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Theoretical studies of the Vibrational spectra and Molecular electrostatic potentials (MEP) of Allopurinol isomers

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ABSTRACT

The harmonic wave numbers of allopurinol were calculated by using of density functional theory with B3LYP/6-311++ G(d,p) level. The molecular electrostatic potentials (MEP) of allopurinol isomers were calculated with help of Spartan 10 software at the B3LYP/6-31++ (d,p) level , and the molecular surface was taken to be the 0.002 au contour of the electron density. These MEP map surfaces show that different colors, the red color shows positive potentials and blue color shows negative potentials. From the MEP results, the positive potentials sites are located an electronegative nitrogen and oxygen atoms and the negative potentials sites are located around the hydrogen atoms in the isomers. These potentials sites are mainly give the information about intermolecular interactions possible in the molecule.

Introduction

Allopurinol (ALP) and its mayor metabolite oxypurinol (OXP) are potent inhibitors of xanthine oxidase, the enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid. Allopurinol is commonly used in the treatment of chronic gout or of hyperuricaemia associated with leukemia, radiotherapy, anti-neoplastic agents and treatment with diuretics[1]. Gout is the most common form of inflammatory arthritis affecting men, and prevalence rates are increasing worldwide [2]. The principal manifestations of disease occur because of hyperuricemia leading to deposition of monosodium urate crystals within the joints. Allopurinol is recommended as first-line urate-lowering therapy in patients with gout and renal impairment [3,4]. This agent has the benefits of once daily dosing and has efficacy in patients with renal impairment. However, allopurinol dosing may be problematic in patients with renal impairment because of the risk of serious toxicity. The present communication deals with the investigation of the structural, molecular electrostatic potentials and vibrational spectra of allopurional, looking at the biological importance of the allopurinol.

Computational details

In the theoretical calculations, one of the most important steps is Geometry optimization. All Allopurinol isomers molecules have been optimized with density functional theory (DFT)[5], employing Becke's three parameter hybrid exchange functional with Lee-Yang-Parr correlation functional (B3LYP) with 6-311++ G(d,p) basis set [6-8]. All calculations were performed using the Gaussian 09 program [9]. No imaginary wave numbers were observed, that confirmed the geometry to be located at true local minima on the potential energy surface and using of Gaussivew 5.05 program [10], the vibrational wave number assignments have been carried out by combining the results. The calculated IR spectra have been plotted using with a band width of FWHM of 20 cm^{-1} and are shown in Fig 2.Our research was focused on the characterization of the molecular surface electrostatic potential of six allopurinol isomers studied, whose structures and names are shown in Figure 1. The molecular surface electrostatic potentials (ESP) were calculated at the B3LYP/6-31++ (d,p) level , by using of the SPARTAN'10 program[11] and the molecular surface was taken to be the 0.002 a.u contour of the electron density[12].

Results and Discussion

Geometry optimization

The equilibrium geometry optimization for allopurinol molecule has been performed by energy minimization, using DFT at the B3LYP level, employing the basis set 6-311++ G (*d,p*). The optimized geometry of molecule under study are confirmed to be located at the local true minima on potential energy surface, as the calculated vibrational spectra has no imaginary frequency observed. The optimized molecular structure thus obtained representing the numbering scheme of the atoms is shown in Fig. 1 and the optimized bond lengths are presented in Table.1.

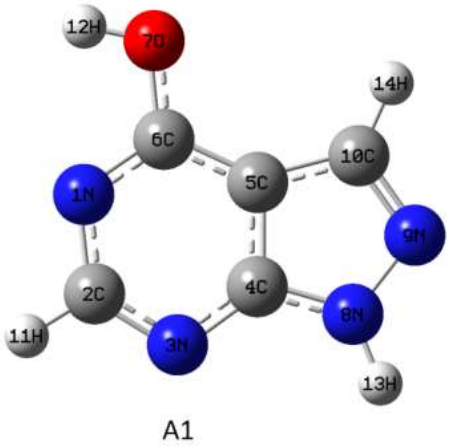

Fig .1. Optimized geometry molecular structure of allopurinol

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Table 1. Optimized geometrical parameters of allopurinol obtained by B3LYP/6-311++G(d,p) density functional calculations.

