ELECTRONIC, THERMODYNAMIC PROPERTIES, NONLINEAR OPTICAL RESPONSES, AND MOLECULAR DOCKING STUDIES ON CEPHALEXIN

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ABSTRACT

The topology analysis of electron localization function (ELF), localized orbital locator (LOL), the study of nonlinear optical properties, thermal properties, and biological activities of cephalexin have been performed using DFT/B3LYP and employing 6-311++G(d,p) basis sets. The Mulliken atomic charge on atoms has been calculated. The quantities describing nonlinear optical (NLO) properties like molecular polarizability (α), first hyperpolarizability (β), and second hyperpolarizability (γ) were comparable to the values of urea. The computed value of the second hyperpolarizability was found to be negative, which is an important feature for the system of controllable NLO devices. The thermodynamic properties like heat capacity (S), enthalpy (H), and entropy (S) are positively correlated with the temperature. Further, the title molecule shows good potentiality for binding with the selected target protein matrix metalloproteinase-2.

Keywords: Cephalexin, ELF, LOL, nonlinear optical properties, thermodynamics, molecular docking

INTRODUCTION

Cephalexin, C16H17N3O4S, is an antibiotic from the first-generation cephalosporin (Nguyen and Graber, 2020). It is active against most gram-positive and many gram-negative bacteria (Speight et al., 1972). Cephalexin, a white to cream-colored crystalline powder, is stable below a mild acidic condition (Manelli, 1975). It is used to treat respiratory tract infections, Gonorrhea, urinary tract infections, and several infections due to susceptible organisms (Bailey et al., 1970; Speight et al., 1972).

The recent work on cephalexin reflects the DFT study on structural, chemical, and spectroscopic properties. Cephalexin at normal temperature has two stable conformers (Chaudhary et al., 2021). Moreover, organic molecules exhibit significant non-linear optical properties (NLO) (Kariper, 2017) and compounds with nitrogen and Sulphur contribute to various biological activities (Joshi et al., 2018). Thus, the present work deals with non-linear optical properties, topology analysis, thermal properties, and biological activities. The electron localization function (ELF) and localized orbital locator (LOL) have been plotted to depict the electron localization. The quantities like static dipole moment, molecular polarizability, first hyperpolarizability, and second hyperpolarizability have been calculated. Further, these properties are compared with the value of urea.

The correlation of thermodynamic properties like heat capacity, enthalpy, entropy, and temperature is studied. Ultimately, the non-covalent interaction of cephalexin with matrix metalloproteinase-2 has been investigated using a molecular docking approach. The optimized structure of cephalexin is shown in Fig. 1.

Figure 1 Optimized structure of cephalexin.
MATeRIALS AND METHODS
Computational and theoretical details
The software package Gaussian 09 (Frisch et al., 2009) was used for various computational studies in the present work. The density functional theory (DFT) using the B3LYP exchange correlation function with a basis set 6-311+G(dp) has been used for the calculation (Becke, 1993;Parr, 1980). Further, GaussView 05 (Dennington et al., 2009) was used for visualizing the optimized structure of the title molecule. The topology study, Electron Localization Function (ELF), and Localized Molecular Orbital (LOL) have been performed using Multiwfn 3.4.1 software (Lu and Chen, 2012). The ELF function is defined by the equation (Silvi & Savin, 1994; Yang, 2010).

\[ \text{ELF} = \frac{1}{1 + \left| \frac{\rho}{\rho_0} \right|^2} \]  

(1)

With \( D = \frac{1}{2} \sum_i |\nabla \rho_i|^2 \) and \( D_h = \frac{3}{2} \left( \frac{3\pi^2}{20} \right)^{2/3} \rho_0 \)

Where, \( D \) and \( D_h \) represent excess kinetic energy and reference value, respectively.

