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Quantum chemical study of Etodolac (Lodine)

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Abstract

The molecular geometry and vibrational frequencies of lowest energy conformer of Etodolac in the ground state has been calculated by Semi-empirical PM3 Method. The observed frequencies of Etodolac and the calculated frequencies are nearly the same. Vibrational assignments of all the fundamentals were made using Gauss view program. The frontier orbital gap (HOMO-LUMO gap) and dipole moment values for both the conformers are also calculated.

Keywords- FTIR Spectra, Semi-empirical, Etodolac, Vibrational spectra, HOMO-LUMO

INTRODUCTION

Etodolac belongs to a class of drugs called nonsteroidal anti-inflammatory drugs (NSAIDs). Other members of this class include ibuprofen (Motrin, Advil, Nuprin, etc.), naproxen (Aleve, Naprosyn), indomethacin (Indocin), nabumetone (Relafen) and numerous others. These drugs are used for the management of mild to moderate pain, fever, and inflammation. They work by reducing the levels of prostaglandins, which are chemicals that are responsible for pain and the fever and tenderness that occur with inflammation. Etodolac blocks the enzyme that makes prostaglandins (cyclooxygenase), resulting in lower concentrations of prostaglandins. As a consequence, inflammation, pain and fever are reduced. Etodolac is used for the treatment of inflammation and pain caused by osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. It is also used for treating soft tissue injuries, such as tendinitis and bursitis, and the treatment of menstrual cramps [1]. The main objective of the present study is to investigate in detail the vibrational spectra of important biological molecule (Etodolac), which can presumably help in understanding its vibrational behavior. To the best of our knowledge no detailed quantum chemical calculations have been performed on Etodolac so far in the literature.

RESULTS AND DISCUSSION

Molecular structure and Thermodynamic properties

The lowest energy conformer is shown in fig- 2 (I).The optimized structure parameters of Etodolac, calculated by PM3 method are listed in Table 1 in accordance with the atom numbering scheme given in Fig 2 (I). On the basis of vibrational analysis, the standard thermodynamic functions: internal thermal energy (E), constant volume heat capacity C_v and entropy S have been calculated and are given in the Table 2, respectively.

Table-1: Range of Bond lengths and bond angles for Etodolac (Confor.1)

Parameters	**PM3**
Bond Lengths	
(C-C)	1.441-1.554
(C=C)	1.379
(C-O)	1.353
(C=O)	1.219
(C-H)	1.094-1.108
(O-H)	0.952
(C-N)	1.421-1.422
(N-H)	0.990
Bond Angles	
(C-C-C)	112.12-115.29
(C=C-C)	121.59
(C-C-H)	107.98-111.07
(C-O-C)	117.57
(C-O-H)	109.89
(C-C=O)	128.55
(O=C-O)	115.61
(H-C-H)	106.27-107.90
(C-C-N)	126.71
(C-N-C)	107.12

Table-2: The Thermodynamic Properties of Etodolac (Confor.1) at PM3 level of theory

	E (thermal) (KCal/Mol)	CV (Cal/Mol-Kelvin)	S (Cal/Mol-Kelvin)
Total	233.202	77.000	146.863
Translational	0.889	2.981	42.862
Rotational	0.889	2.981	34.093
Vibrational	231.424	71.039	69.908

Electronic properties

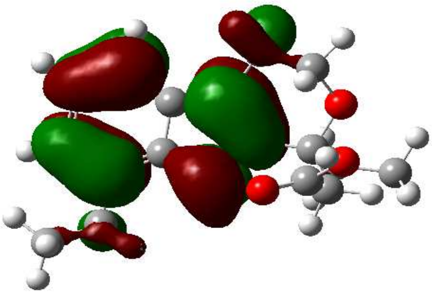
The most important orbitals in a molecules are the frontier molecular orbitals, called highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). These orbitals determine the way the molecule interacts with other species. The frontier orbital gap helps to characterize the chemical reactivity and kinetic stability of the molecule. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability and is also termed as soft molecule [2]. The lower value for frontier orbital gap in case of conformer 1 makes it less reactive and more stable (refer to Table 3). The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor. The 3D plots of the frontier orbitals HOMO, LUMO and total electron density (ED) figures for most stable molecules are shown in Fig. 1. The dipole moment in a molecule is another important electronic property that results from non-uniform distribution of charges on the various atoms in a molecule. It is mainly used to study the intermolecular interactions involving the Vander wal type dipole–dipole forces, etc., because larger the dipole moment, stronger will be the intermolecular interactions. The energy, calculated frontier orbital gap and dipole moment values for both the conformers are also given in Table 3.