Bond length	Value(A^0)	Bond angle	Value(^{0})
N1-C2	1.3511	(C2,N1,C6)	118.1366
N1-C6	1.3235	(N1,C2,N3)	127.7042
C2-N3	1.3243	(N1,C2,11)	115.5212
C2-H11	1.085	(N3,C2,11)	116.7746
N3-C4	1.3407	(C2,N3,C4)	112.5789
C4-C5	1.4104	(N3,C4,C5)	126.2164
C4-N8	1.3558	(N3,C4,N8)	128.0649
C5-C6	1.403	(C5,C4,N8)	105.7186
C5-C10	1.4251	(C4,C5,C6)	114.3371
C6-O7	1.3399	(C4,C5,C10)	104.9388
O7-H12	0.9692	(C6,C5,C10)	140.7241
C8-N9	1.3627	(N1,C6,C5)	121.0268
N8-H13	1.0078	(N1,C6,O7)	118.6998
N9-C10	1.3178	(C5,C6,O7)	120.2734
C10-H14	1.0788	(C4,N8,N9)	112.286
		(N8,N9,C10)	106.3901
		(C5,C10,N9)	110.6665

Vibrational analysis

The optimized molecular structure of allopurinol belongs to the C_1 point group as it does not display any special symmetry. Allopurinol has 36 fundamentals are distributed amongst the symmetry species. As a result of this all the normal modes of allopurinol found to be infrared active. The calculated wave numbers along with their respective dominant normal modes are presented in Table 2 and the calculated IR spectra shown in fig 2.

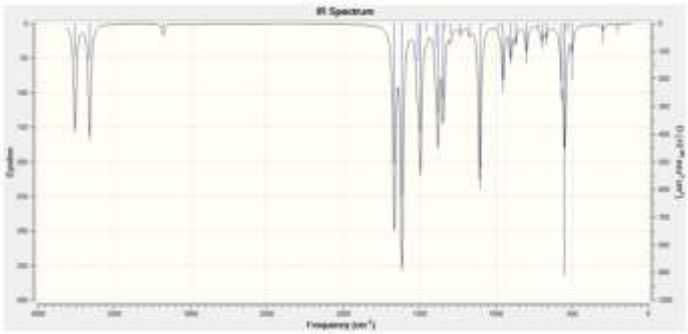


Fig 2. The calculated IR spectra of allopurinol molecule by Using of DFT(B3LYP)/6-311++G(d,p) level

O-H, N-H and C-H vibrations:

Generally the free O-H group absorbs at 3615 cm^{-1} . In the present study, the band found at 3755 cm^{-1} has been designated to O-H stretching vibration, the in-plane bending mode of O-H group is identified at 1345 cm^{-1} and out-of-plane mode is assigned at 296 cm^{-1} for the title compound. In heterocyclic compounds, the N-H stretching vibrations occur at 3500-3000 cm^{-1} region. In the present investigation, the N-H stretching vibration of allopurinol is identified at 3659 cm^{-1}.The assignment of N-H in plane and out-plane bending at 1296 cm^{-1} and 901 cm^{-1} respectively.

The C-H stretching vibrations are identified at 3249 and 3177cm^{-1} and the C-H bending vibrations are expected to interact a little around 1600 – 1300 cm^{-1} with ring vibrations. Hence in the present study, the bands observed at 1334 and 1296 cm^{-1} have been assigned to C-H in-plane bending modes. The bands at 869 and 797 cm^{-1} are associated with C-H out-of-plane bending modes.

C-C and C-N vibrations:

The ring carbon-carbon stretching vibrations occur in the region 1625-1430 cm^{-1} in benzene derivatives are due to C-C stretching vibrations. Accordingly, in the present study, the C - C band observed at 1663 cm^{-1}.The ring out of plane bending modes of allopurinol are also listed in table 2. The identification of C-N stretching frequencies in the side chain is a rather difficult task, since there are problems in identifying these frequencies from other vibrations. The C-N stretching usually lies in the region 1400-1200 cm^{-1}. In this study, the C-N stretching vibrations of allopurinol are identified between 1514 - 1377 cm^{-1}. The remaining all vibrations are presented in the table against to their assignments.

Molecular Electrostatic Potentials:

The electrostatic potential V(r) that is created in the space around a molecule by its nuclei and electrons (treated as static distributions of charge) is a very useful property for analyzing and predicting molecular reactive behavior. It is rigorously defined and can be determined experimentally as well as computationally. The potential has been particularly useful as an indicator of the sites or regions of a molecule to which an approaching electrophile is initially attracted, and it has also been applied successfully to the study of interactions that involve a certain optimum relative orientation of the reactants, such as between a drug and its cellular receptor. For large biologically active molecules, multi pole expansions and superposition of potentials computed for subunits have been found to be effective. A large number of chemical and biochemical systems and processes have now been studied in terms of electrostatic potentials.