The molecular polarizability, electric dipole moment, first hyperpolarizability, and second hyperpolarizability have been computed using a finite field approach employing a 6311+G(dp) basis set. Using the finite field, the energy in the static electric field is expanded in terms of the Taylor’s series (Kumar et al., 2017).

\[ E(F) = E(0) - \sum_i \mu_i F_i - \frac{1}{2} \sum_{i,j} \alpha_{ij} F_i F_j - \frac{1}{6} \sum_{i,j,k} \beta_{ijk} F_i F_j F_k - \frac{1}{24} \sum_{i,j,k,l} \gamma_{ijkl} F_i F_j F_k F_l \]  

(2)

Here, \( E(0) \) is the total energy in the absence of an electrical field, and the quantities \( \mu_i, \alpha_{ij}, \beta_{ijk} \) and \( \gamma_{ijkl} \) represent the dipole moment, the polarizability, the first hyperpolarizability, and second hyperpolarizability, respectively. The subscripts \( i, j, k \) and \( l \) represent the Cartesian coordinates. The subscripts \( i, j, k \) represent the Cartesian coordinates. The total static dipole moment \( (\mu_0) \), mean polarizability \( (\alpha_0) \), anisotropy of polarizability \( (\Delta \alpha) \), first hyperpolarizability \( (\beta_0) \), and second hyperpolarizability \( (\gamma_0) \) that describe the non-linear optical phenomena of the molecule can be determined by the equations (Kumar et al., 2017; Joshi et al., 2013) as follows:

\[ \mu_0 = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2} \]  

(3)

\[ |\alpha_0| = \frac{1}{2}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}) \]  

(4)

\[ \Delta \alpha = 2^{-1/2} \left[ (\alpha_{xx} - \alpha_{yy})^2 + (\alpha_{xy} - \alpha_{yx})^2 + (\alpha_{yx} - \alpha_{xy})^2 + 6\alpha_{zz}^2 \right]^{1/2} \]  

(5)

\[ \beta_0 = \left[ (\beta_{xzx} + \beta_{xyz})^2 + (\beta_{xyx} + \beta_{yxz})^2 + (\beta_{xxz} + \beta_{xzy})^2 + (\beta_{xyy} + \beta_{yxz})^2 \right]^{1/2} \]  

(6)

\[ \gamma_0 = \frac{1}{2} \left[ (\gamma_{xxx} + \gamma_{yyx} + \gamma_{zzx} + 2\gamma_{xyx} + \gamma_{yxz} + \gamma_{zzz}) \right] \]  

(7)

The dipole moment, molecular polarizability, first hyperpolarizability, and second hyperpolarizability are first rank (vector), second rank, third rank, and fourth rank tensors, respectively.

The Gaussian 09 at the B3LYP/6-311+G(dp) level, has been used to compute thermodynamic quantities like entropy, heat capacity, and enthalpy in the gas phase. The thermodynamic contributions of translational motion, rotational motion, electronic motion, and vibrational motion are obtained in terms of the partition function, \( q(V,T) \). The given equations (Ochterski, 2000) are used to determine the various thermodynamic quantities.

Total entropy, \( S_{\text{total}} = S_{\text{translational}} + S_{\text{rotational}} + S_{\text{vibrational}} + S_{\text{electronic}} \)  

Total internal energy, \( E_{\text{total}} = E_{\text{translational}} + E_{\text{rotational}} + E_{\text{vibrational}} + E_{\text{electronic}} \)  

Total heat capacity, \( C_{\text{total}} = C_{\text{translational}} + C_{\text{rotational}} + C_{\text{vibrational}} + C_{\text{electronic}} \)  

Corrected enthalpy, \( H_{\text{corrected}} = E_{\text{total}} + k_B T \)

where, different entropy contributions from translational, rotational, vibrational and electronic motion are

\[ S_{\text{translational}} = R \left( \ln q_v + \frac{3}{2} \right) \]  

\[ S_{\text{rotational}} = R \left( \ln q_r + \frac{3}{2} \right) \]  

\[ S_{\text{vibrational}} = R \left( \sum_k \left( \frac{\Theta_{v_K}}{e^{\Theta_{v_K}/T}} - e^{-\Theta_{v_K}/T} \right) \right) \]

\[ E_{\text{electronic}} = (\ln q_e + 0) \]

