor orbitals to $\sigma^*(O1-C12)$, $\pi^*(C9-C11)$ and $\pi^*(C8-C10)$ acceptor orbitals with stabilization energies of 31.10, 25.32,

| Parameters Bond length (Å) | Experimental | B3LYP/6-311++G(d,p) | Parameters Bond angle (°) | Experimental | B3LYP/6-311++G(d,p) |
|---------------------------|--------------|----------------------|---------------------------|--------------|----------------------|
| O1–C12                    | 1.328        | 1.346                | C12–O1–H21                | 108.2        | 107.9                |
| O1–H21                    | 0.980        | 0.970                | O1–C12–O2                 | 122.8        | 123.8                |
| O2–C12                    | 1.205        | 1.205                | O1–C12–C6                 | 112.7        | 111.1                |
| N3–C5                     | 1.376        | 1.371                | O1–H21–O2                 | 76.1         | 74.1                 |
| N3–C6                     | 1.456        | 1.436                | O2–C12–C5                 | 121.5        | 125.0                |
| N3–H14                    | 0.860        | 1.010                | C12–O2–H14                | 82.6         | 85.7                 |
| N4–C13                    | 1.138        | 1.157                | C12–O2–H21                | 56.1         | 54.2                 |
| C5–C7                     | 1.393        | 1.409                | C5–N3–C6                  | 124.8        | 124.7                |
| C5–C8                     | 1.393        | 1.412                | C5–N3–H14                 | 118.5        | 119.5                |
| C6–C12                    | 1.476        | 1.514                | N3–C5–C7                  | 122.4        | 122.1                |
| C6–H15                    | 0.970        | 1.099                | N3–C5–C8                  | 122.4        | 119.6                |
| C6–H16                    | 0.970        | 1.099                | N6–N3–H14                 | 114.1        | 115.8                |
| C7–C9                     | 1.377        | 1.387                | N3–C6–C12                 | 105.7        | 109.5                |
| C7–H17                    | 0.970        | 1.083                | N3–C6–H15                 | 114.1        | 112.6                |
| C8–C10                    | 1.377        | 1.380                | C3–C6–H16                 | 111.2        | 112.6                |
| C8–H18                    | 0.970        | 1.085                | N3–H14–O2                 | 108.7        | 105.9                |
| C9–C11                    | 1.396        | 1.401                | N4–C13–C11                | 178.3        | 180.0                |
| C9–H19                    | 0.970        | 1.083                | C7–C5–C8                  | 118.3        | 118.3                |
| C10–C11                   | 1.396        | 1.407                | C5–C7–C9                  | 120.8        | 120.5                |
| C10–H20                   | 0.970        | 1.083                | C5–C7–H17                 | 120.9        | 120.5                |
| C11–C13                   | 1.396        | 1.426                | C5–C8–C10                 | 120.8        | 120.9                |
| O2–H14                    | 2.210        | 2.254                | C5–C8–H18                 | 119.5        | 119.3                |
| O2–H21                    | 2.220        | 2.316                | C12–C6–H15                | 109.5        | 107.7                |