Definition and Significance

Any distribution of electrical charge, such as the electrons and nuclei of a molecule, creates an electrical potential $V(\vec{r})$ in the surrounding space. $V(\vec{r})$ may be regarded as the potential of the molecule for interacting with an electrical charge located at the point $\vec{r}$. For example, an approaching point will charge ± Q will interact with this electrical potential, with an energy of interaction equal to exactly ± Q$V(\vec{r})$, where $V(\vec{r})$ is the position of the point charge. Thus a positive point charge is attracted to those regions in which $V(\vec{r})$ is negative, since this leads to a negative (stabilizing) interaction energy, and it is repelled from regions of positive potential, in which the interaction energy is positive and destabilizing.

A knowledge of the electrical potential, A knowledge of the electrical potential, $V(\vec{r})$, around, around a molecule should therefore help considerably in interpreting its reactive behavior toward charged species (even, qualitatively, when they are larger than point charges) and in predicting the sites of the molecule at which they are most likely to react. Indeed, over the past 25 years, the electrical potential has become a well established tool for the elucidation of molecular reactive properties [13-15]. The electrostatic potential has been used primarily for predicting sites and relative reactivities towards electrophilic attack, and in studies of biological recognition and hydrogen bonding interactions [13,16].

If a molecule has an electronic density function ρ(r), then its electrostatic potential at any point's is given rigorously by eq. (1)[17]

$$V(\vec{r}) = \sum_A \frac{Z_A}{\left|\vec{R}_A - \vec{r}\right|} - \int \frac{\rho(\vec{r}')d\vec{r}'}{\left|\vec{r}' - \vec{r}\right|} \qquad (1)$$

Z_A is the charge on the nucleus A, located at R_A. The first term on the right side of eq. (1) represents the contribution of the nuclei, which is positive; the second term brings in the effect of the electrons, which is negative.

Table 2. Vibrational wavenumbers obtained for allopurinol at B3LYP/6-311++G(d,p) level: [(wavenumbers in cm^{-1}) ; IR intensities(km mol^{-1}); Redued mass (amu), force constants in m dyne A^{-1})]

S.NO	Freque	Red. masses	Frc consts	IR Inten	Assignments
1	3755.79	1.0643	8.8457	111.856	O7-H12 Stretching
2	3659.71	1.0818	8.5365	120.079	N8-H13 Stretching
3	3249.95	1.0972	6.8278	0.6871	C10-H14 Stretching
4	3177.66	1.0914	6.4928	12.3217	C2-H11 Stretching
5	1663.26	7.013	11.4308	210.06	C6-C5 Stretching
6	1614.07	5.9784	9.1765	250.464	C4-N3 Stretching
7	1514.17	4.0618	5.4868	50.4143	C10-N9 Stretching
8	1492.93	4.6582	6.1171	145.143	C6-O7+C10-N9 Stretching
9	1453.64	2.9454	3.667	9.7057	C4-8N Stretching
10	1393.26	2.7253	3.117	29.5551	C2-H11 out of plane bending
11	1377.8	5.0178	5.6122	111.404	C2-N3 Stretching
12	1343.7	2.809	2.9881	90.4149	O7-H12 Bending
13	1334.11	2.3906	2.507	5.3923	C2-h11 Bending
14	1296.2	2.1407	2.1191	13.2072	N8-H13 Bending
15	1231.43	1.5422	1.3779	9.1251	C10-H14 Bending
16	1171.64	4.9465	4.0008	8.6474	Ring 1 bending
17	1104.58	3.5867	2.5783	165.466	Ring 2 bending
18	1080.34	3.5193	2.4201	1.9468	C-H out of plane bending
19	977.091	1.4499	0.8156	4.811	Ring 2 anti symmetric deformation
20	951.892	4.1904	2.2371	58.7097	Ring 2 anti symmetric deformation
21	901.284	8.7847	4.2044	33.1205	Rings deformation
22	869.546	1.3256	0.5905	17.3164	Rings deformation
23	797.738	7.2551	2.7203	28.5257	Ring 1 torsion
24	718.862	7.6962	2.3433	2.5149	Ring 2 torsion
25	697.064	8.1365	2.3293	15.4575	Ring 2 trigonal deformation
26	667.237	3.4738	0.9112	12.4371	Ring 2 torsion trigonal deformation
27	615.871	6.3418	1.4172	0.7006	Ring 2 anti symmetric deformation
28	567.55	2.5205	0.4783	39.3242	O-H wagging deforrmation
29	547.831	1.1527	0.2038	125.135	C-H wagging deforrmation
30	532.357	10.4544	1.7456	0.4086	N-H wagging deforrmation
31	529.032	5.2556	0.8666	3.9395	C-O deformation
32	500.204	1.5826	0.2333	25.1314	Butterfly
33	298.382	5.723	0.3002	5.2548	Butterfly
34	296.055	6.9115	0.3569	1.7177	Butterfly
35	202.195	7.361	0.1773	1.6978	Butterfly
36	166.936	5.5199	0.0906	0.0031	Butterfly