Similarly, internal thermal energy and heat capacity contributions due to different motions are

\[ E_{\text{translational}} = \frac{3}{2} R T \]  

\[ E_{\text{rotational}} = R T \]  

\[ E_{\text{vibrational}} = \frac{3}{2} R \left( \frac{1}{e^{\Theta_{v_K}/T} - 1} \right) \]  

\[ C_{\text{translational}} = \frac{3}{2} R \]  

\[ C_{\text{rotational}} = R \]  

\[ C_{\text{vibrational}} = \frac{3}{2} R \left( \frac{1}{e^{\Theta_{v_K}/T} - 1} \right) \]

The electronic contribution term for both thermal energy and heat capacity is zero.

The study of intermolecular non-covalent interactions between target proteins and cephalaxin, the flexible-rigid blind docking, has been performed using AutoDockVina software (Trott and Olson, 2010). The result of AutoDockVina has been visualized and interpreted with the help of bio visualizer software (Studio, 2009). Generally, the binding affinity of a docked complex is determined on the basis of the scoring function. The scoring function for AutoDockVina can be obtained using the equation (Tanehuk et al., 2016).

\[ \Delta G_{\text{binding}} = \Delta G_{\text{H-bond}} + \Delta G_{\text{hydrophobic}} + \Delta G_{\text{repulsion}} + \Delta G_{\text{gauss}} + \Delta G_{\text{AutoDock Vina score}} \]  

(12)
where $\Delta G_{-\text{bond}}$ represents the change in the binding energy due to hydrogen bond, $\Delta G_{\text{hydrophobic}}$, due to hydrophobic interaction $\Delta G_{\text{gauss}}(d) = e^{-(d/0.5)^2}$ and $\Delta G_{\text{gauss}}(d) = e^{-(d-3)/2}$, due to steric effects, $\Delta G_{\text{repulsion}}$, due to repulsion and $\Delta G_{\text{AutoDock Vina score}}$, due to rotational bonds penalty.

RESULTS AND DISCUSSION

ELF and LOL

Electron localization function (ELF) and localized orbital locator (LOL) are described on the basis of electron density by Becke and Edgecombe (Becke and Edgecombe, 1990; Schmider and Becke, 2002). The ELF and LOL display similar interpretations, however, ELF is based on kinetic energy density and the LOL on gradients of localized orbital locators (Chaudhary et al., 2021). ELF measures Pauli repulsion effects (Abraham et al., 2019).

The quantitative values of ELF and LOL come down in the range of 0-1 where the degree of localization for electrons is high for values greater than 0.5 and the degree of delocalization is high for the value less than 0.5 (Chaudhary et al., 2021). The Multiwfn software has been used to plot the ELF and LOL maps of the title molecule. The ELF and LOL plot of the title molecule have been shown in Figs. 2 and 3. In the ELF and LOL, the red region represents the localized electrons, and the blue region represents the delocalized electrons. The red zone between every two atoms represents the bond critical point (BCP).

![Figure 2](image-url) Electron localization function (ELF) of cephalexin.

The red zone across nitrogen and oxygen represents the lone pair associated with them. Similarly, high electron localization is depicted across hydrogen atoms due to maximum Pauli repulsion. On the other hand, a blue color zone is found across non-hydrogen heavy atoms. The blue color, at the center of the atoms, represents the atomic shell and the ring-like structures indicate the electron delocalization of electrons between core and valence electrons.