* Reference [13].
| Mode | Experimental (cm\(^{-1}\)) | DFT | Assignments (PED\(^{\dagger}\)) |
|------|-----------------------------|-----|----------------------------------|
|      | FT-IR                       | FT-Raman | \(^{\ddagger}\)IR intensity \(^{\ddagger}\)Raman activity |
|      |                             |       |                                  |
| 1    | 3640                        | 32   | 20                               | yOH(100) |
| 2    | 3493                        | 42   | 16                               | yNH(100) |
| 3    | 3099                        | 2    | 14                               | yCH(98)  |
| 4    | 3093                        | 1    | 10                               | yCH(98)  |
| 5    | 3084                        | 2    | 5                                | yCH(99)  |
| 6    | 3068                        | 2    | 7                                | yCH(100) |
| 7    | 2912                        | 3    | 8                                | yCH(99)  |
| 8    | 2895                        | 18   | 19                               | yCH(99)  |
| 9    | 2246                        | 38   | 100                              | yNC(90)  |
| 10   | 1761                        | 91   | 1                                | yOC(85)  |
| 11   | 1601                        | 100  | 33                               | yCC(56) + \(\gamma\)HCC(18) |
| 12   | 1549                        | 13   | 0                                | yCC(47) + \(\gamma\)HNC(17) |
| 13   | 1512                        | 84   | 1                                | yNC(33) + \(\gamma\)HCC(25) + \(\gamma\)HNC(21) |
| 14   | 1473                        | 5    | 3                                | \(\gamma\)HCCO(17) + \(\gamma\)HCC(13) + \(\gamma\)HNC(27) |
| 15   | 1444                        | 10   | 1                                | \(\gamma\)HCC(70) + \(\gamma\)HCCO(14) |
| 16   | 1407                        | 0    | 0                                | \(\gamma\)CC(37) + \(\gamma\)HCC(24) |
| 17   | 1367                        | 54   | 1                                | \(\gamma\)OC(112) + \(\gamma\)CC(11) + \(\gamma\)HCCO(24) |
| 18   | 1319                        | 24   | 1                                | \(\gamma\)CC(38) + \(\gamma\)HCC(16) |
| 19   | 1288                        | 1    | 0                                | \(\gamma\)CC(24) + \(\gamma\)HCC(59) |
| 20   | 1278                        | 6    | 1                                | \(\gamma\)HCCO(34) + \(\gamma\)HCCO(10) |
| 21   | 1239                        | 2    | 1                                | \(\gamma\)CC(13) + \(\gamma\)HNC(18) + \(\gamma\)HCCO(13) |
| 22   | 1205                        | 0    | 1                                | \(\gamma\)HCCO(60) + \(\gamma\)HCCO(28) |
| 23   | 1197                        | 0    | 5                                | \(\gamma\)CC(41) + \(\gamma\)HCC(31) |
| 24   | 1164                        | 4    | 6                                | \(\gamma\)CC(22) + \(\gamma\)HCC(53) |
| 25   | 1148                        | 50   | 4                                | \(\gamma\)NC(19) + \(\gamma\)OC(12) + \(\gamma\)HCC(11) + \(\gamma\)HCCO(10) |
| 26   | 1117                        | 78   | 0                                | \(\gamma\)NC(11) + \(\gamma\)HCC(23) + \(\gamma\)OC(27) + \(\gamma\)HOC(16) |
| 27   | 1099                        | 16   | 1                                | \(\gamma\)NC(28) + \(\gamma\)HCCO(24) |
| 28   | 992                         | 1    | 0                                | \(\gamma\)HCCO(14) + \(\gamma\)HCC(24) + \(\gamma\)HCCO(50) |
| 29   | 990                         | 0    | 0                                | \(\gamma\)CC(68) + \(\gamma\)HCC(14) |
| 30   | 940                         | 0    | 0                                | \(\gamma\)HCCO(80) + \(\gamma\)COC(12) |
| 31   | 927                         | 0    | 0                                | \(\gamma\)HCCO(64) + \(\gamma\)COC(14) |
| 32   | 877                         | 4    | 3                                | \(\gamma\)CNC(20) + \(\gamma\)CC(39) + \(\gamma\)HCCO(10) |
| 33   | 829                         | 1    | 2                                | \(\gamma\)CC(36) + \(\gamma\)CNC(14) + \(\gamma\)CNC(13) |
| 34   | 808                         | 18   | 0                                | \(\gamma\)HCC(64) + \(\gamma\)COC(27) |
| 35   | 790                         | 1    | 0                                | \(\gamma\)HCCO(91) + \(\gamma\)CNC(13) |
| 36   | 724                         | 3    | 1                                | \(\gamma\)CC(43) |
| 37   | 711                         | 0    | 0                                | \(\gamma\)HCCO(25) + \(\gamma\)COC(56) |
| 38   | 644                         | 0    | 0                                | \(\gamma\)CC(68) + \(\gamma\)CC(16) |
| 39   | 633                         | 31   | 0                                | \(\gamma\)HOC(82) |
| 40   | 609                         | 11   | 0                                | \(\gamma\)OC(59) |
| 41   | 555                         | 0    | 0                                | \(\gamma\)OC(82) |
| 42   | 547                         | 6    | 0                                | \(\gamma\)NC(45) + \(\gamma\)COC(23) + \(\gamma\)HCCO(19) |
| 43   | 506                         | 9    | 0                                | \(\gamma\)HCCO(72) + \(\gamma\)HCC(10) |
| 44   | 503                         | 5    | 0                                | \(\gamma\)CC(61) |
| 45   | 470                         | 1    | 0                                | \(\gamma\)NC(20) + \(\gamma\)COC(57) |
| 46   | 462                         | 4    | 0                                | \(\gamma\)CC(54) + \(\gamma\)CC(15) |
| 47   | 404                         | 0    | 0                                | \(\gamma\)HCC(15) + \(\gamma\)COC(79) |
| 48   | 387                         | 17   | 0                                | \(\gamma\)HNC(24) |
| 49   | 314                         | 0    | 0                                | \(\gamma\)CC(68) + \(\gamma\)NC(10) |
| 50   | 243                         | 0    | 0                                | \(\gamma\)CCCC(71) + \(\gamma\)NC(18) |
| 51   | 218                         | 1    | 0                                | \(\gamma\)CCN(53) |
| 52   | 159                         | 1    | 0                                | \(\gamma\)NC(88) |
| 53   | 104                         | 3    | 0                                | \(\gamma\)NC(68) + \(\gamma\)HCCO(18) |
| 54   | 98                          | 2    | 0                                | \(\gamma\)CCCC(71) + \(\gamma\)NC(11) |
| 55   | 81                          | 1    | 0                                | \(\gamma\)NC(79) |
| 56   | 58                          | 0    | 0                                | \(\gamma\)CNC(73) + \(\gamma\)CNC(12) |
| 57   | 4                           | 0    | 0                                | \(\gamma\)CNC(79) |
23.46 kcal/mol. The intramolecular hydrogen bonding is formed by the overlap between σ(C16–H15), σ(C16–H16), σ(C9–H19), σ(C10–H20) to σ*(N3–H14), σ*(N3–H14), σ*(C9–H19), σ*(C7–H17), σ*(C18–H18) with a stabilization energy of 1.71, 1.87, 0.50, 0.54 and 0.52 kcal/mol respectively.