Table 3: Energy (a.u.), Band gap (eV) and Dipole moment (D) of Etodolac conformers

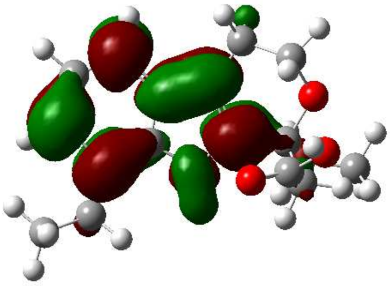
	Energy	LUMO	HOMO	Band gap	Dipole moment
Confor.1	-0.18055710 a.u.	-0.00624	-0.30729	8.18856	1.2872
Confor.2	-0.17860100 a.u.	-0.02325	-0.31173	7.84665	5.3275

Molecular surfaces **Conformer 1**

HOMO



LUMO



Total Density

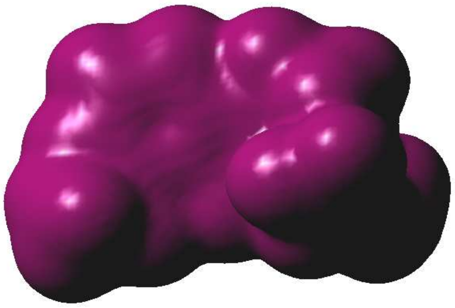
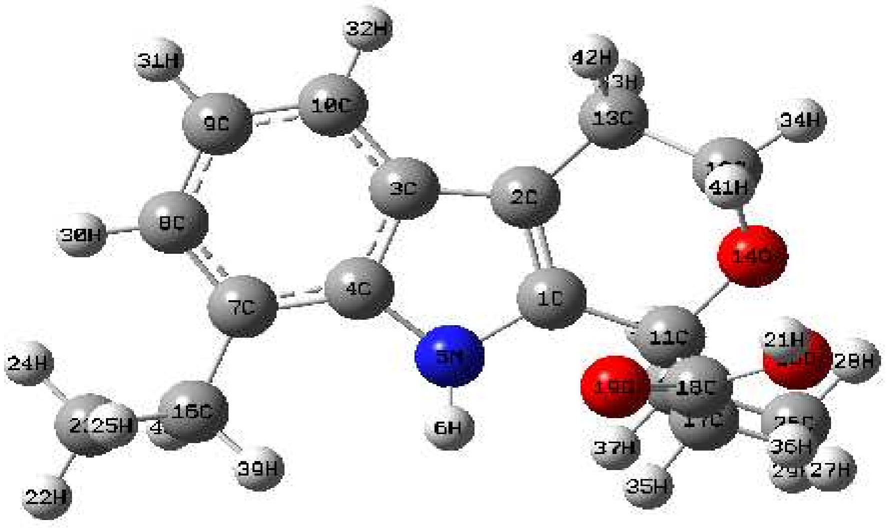


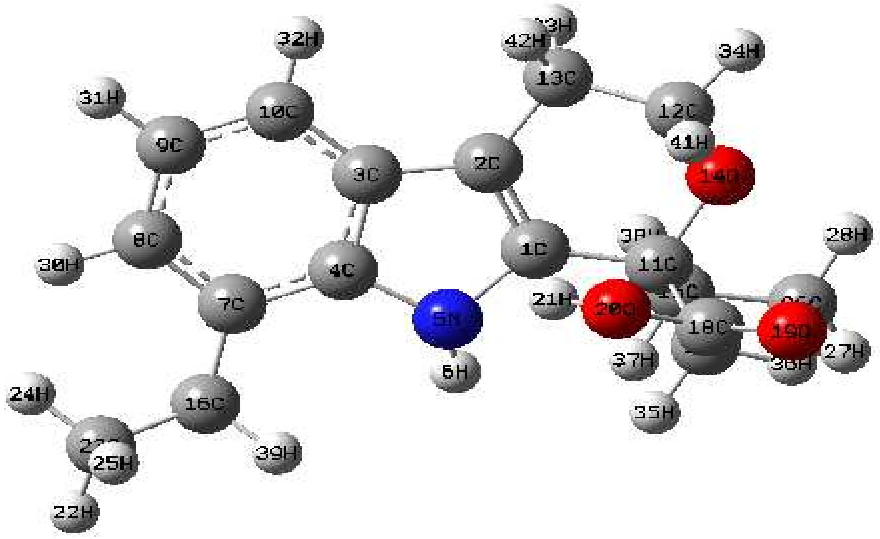
Fig 1: Molecular surfaces

Assignments of vibrational spectra

Assignments of the IR frequencies are achieved by comparing the band positions and intensities observed in the IR spectra with wave numbers and intensities from molecular modeling calculations. The molecule Etodolac (Fig 2) has 42 atoms with 120 normal modes of vibration. The calculated vibrational frequencies and the experimental values (Fig-3) are listed in Table 4. Here we are discussing only FTIR active modes in Table 4. The experimental frequencies of Etodolac and frequencies calculated by PM3 method are nearly the same.