Mulliken charges

Mulliken population analysis is complementary to molecular electrostatic potential (MEP) and it provides the net atomic population in the molecule (Kumar et al., 2017). Atomic charges affect different molecular properties, including dipole moment, polarizability and hyperpolarizability, and further help in understanding ionization potential and chemical potential (Abraham et al., 2017). The Mulliken charge associated with various atoms of cephalexin has been obtained using the B3LYP/6-311++G(d,p) level of theory. The calculated Mulliken charges of various atoms of the title compound is illustrated in Table 1 and presented by a simple bar diagram in Fig. 4. The atomic charge on all hydrogen atoms and atoms N6, N7, C9, C12, C14, C19, and C21 have positive charges ($0.1596-0.5247|e|$) and all the remaining atoms have negative charges. The carbon atom C13 has the highest magnitude of negative atomic charge ($-0.9247|e|$) since it is attached to less electronegative atom S1. The other atoms like O2, O3, O4, O5 have atomic charges in the range of $-0.1704|e|$ to $-0.3149|e|$ and N8 has $-0.3104|e|$. The net negative charge on oxygen atoms (electron donor) and the positive charge on hydrogen atoms have a significant role in intermolecular hydrogen bonding as observed in the section on molecular docking.
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The presence of an electric field is the function of the electric fields (Issaoui et al., 2015). The delocalization of π electrons in the molecule deals with the NLO properties of the system (Kariper, 2017). In the last few years, NLO properties have been of great interest due to their potential applications in telecommunication, data storage, optical signal processing, etc. (Koparir, 2013; Joshi, 2016). The dipole moment (µ0), mean polarizability (α0), anisotropy of polarizability (Δα), first hyperpolarizability (β0), and second hyperpolarizability (γ0) of cephalixin are illustrated in Table 2. The calculated values of µ0, |α0|, Δα, β0, and γ0 are 3.1362 Debye, 3.1362 Debye, 21.4940 *10⁻²⁴esu, 36.0946*10⁻²⁴esu, 0.4440*10⁻³⁰esu and -0.12849*10⁻³⁰esu. Urea is the standard, conventional molecule which is used to institute the threshold value for the comparative study of NLO properties of different molecules (Abraham et al., 2017). The dipole moment of the title molecule is higher than the value of urea (1.3732, Debye). However, the first hyperpolarizability (β0) is comparable to the value of urea (0.3728*10⁻³⁰esu), so the molecule exhibits significant NLO properties. On the other hand, the value of second hyperpolarizability (γ0) is negative. In quantum optics, the negative value of γ0 is very important because it causes a defocusing effect of an incident beam and such molecular systems can be good candidates for systems of controllable nonlinear properties (Nakano et al., 1996; Kumar et al., 2017).

### Table 2: The calculated dipole moment (µ0), mean polarizability[α0], anisotropy of polarizability (Δα) first hyperpolarizability (β0), and second hyperpolarizability(γ0) of cephalixin.

| Dipole moment (Debye) | Polarizability (*10⁻²⁴esu) | First Hyperpolarizability (*10⁻³⁰esu) | Second hyperpolarizability (*10⁻³⁰esu) |
|-----------------------|-----------------------------|--------------------------------------|---------------------------------------|
| µ0 = 0.5882           | αxx = -140.4955             | βxxx = 14.7286                       | γxxxx = -0.9060.7026                  |
| µ0 = 2.9643           | αxy = -2.4790               | βxy = -40.9736                       | γyyyy = -2271.7508                   |
| µ0 = -0.8380          | αyz = -143.0230             | βyz = 22.0851                        | γzzz = -1421.9954                    |
| µ0 = 3.1362           | αzx = -17.9694              | βzx = 32.0184                        | γxyx = -1683.9580                    |
| µ0(Urea) = 1.3732     | αyz = -5.6946               | βyz = -7.2215                        | γzzz = -1756.0085                    |
|                      | Δα = 12.0654                | βyz = 6.9303                         | γ0 = -0.12849                       |