4.4. NMR spectroscopy

\(^1\)H NMR spectrum provides information about the number of different types of protons and also the nature immediate environment to each of them. The \(^{13}\)C NMR spectrum also provides the structural information with regard to different carbon atom present in the molecule. The Gauge-Independent Atomic Orbital (GIAO) method [29, 30, 31]\(^{13}\)C and \(^1\)H chemical shift calculation of the 24CPA have been made by B3LYP with 6–311++G(d,p) basis set. The experimental \(^{13}\)C and proton \(^1\)H spectra are present in Figure 4(a) and Figure 4(b) respectively. The theoretical \(^{13}\)C and \(^1\)H chemical shift values of the title compound are generally compared to the experimental \(^{13}\)C and \(^1\)H chemical shift values. The results are shown in Table 4. In our present investigation the carbons chemical shifts are found at 172.83, 152.74, 134.38, 121.58, 113.15, and 44.72 ppm for the atoms C1, C5, C10, C13, C7, and C6 consecutively. The corresponding computational chemical shifts are observed in 180.76, 153.02, 140.06, 123.80, 113.03, and 44.09 ppm. The experimental proton chemical shifts of 24CPA are observed at 7.44, 7.43, 6.61, 6.62, 4.35, 3.89, and 2.51 ppm. The correlated computational shifts are 7.67, 7.59, 6.77, 6.57, 4.55, 3.88, and 3.86 ppm respectively. These results show that experimental and computed simulated chemical shifts are amicable with each other.

4.5. HOMO-LUMO analysis

HOMO and LUMO are related to the ionization potential and electron affinity of the molecule respectively. The electron-donating nature, accepting nature and stability of the molecule is obtained by the HOMO-LUMO energy gap [32]. The graphical representation of HOMO and LUMO is shown in Figure 5. The other important parameters of the title compound such as ionization potential, electron affinity, electronegativity, Chemical potential, chemical hardness, chemical softness, and electrophilicity index are calculated. The above properties are enlisted in Table 5. From these table we obtained HOMO orbital has a large number of electrons with energy -6.2056 eV is donating electrons to LUMO orbital having fewer electrons with energy -1.2901 eV and the energy gap is 4.9155 eV. This bandgap confirms 24CPA has very stable, charge transfer takes place within the molecule, and has bioactive nature [33, 34].