(I) (E = -0.18055710 a.u.)



(II) E = -0.17860100 a.u.

Fig 2 (I & II): Two stable lowest energy conformers of Etodolac

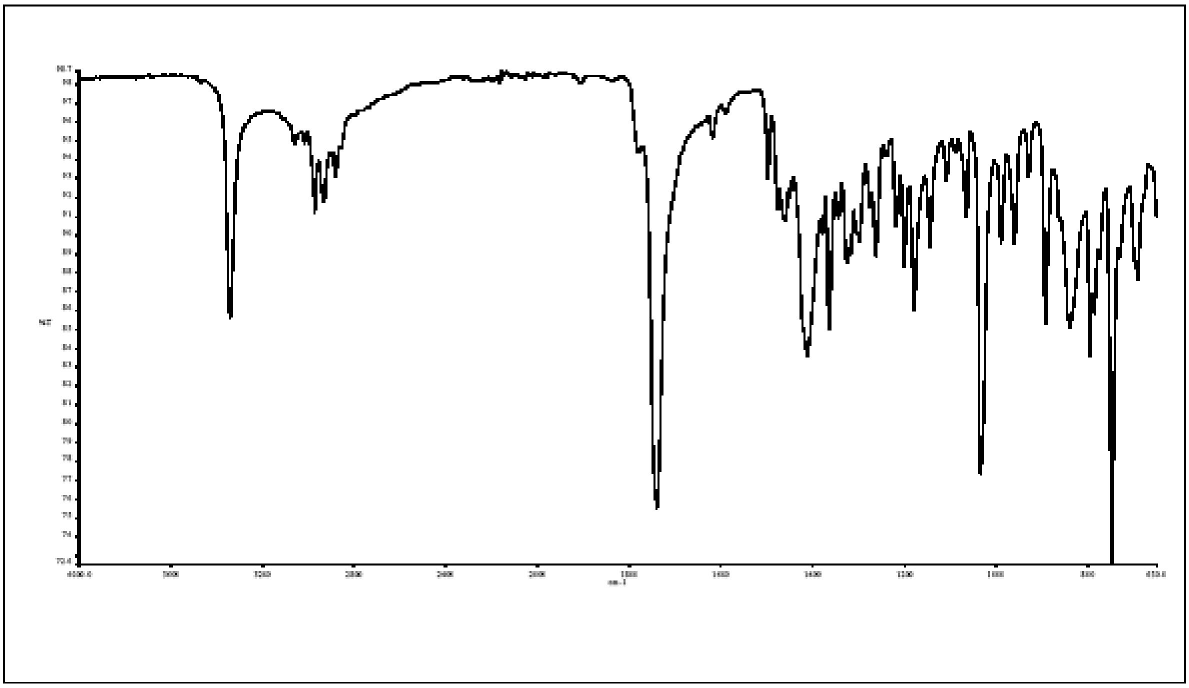


Fig 3: FTIR spectra of Etodolac

Spectral region over 2800 cm^{-1}

The bands located in the high frequency region of the spectra of Etodolac are easy to identify and belong to O-H, N-H and C–H stretching modes. The characteristic ν_{OH} stretching vibration is expected to appear at 3760 cm^{-1}, which is in good agreement with the experimental data. The characteristic ν_{CH} stretching vibrations of double ring structure are expected to appear in 2800-3100 cm^{-1} frequency ranges. The ν_{CH} stretching vibrations of the title compound were observed at 2930 and 3004 cm^{-1} and the corresponding bands are given at 2930 and 3000 cm^{-1} in the experimental spectrum.

Spectral region 1750–1000 cm^{-1}

In middle region, the stretching vibration of the C=C band observed at 1736 cm^{-1} and corresponding band is given at 1745 cm^{-1} in FTIR spectrum. The H-C–H scissor predicted at 1354 cm^{-1} is in reasonable agreement with the 1360 cm^{-1} observed in FTIR. (C–C–H) angle-bending mode observed at 1142 and 1197 cm^{-1} and corresponding band is given at 1150 and 1195 cm^{-1} in FTIR spectrum.

Spectral region 1000–650 cm^{-1}

The twisting along with the out of plane ring bend, all of them appear in the frequency range 1000-650 cm^{-1}.The experimental modes 735, 795 and 835 cm^{-1} matches well with the modes 735, 790 and 829 cm^{-1} (Due to twisting vibration).

Spectral region below 650 cm^{-1}

There are some frequencies in lower region due to the torsion modes like 392, 475, 505 and 536 cm^{-1} having appreciable IR intensity. Furthermore, the study of low frequency vibrations is of great significance, because it gives information on weak intermolecular interactions, which take place in enzyme reactions [3].