### Thermodynamic properties

The temperature has a direct effect on the chemical reactivity and the mechanism of drug action (Basha et al., 2019; Choudhary et al., 2014). The thermodynamic parameters are estimated from the Boltzmann distribution and partition function (Singh et al., 2016). Thermodynamic properties like heat capacity, enthalpy,
entropy, zero-point energy, total energy, and rotational constant of cephalaxin have been illustrated in Table 3. To study the thermal behavior of cephalaxin, the temperature varied from 50 K to 600 K, and the respective values of thermodynamic quantities are noted. Hence, the quadratic equations, from 13 to 15, have been obtained from the second-order polynomial fit between the thermodynamic quantities (a dependent variable) and the temperature (an independent variable). The graph showing quadratic fit in Fig. 5 demonstrates the positive correlation of enthalpy \( (H^\circ_m) \), heat capacity \( (C^\circ_{p,m}) \), entropy \( (S^\circ_m) \), and temperature. The value of \( R^2 \) for \( H^\circ_m \), \( C^\circ_{p,m} \) and \( S^\circ_m \) is obtained as 1, 0.996, and 0.9994, respectively. The quantitative value of the thermodynamic parameters increases with the increase in temperature, which is due to the increase in vibrational motion with an increase in temperature. Furthermore, the specific heat capacity of the title compound at room temperature (298.15 K) has been calculated to be 1022.07 J/kg-K (355.06 J/Mol-K), which is slightly smaller than the value, 1322.77 J/kg-K of amino acid, glycine (Spink & Wadsö, 1975). However, the specific heat capacity of cephalaxin is very close to the estimated value (960.36 J/kg-K) of a biologically active molecule, alkaloid aristolochic acid I (Joshi et al., 2013).

\[ H^\circ_m = 833.7112 + 0.0629T + 4.7996 \times 10^{-4}T^2 \quad (R^2 = 1) \]  
\[ C^\circ_{p,m} = 31.7992 + 1.2119T - 4.1214 \times 10^{-4}T^2 \quad (R^2 = 0.9996) \]  
\[ S^\circ_m = 269.5741 + 1.5674T - 5.1161 \times 10^{-4}T^2 \quad (R^2 = 0.9994) \]

The above equations can also be further utilized during the study of the interaction of the title molecule with another compound. They help to predict the Gibbs free energy and then the spontaneity of the reaction. In addition, these give useful details that can be used for the analysis of thermodynamic energies and can be used to estimate the direction of chemical reaction using the second law of thermodynamics in the thermochemical field (Joshi et al., 2013).

![Graph showing quadratic fit between enthalpy, heat capacity, entropy, and temperature for cephalaxin.](image)

**Figure 5** Correlation of enthalpy, heat capacity, entropy and temperature for cephalaxin.

| Temperature (K) | Enthalpy (kJ/mol) | Heat capacity (J/mol-K) | Entropy (J/mol-K) | Zero-point energy (Joules/mol) | Total energy (eV) |
|----------------|-------------------|-------------------------|------------------|--------------------------------|------------------|
| 50             | 838.6870          | 97.00186                | 336.72           | 835576                         | -40371.2566      |
| 100            | 844.8877          | 149.9211                | 426.3036         | 835576.1                       | -40371.2566      |
| 150            | 853.6448          | 200.4513                | 500.0298         | 835576                         | -40371.2566      |
| 200            | 864.9458          | 251.7471                | 567.0743         | 835576.1                       | -40371.2566      |
| 250            | 878.8450          | 304.2981                | 630.7296         | 835576.1                       | -40371.2566      |
| 300            | 895.3760          | 356.8952                | 692.3934         | 835576.1                       | -40371.2566      |
| 350            | 914.5011          | 407.7141                | 752.5635         | 835574.9                       | -40371.2566      |
| 400            | 936.0947          | 455.2778                | 811.2483         | 835576                         | -40371.2566      |
| 450            | 959.9644          | 498.8081                | 868.4059         | 835576                         | -40371.2566      |
| 500            | 985.9052          | 538.0959                | 923.7895         | 835580.2                       | -40371.2566      |
| 550            | 1013.7037         | 573.3293                | 977.6627         | 835576.1                       | -40371.2566      |
| 600            | 1043.1758         | 604.8725                | 1029.641         | 835576.1                       | -40371.2566      |
Molecular docking