4.6. UV-visible spectra

The experimental UV-Vis spectrum of 24CPA is compared with the simulated spectrum with different solvents by Time-dependent density functional theory (TD-DFT) and B3LYP method [35, 36, 37] with different solvents as shown in Figure 6. The maximum absorption wavelength is noted for the compound with different solvents. When the concentration increases absorption wavelength also increases as shown in Table 6. The UV-absorption wavelength is available at 220, 265, and 281 nm in the experimental spectrum due to the various transition of electrons. The more intense peak is at 281 nm due to \(\pi - \pi^*\) transition. When the solvent is gas the major contribution occurs at 263 nm with 61%. When the solvent is water maximum absorption wavelength observed at 263 with 63% contribution. Similarly, at the same wavelength with a major contribution of 61% found when the electron transition from \(\pi\) to \(\pi^*\).

4.7. Molecular electrostatic potential

Molecular electrostatic potential is fundamentally a measure of the strength of the nearby charges, nuclei and electrons, at a particular position. The shape and size of the molecule are obtained by molecular
Table 3. Donor and Acceptor interactions in NBO analysis for 24CPA to find the bond type and energy values.

| DonorNBO(i) | Type | ED/e | AcceptorNBO(j) | Type | ED/e | E(2) | E(j)-E(i) | E(i,j) |
|-------------|------|------|----------------|------|------|-------|-----------|--------|
| C5–C7       | π    | 1.6192 | C8–C10        | σ*   | 0.3030 | 15.47 | 0.29      | 0.06   |
| C5–C7       | π    | 1.6192 | C9–C11        | σ*   | 0.4105 | 25.32 | 0.29      | 0.08   |
| C8–C10      | π    | 1.7906 | C5–C7         | σ*   | 0.4132 | 23.43 | 0.28      | 0.08   |
| C9–C11      | π    | 1.6593 | C5–C7         | σ*   | 0.4105 | 16.15 | 0.28      | 0.08   |
| C9–C11      | π    | 1.6593 | C8–C10        | σ*   | 0.3030 | 15.04 | 0.28      | 0.06   |
| C9–C11      | π    | 1.6593 | C9–C11        | σ*   | 0.4132 | 15.44 | 0.28      | 0.07   |
| C9–C11      | π    | 1.6593 | N4–C13        | σ*   | 0.0889 | 19.32 | 0.37      | 0.08   |
| O1          | LP(2)| 1.8238 | O2–C12        | σ*   | 0.2132 | 44.63 | 0.34      | 0.11   |
| O2          | LP(2)| 1.8543 | O1–C12        | σ*   | 0.0917 | 31.10 | 0.61      | 0.12   |
| O2          | LP(2)| 1.8543 | C6–C12        | σ*   | 0.0579 | 16.61 | 0.65      | 0.10   |
| N3          | LP(1)| 1.7681 | C5–C7         | σ*   | 0.4132 | 38.27 | 0.28      | 0.10   |
| N9          | LP(1)| 1.9714 | C11–C13       | σ*   | 0.0325 | 11.45 | 1.02      | 0.10   |
| N9          | LP(1)| 1.9714 | N4–C13        | σ*   | 0.0889 | 21.72 | 0.09      | 0.08   |
| C6–H15      | σ    | 1.9644 | N3–H14        | σ*   | 0.0191 | 1.71  | 0.94      | 0.04   |
| C6–H16      | σ    | 1.9651 | N3–H14        | σ*   | 0.0191 | 1.87  | 0.94      | 0.04   |
| C7–H17      | σ    | 1.9767 | C9–H19        | σ*   | 0.0113 | 0.50  | 0.96      | 0.02   |
| C9–H19      | σ    | 1.9796 | C7–H17        | σ*   | 0.0127 | 0.54  | 0.95      | 0.02   |
| C10–H20     | σ    | 1.9795 | C8–H18        | σ*   | 0.0127 | 0.52  | 0.95      | 0.02   |

Figure 4. (a) Experimental 13C NMR spectrum of 24CPA. (b) Experimental 1H NMR spectrum of 24CPA.