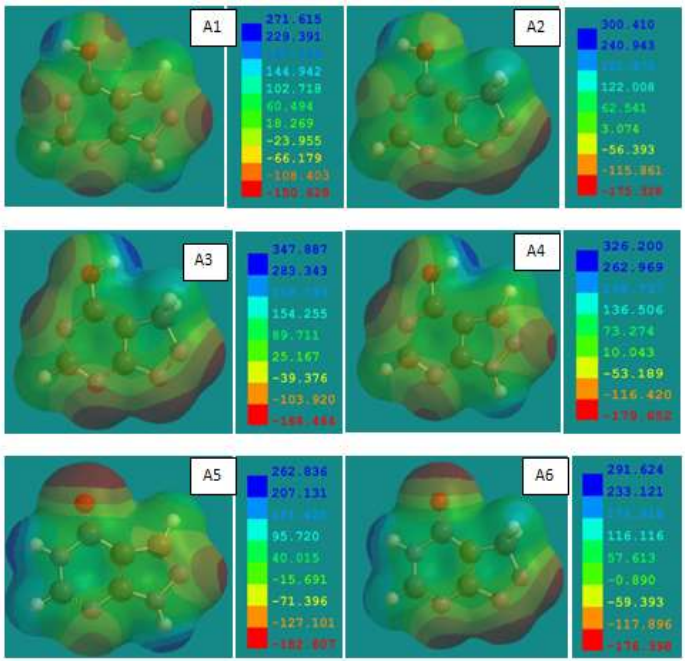
Electrostatic potential maps: The electrostatic potential map shows the value of the electrostatic potential onto an electron density surface to get a description of the electrostatic characteristics of the target drug [18]. By convention, colors toward red depict negative potential, while colors toward blue depict positive potential and colors in between depict intermediate values of the potential. Thus, this drug has both, negative and positive well defined regions, which increase the interaction possibilities from an electrostatic point of view. The MEP is related to the electronic density and is a very useful descriptor in determining the sites for electrophilic and nucleophilic reactions as well as hydrogen bonding interactions [19]. It has been demonstrated that the positive region (red color) can serve as a channel for the approach of nucleophiles and the negative region (blue color) can serve as a channel for the approach of electrophiles [20].

In the present study, we calculated both positive $V_{s,max}$ and negative $V_{s,min}$, whose respective values are given in Table 3 and the electrostatic potentials maps depicted in Figurer 3 for the studied molecule isomers. The most positive values of VS(**r**), the $V_{S,max}$, are associated with hydrogens of covalently-bonded carbon and nitrogen atoms. Negative regions are often smaller than the positive, but tend to be stronger, with the most negative values, the $V_{S,min}$, being near lone pairs of nitrogen and oxygen atoms and π electrons of aromatic ring. The strongly negative electrostatic potentials produced by the ring nitrogens make these attractive sites for electrophiles.

Table 3. The $V_{s,max}$ and $V_{s,min}$ (kcal/mol) of molecular surface electrostatic potentials of the allopurinol isomers calculated by B3LYP/6-311++G(d,p) level of basis set with Spartan 10.

Isomer	$V_{s,max}$	$V_{s,min}$
A1	272.973	-150.624
A2	300.410	-175.328
A3	347.887	-168.464
A4	326.200	-179.652
A5	262.836	-182.807
A6	291.624	-176.390

The order of $V_{s,min}$ values in kcal/mole: A5 > A4 > A6 > A2 > A3 > A1 and the order of $V_{s,max}$ in kcal/mole: A3 > A4 > A2 > A6 > A1 > A5. Therefore the C-H, N-H, and O-H bonds create positive regions of potential that may be considered barriers for electrophilic reaction channels due to the differences in atomic electronegativity. Electrostatic potentials in zones near N and O atoms (described with lone electron pairs) show deep negative holes. Negative potential values may often be found above and below the aromatic rings. Although it might seem that they are due to the π charges, they correlate better with total ab initio charges.



Figurer .3. The (MEP) Maps of the molecular electrostatic potentials of the allopurinol isomers.

Conclusion

The DFT based computational method approach provides the most reliable information on the vibrational frequencies of allopurinol. The combined use of B3LYP functional and standard basis set 6-311++G9d,p) provides an excellent agreement between accuracy and computational efficiency of vibrational spectra of allopurinol. The assignments of most of the fundamentals provided in the present work are believed to be unambiguous. According to MEP calculated results, the MEP map shows that the negative potential sites are on electronegative N and O atoms as well as the positive potential sites are around the hydrogen atoms. These sites give information about the region from where the compound can have intermolecular interactions.

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