Table 4: Comparison of the observed and calculated Vibrational spectra of Etodolac (Confor.1) by PM3 method

PM3 (CALC.)	I-R (INT.)	I-R (EXP.)	VIBRATIONAL ASSIGNMENTS
392	139.22	-	τ (rings)
409	22.580	-	ω (N-H)
435	24.179	-	τ (rings)
460	16.046	-	τ (C-O) adj. rings
475	28.534	-	τ (C-O) adj. rings
479	17.918	-	τ (rings)
505	67.756	-	ω (O-H)
511	12.976	-	τ (rings)
536	28.739	-	τ (rings)
608	13.950	-	τ (C-C)
630	18.246	-	τ (rings)
679	10.261	675	β (C-C-C) + β (C-C-H)
735	17.150	735	t (CH3)
790	16.409	795	t (CH3)
829	8.2022	835	t (CH3)
937	5.8188	935	t (CH3)
1049	2.9467	1040	t (CH2)
1142	10.300	1150	β (C-C-H)
1197	7.0491	1195	β (C-C-H) + β (C-N-H)
1212	54.532	1210	β (C-O-H)
1268	16.998	1275	β (C-C-H) + γ (C-CH2)
1283	17.193	1285	γ (C-CH2)
1309	12.292	1315	β (H-C-H) + β (O-C-H)
1354	23.629	1360	S (H-C-H)
1358	13.885	1365	β (H-C-H)
1375	6.2387	1380	β (H-C-H)
1407	39.295	1410	β (H-C-H)
1427	140.03	1425	β (H-C-H) + β (C-N-H)
1435	48.629	1440	ν (C-N) + ν (C-C) + β (H-C-H)
1457	23.255	1460	ν (C-C) + β (C-C-H)
1736	17.231	1745	ν (C=C)
1927	278.18	1925	ν (C=O)
2847	20.148	2850	ν (C-H)
2930	24.970	2930	ν (C-H)
2987	16.371	2985	ν (C-H)
3004	26.948	3000	ν (C-H)
3348	10.673	3340	ν (N-H)
3760	33.323	3750	ν (O-H)

Abbreviations: *ν: Stretching, β: in plane bending; γ: out of plane bending, τ: torsion, t: twist, S: scissoring int.: intensity.*

Knowledge of low frequency mode is also essential for the interpretation of the effect of electromagnetic radiation on biological systems [4]. Although experimental FTIR spectrum is from 4000-650 cm^{-1} but in the present work the whole frequency assignments including lower region has been discussed. The aim of this paper is to obtain direct information on lower and higher frequency vibrations of such biological molecule.

MATERIALS AND METHODS

The experimental and computational methods are given in this section to analyze Etodolac.

Experimental (Structure and Spectra)

The two conformers of the title compound Etodolac have been generated by Gauss View. The FTIR spectra of Etodolac were taken from the literature [5].

Fourier Transform Infrared Spectroscopy (FTIR/ATR):

Instrument	Perkin Elmer Spectrum One
Number of Scans	16
Resolution	4.000 cm^{-1}
Wavenumber Range	4000 cm 1 to 650 cm^{-1}

Computational Methods

All the calculations were performed by using the PM3 method using the GAUSSIAN 03 suite of program [6]. Semi-empirical methods such as AM1 and PM3, simplify the Schrödinger equation considerably by simplifying certain integrals in the calculations, but then compensate for this by parameterization of some of them so that the calculations reproduce experimental information on for example, the entropy, once the various approximations are made, the molecular properties to which the parameters are fitted, and the molecules used in the fitting, define a model Hamiltonian, of which the most commonly used are AM1 and PM3 Hamiltonians. A major advantage of the semi-empirical method is the speed of computation compared to full Ab-initio calculations. The vibrational frequencies for this molecule were calculated with this method and then scaled [7] by 0.9761 respectively. The aim of this study is to calculate vibrational spectra and thermodynamic properties of Etodolac. By combining the results of the GAUSSVIEW'S program [8] with symmetry considerations, vibrational frequency assignments were made with a high degree of accuracy**.**

CONCLUSION

The frequency assignments for Etodolac have been done for the first time from FTIR spectra. The equilibrium geometries and harmonic frequencies of Etodolac were determined and analyzed at PM3 level of theory. The difference between the observed and scaled frequencies is very small. The calculated vibrational frequencies and the experimental values (FTIR) indicate that PM3 method can explain the vibrational spectra of the title compound well. It can also be concluded that with a comparable results and lower computational time, semi empirical method could be used to study the spectra of Etodolac. On the other hand for accurate and precise structural and vibrational data, DFT method could be used with a good agreement with experimental results, as it takes electron-electron correlation into account.

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