Table 4. Experimental and Theoretical (DFT) 13C and 1H chemical shifts of 24CPA.

| Atom | Experimental ppm | DFT/B3LYP ppm |
|------|------------------|---------------|
| H19  | 7.44             | 7.67          |
| H20  | 7.43             | 7.59          |
| H18  | 6.61             | 6.77          |
| H21  | 6.62             | 6.57          |
| H17  | -                | 6.53          |
| H14  | 4.35             | 4.55          |
| H16  | 3.89             | 3.88          |
| H15  | 2.51             | 3.86          |
| C1   | 172.83           | 180.76        |
| C5   | 152.74           | 153.02        |
| C9   | -                | 141.08        |
| C10  | 134.38           | 140.06        |
| C13  | 121.58           | 123.80        |
| C8   | -                | 117.61        |
| C7   | 113.15           | 113.03        |
| C11  | -                | 105.77        |
| C6   | 44.72            | 44.09         |

Figure 5. HOMO-LUMO diagram of 24CPA for the energy gap.
electrostatic potential (MEP) in terms of colors \[38, 39\]. The MEP diagram of 24CPA is shown in Figure 7. The negative and positive region is of this compound is between -7.600e-2 and +7.600e-2. The most negative region is called the nucleophilic site and it is represented by red color. The most positive region is called the electrophilic site and it is represented by blue color. For this compound around the nitrogen atom N4, it is more negative shown by red color. Near two oxygen atoms are also slightly negative shown by blue color. The remaining portions of the compound are represented by the blue color nucleophilic region. So the reactive areas of the compound easily identified based on the electron and proton interactions show biological activity.

4.8. Fukui function

In computational chemistry based on Mulliken population analysis the quantitative information of each atom whether it is electrophilic or nucleophilic is obtained by Fukui function \[40, 41\]. The reactivity of 24CPA with another molecule can be obtained using this function. The individual charges of the Fukui function are obtained by Mulliken population analysis. Fukui functions are determined by the following expression,

The nucleophilic attack \[ - f^-(\tau) = q_r(N + 1) - q_r(N) \]

The electrophilic attack \[ - f^+ (\tau) = q_r(N) - q_r(N-1) \]

and radical attack \[ - f^0 (\tau) = (q_r(N + 1) - q_r(N - 1))/2 \]

where \( q_r \) is the atomic charge at the \( r \)th atomic site, neutral (N), anionic (N-1), cationic (N+1) chemical species. Where \(+, - , 0\) signs are nucleophilic, electrophilic, and radical attack respectively. From the below formula the Dual descriptor \( \Delta f(r) \) is calculated \[42\].

Dual descriptor \( \Delta f(r) = f^+(\tau) - f^-(\tau) \)

When \( \Delta f(r) \) is positive the atom is nucleophilic and when \( \Delta f(r) \) is negative the atom is electrophilic attack. Table 7 provides the complete details of Mulliken atomic charges, Fukui functions, local softness and dual descriptor values for each atom of the molecule. The dual descriptor for nucleophilic attack in the following order C6 > C7 > C11 > H14 > C13 > N3 > N4 > O2 > H17 > H20. The negative dual descriptor for electrophilic attack H21 > H15 > C10 > C12 > H16 > C8 > H19 > H18 > O1 > C5 > C9.

4.9. Effect of temperature

The important thermodynamic parameters of the title compound such that entropy \( (S_0 m) \), enthalpy \( (H_0 m) \) and heat capacity \( (C_p m) \) of 24CPA is calculated using the Perl script and Gaussian output file with B3LYP and 6-311++G(d,p) basis set \[43, 44\]. The output values are listed as shown in Table 8. From the values, we found that when the temperature increases entropy, heat capacity, and enthalpy also increases as shown in Figure 8. This shows that this compound possesses good thermal and chemical stability.

4.10. Drug-likeness

In order to initially evaluate possible potential to be used as an active component in some new pharmaceutical product, the drug likeness of the title molecule is analyzed. The studied drug likeness parameters in this work encompassed: The Hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), molar refractivity (MR), Topological polar surface area
Blood-brain barrier penetration (BBB), log \( k_p \) and Bioavailability score. The values of these parameters have been summarized in Table 9. These calculations are based on Lipinski’s rule [45]. According to the rule, the HBD and HBA values should be less than 10, the limit of TPSA is less than 140 Å², the molar refractivity is between 40 and 130, and the MR value of should be 40.5 to 59.32 for all the compounds. From the table the GI absorption is high, BBB permeant is available, skin permeability (log \( K_p \)) is between -5.83 to -7.50 and the bioavailability score is high.