In medicinal chemistry, for entire potential drug targets, the study of drug-protein interaction can be performed either using an experimental method or a computational method. Molecular docking conducted on AutoDockVina is a popular computational technique that is used to calculate the quantitative parameters of ligand and protein interaction (Ferreira da Costa et al., 2018). It helps to anticipate the binding mode and affinity between ligand and receptor protein interactions. In the present work, for the docking analysis, the target protein (matrix metalloproteinase-2) (MMP-2) has been predicted with the help of online software, the Swiss Target Prediction (Daina et al., 2019). The invasive features of certain human malignancies, such as colon and breast tumors, are influenced by matrix metalloproteinases (Kanayama et al., 1998) MMP-2 has a key role in the pathophysiology of inflammatory and cancerous disorders in a variety of organs, including the lungs (Chakrabarti and Patel, 2005). Hence, docking analysis has been performed with this particular protein to know the biological activities of cephalexin with this protein. The PDB code was downloaded from the RSCB protein data bank (Rose et al., 2010).

The Ramachandran plots in Fig. 6 demonstrate the phi-psi torsional angles of the residues of the protein. It shows that maximum residues lie inside the blue line the, allowed region. The ligand molecule cephalexin was prepared by optimizing it using Gaussian 09 at B3LYP/6-311++G(d,p) level. Thus, the most stable state corresponding to the minimum ground state energy is obtained. Water was removed and the polar hydrogen was added to the receptor protein with the help of AutoDock. A docking simulation has been formed using AutoDockVina. The Discovery studio was used to observe the ligand protein interactions. The center of the binding active sites is located at \( x = -0.044, y = 0.009, z = -0.151 \) and it is limited in the grid box of size 40 Å \( \times \) 40 Å \( \times \) 40 Å of spacing 0.375 Å. The docked structure of cephalexin-1J7M is presented in Fig. 7. The various docking parameters are displayed in Table 4. The title molecule is strongly bound to the protein 1J7M protein with a binding affinity \(-5.9\ \text{kcal/mol}\). The electropositive atoms H35, H27, and the electronegative atom O2 interact non-covalently with residues GLU27, SER28, LYS25, and GLU27 of the proteins. Thus, the formation of a total of four hydrogen bonds takes place and the length of these bonds falls in the range of 1.8814 Å to 2.5723 Å. Further, the root mean square deviation (RMSD) between the docked structure and its initial structure is less than 1.2 Å which is less than 2 Å. Hence, in general, cephalexin shows good binding activity with the protein matrix metalloproteinase-2 (PDB code: 1J7M).
CONCLUSIONS
In the present work, the analysis of electron localization function (ELF) and localized orbital locator (LOL) and non-linear optical properties, thermal properties, as well as biological activities of cephalexin has been performed using DFT/B3LYP employing 6-311++G(d,p) basis sets. The ELF and LOL map show that the localization of electrons is higher across oxygen, nitrogen and hydrogen, and carbon atoms. The calculated Mulliken atomic charges associated with carbon atoms C13 and C9 are found to be $-0.9247|e|$ and $0.5247|e|$, which are the highest negative charge and the highest positive charges, respectively. The nonlinear optical properties (NLO) have been computed. The estimated value of first hyperpolarizability ($0.4440 \times 10^{-30}$ esu) is comparable to the value of the standard molecule, urea. These properties represent the significant NLO properties. In addition, the molecule has negative second hyperpolarizability ($-0.12849 \times 10^{-35}$ esu) which is very important for constructing controllable NLO devices. Furthermore, the quadratic fits, demonstrating the nature of the correlation between enthalpy, heat capacity, entropy, and temperature, are useful for the thermodynamic energies analysis. Furthermore, the binding sites of the title molecule and the protein matrix metalloproteinase-2 have been predicted. The binding affinity of the protein-molecule complex was predicted to be $-5.9$ kcal/mol. Thus, the molecular docking study theoretically proves that the title molecule has a good binding potential against the protein 1J7M.

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AUTHOR CONTRIBUTIONS
Both authors contributed equally.

CONFLICT OF INTEREST
The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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