Table 7. To identify the quantitative reactive areas by Fukui function (\( f_r \)), local softness (s\( f_r \)) and Dual descriptor for 24CPA.

| Atom | Mulliken atomic charges | Fukui functions | local softness | Df |
|------|-------------------------|-----------------|----------------|----|
| N(1) | -0.1707 -0.2098 -0.1485| -0.0391 -0.2222 -0.0306 | -0.0082 -0.0046 -0.0064 | -0.0169 |
| O2   | -0.2886 -0.2858 -0.2466| 0.0028 -0.0420 -0.0196 | 0.0006 -0.0088 -0.0041 | 0.0447 |
| N3   | -0.1600 -0.2269 0.0128  | -0.0670 -0.1728 -0.1199 | -0.0140 -0.0361 -0.0251 | 0.1058 |
| N4   | -0.1812 -0.2761 -0.0265 | -0.0949 -0.1547 -0.1248 | -0.0198 -0.0323 -0.0261 | 0.0598 |
| C5   | -0.3094 -0.3022 0.3323  | 0.0073 0.2292 0.0151 | 0.0015 0.0048 0.0032 | -0.0156 |
| C6   | -0.4285 1.0802 -0.4854 | 1.5087 0.0569 0.7828 | 0.3155 0.0119 0.1637 | 1.4518 |
| C7   | 0.2198 0.3435 0.2545  | 0.1237 -0.0347 0.0445 | 0.0259 -0.0072 0.0093 | 0.1584 |
| C8   | -0.3007 -0.4126 -0.2532 | -0.1118 -0.0475 -0.0797 | -0.0234 -0.0099 -0.0167 | -0.0643 |
| C9   | 0.1518 0.0958 0.2014  | -0.0561 -0.0495 -0.0528 | -0.0117 -0.0104 -0.0110 | -0.0065 |
| C10  | -0.7234 -0.9336 -0.7044 | -0.2102 -0.0191 -0.1146 | -0.0439 -0.0040 -0.0240 | -0.1911 |
| C11  | 1.8125 1.8761 1.8650  | 0.0636 -0.0525 0.0056 | 0.0133 -0.0110 0.0012 | 0.1161 |
| C12  | 0.1506 -0.0168 0.1605  | -0.1675 -0.0098 -0.0886 | -0.0350 -0.0021 -0.0185 | -0.1576 |
| C13  | -1.5120 -1.4418 -1.4748 | 0.0702 -0.0372 0.0165 | 0.0147 -0.0078 0.0035 | 0.1074 |
| H14  | 0.2983 0.3700 0.3401  | 0.0717 -0.0418 0.0150 | 0.0150 -0.0087 0.0031 | 0.1135 |
| H15  | 0.2079 -0.3505 0.2674  | -0.5584 -0.0595 -0.3089 | -0.1168 -0.0124 -0.0646 | -0.4989 |
| H16  | 0.2044 0.0428 0.2632  | -0.1616 -0.0588 -0.1102 | -0.0338 -0.0123 -0.0230 | -0.1028 |
| H17  | 0.1700 0.1290 0.2311  | -0.0410 -0.0611 -0.0511 | -0.0086 -0.0128 -0.0107 | 0.0201 |
| H18  | 0.1432 0.0491 0.2127  | -0.0941 -0.0695 -0.0818 | -0.0197 -0.0145 -0.0171 | -0.0246 |
| H19  | 0.2051 0.1052 0.2664  | -0.0999 -0.0614 -0.0806 | -0.0209 -0.0128 -0.0169 | -0.0385 |
| H20  | 0.2011 0.1584 0.2621  | -0.0427 -0.0610 -0.0519 | -0.0089 -0.0128 -0.0108 | 0.0183 |
| H21  | 0.3098 -0.7940 0.3345  | -1.1037 -0.0248 -0.5642 | -0.2308 -0.0052 -0.1180 | -1.0790 |

Table 8. Effect of Temperature on Thermodynamic properties (Entropy, Heat capacity and enthalpy) for 24CPA.

| T (K) | S (J/mol.K) | Cp (J/mol.K) | ddH (kJ/mol) |
|------|-------------|---------------|---------------|
| 100  | 303.41      | 79.66         | 5.48          |
| 200  | 373.50      | 129.68        | 15.88         |
| 298  | 435.00      | 181.57        | 31.17         |
| 300  | 436.13      | 182.52        | 31.51         |
| 400  | 495.40      | 230.69        | 52.22         |
| 500  | 551.36      | 271.03        | 77.38         |
| 600  | 603.77      | 303.67        | 106.17        |
| 700  | 652.63      | 330.06        | 137.90        |
| 800  | 698.16      | 351.69        | 172.03        |
| 900  | 740.65      | 369.68        | 208.12        |
| 1000 | 780.41      | 384.81        | 245.87        |

Figure 8. Thermodynamic properties of 24CPA with temperature.
The above results fall within the limit and Lipinski rule is followed for drug identification [46].

4.11. Molecular docking

Molecular docking is an important area in the field of structural molecular biology, pharmacogenomics and computer-assisted drug design [47, 48, 49]. In the present study, molecular docking was carried out for protein associated with anti-hypercoagulable. The structure of the target protein 4NV2 was downloaded from the RSCB protein data bank. The quality of the protein is checked with the Ramachandran plot as shown in Figure 9 shows all the residues are available at the allowed region. The optimized molecular structure using density functional theory is helpful to prepare the ligand PDB format. By using Autodock software 24CPA molecule is docked with 4NV2 protein. The binding energy of -5.45 kcal/mol were observed in the protein-ligand binding interaction is shown in Figure 10 and the important properties are listed in Table 10. This low value of binding energy [50] shows that this molecule is a good anti-hypercoagulable drug.

**Table 9. Drug-likeness parameters of 24CPA.**

| Compound | HBD | HBA | MR | TPSA | GI absorption | BBB permeant | CYP1A2 inhibitor | log Kp (cm/s) | Lipinski violations | Bioavailability Score |
|----------|-----|-----|----|------|---------------|--------------|------------------|---------------|---------------------|----------------------|
| 24CPA    | 2   | 3   | 47.04 | 73.12 | High | No | Yes | -7.13 | 0 | 0.56 |

HBD - Hydrogen Bond Donor, HBA - Hydrogen bond acceptor, MR - Molar refractivity, TPSA - Topological polar surface area, GI - Gastrointestinal, BBB - blood-brain barrier penetration, log kp – skin permeability.

**Figure 9. Ramachandran plot of 4NV2 to find the quality of the protein.**

**Figure 10. Docking diagram of the ligand-24CPA and 4NV2 target protein.**

**Table 10. Molecular docking of 24CPA with 4NV2 protein to find the best binding energy with residues and bond distance.**

| Ligand | Bonded residues | No. of hydrogen bond | Bond distance (Å) | Estimated Inhibition Constant (µM) | Binding energy (kcal/mol) | Intermolecular Energy (kcal/mol) |
|--------|-----------------|----------------------|-------------------|------------------------------------|--------------------------|-------------------------------|
| 24CPA  | LYS41/HZ3       | 4                    | 1.9               | 101.56                             | -7.55                    | -6.64                         |
|        | ASP57/CA        |                      | 3.4               |                                     |                          |                               |
|        | THR51/HN        |                      | 2.3               |                                     |                          |                               |
|        | LYS41/O         |                      | 2.6               |                                     |                          |                               |
5. Conclusion

In the present work, quantum computational and spectroscopic vibrational analysis of the title compound was carried out first time. The Molecular geometry parameter bond length and bond angle represent a good agreement with the experimental results. The spectroscopic FT-IR, FT-Raman, NMR, and UV-Vis studies were carried out on 24CPA and compared with the theoretical values obtained by using B3LYP methods with 6-311+G(d,p) basis set. The donor-acceptor interactions and the stability of the title compound is determined by NBO analysis. The HOMO-LUMO energy gap is 4.9155 eV shows that 24CPA is very stable, and charge transfer takes place within the molecule. The thermodynamic parameters and properties of the compound have been calculated. The correlation between the statistical thermodynamic and temperature are also obtained. It was seen that the entropy, enthalpy, and heat capacity increases with increase in temperature owing to the intensities of the molecular vibrations increase with increasing temperature. The drug-likeness studies confirm that the title molecule has pharmaceutically properties. Molecular docking studies binding energy -5.45 kcal/mol confirmed that this compound is a good anti-hypercoagulable agent based on the interactions with the human protein.

Declarations

Author contribution statement

M. Habib Rahuman: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.
S. Muthu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
BR Rajaraman: Performed the experiments; Analyzed and interpreted the data.
M. Raja, Umamahesvari: Analyzed and interpreted the data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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