Density Functional Study of Neutral Allopurinol Tautomeric Forms

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ABSTRACT: Optimized structures and total molecular energy density functional theory calculations for the 14 possible neutral allopurinol tautomers give the decreasing stability order $\underline{N}$(1)-H/$\underline{N}$(5)-H > $\underline{N}$(2)-H/$\underline{N}$(5)-H > cis-enolic/$\underline{N}$(1)-H for the three most stable forms. Several molecular and electronic structure properties, the stabilities in oxidation and reduction processes, the tautomeric equilibrium constants, and the IR vibrational spectra were obtained for these. Those properties corresponding to the ketonic $\underline{N}$(5)-H forms are discussed and compared with the theoretical ones for the two most stable species of the isomer hypoxanthine. A noticeable agreement is found between the predicted properties and the experimental behavior known up to date for both isomers. © 1999 John Wiley & Sons, Inc. J Comput Chem 20: 200–206, 1999

Introduction

Hypoxanthine and allopurinol (Fig. 1) are interesting systems from a Lewis acid–base point of view. Both isomers show very complex

ligand-H$^+$ thermodynamic equilibria in solution[1,2] in which prototropic tautomerism also exists.[1d,2–4] In addition, the very rich metallic coordination behavior they show lies mainly on the existence of several electron donor sites and their disposition in the respective framework, and on the metallic center–heterocycle experimental reaction conditions established.[5]

From the studies quoted above, the respective tautomeric predominance has been found to be dependent on both the solvent physicochemical properties and the heterocyclic metallic coordination. Additionally, there is no clear relationship between the ligand-H$^+$ and ligand-metal thermo-
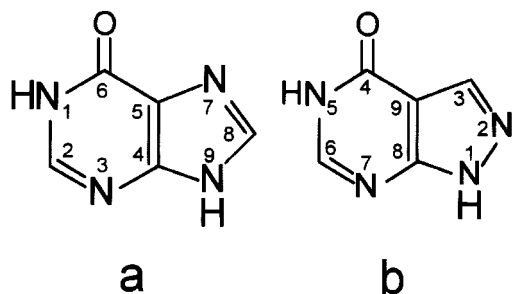
FIGURE 1. Schematic drawing of the structures for the isomers (a) hypoxanthine and (b) allopurinol in their respective N(1)-H / N(9)-H (K19) and N(1)-H / N(5)-H (K15) ketonic forms; the numbering scheme is the one used in this study.

dynamic stabilities for which a common heterocyclic electron donor site is involved. To advance the understanding of some aspects of the heterocycle−Lewis acid interactions thermodynamic stabilities, systematic theoretical studies are essential for both isomers under several protonation levels and tautomeric forms. In this respect, and for allopurinol, previously reported[2a, 6, 7] semiempirical calculations (INDO, MNDO, and MNDO and AM1 levels) were limited to a reduced number of properties for the two energetically most stable neutral tautomers and without details about the calculation methodology and the criteria used for geometry optimization. Nonella and coworkers[8] employed AM1 and *ab initio* methods for the calculation of some properties for only the two most stable ketonic forms of both neutral isomers; however, the structures were constrained to planarity and no minimum energy structures were verified by a frequency analysis. El-Bakali Kassimi and Thakkar[9] carried out *ab initio* calculations of some properties for only the two energetically most stable ketonic tautomers of both neutral isomers; however, no explicit details about the minimum energy structures' verification were given. Hernández and coworkers[10] used a semiempirical (AM1) calculation to eliminate the less stable tautomeric forms; afterward, they performed *ab initio* and density functional theory (DFT) energy calculations for the seven tautomers of both neutral isomers; in this case, the minimum energy structures' verification was made by a frequency analysis.

In the hope to advance the exploration of the isomers' properties and as part of our research program related to the purine derivative and isomer−Lewis acid interactions, we recently carried out[11] preliminary DFT calculations for the six neutral hypoxanthine and allopurinol ketonic forms and analyzed some properties of the two most stable respective tautomers. Afterward we made[12] exhaustive and systematic DFT molecular energy calculations for all the possible neutral hypoxanthine ketonic and enolic tautomers with the minimum energy structures' verification by a frequency analysis and studied several properties of the six most stable tautomers, together with the tautomeric equilibrium constants as a function of temperature and the IR vibrational spectra.

In the next step the corresponding systematic DFT study for the neutral allopurinol tautomers was carried out. In this the attention was focused on the relative energetic stability of all the possible tautomeric forms, several molecular and electronic structure properties, some of the features of the tautomeric equilibria thermodynamics, and the IR vibrational spectra for the three energetically most stable tautomers. In this article those for the two most stable ones are discussed and compared with the theoretical properties of the two most stable hypoxanthine isomer tautomers. A comparison of such properties with the respective experimental isomeric behavior is also made.

Methods

The total molecular energies by geometry optimization for the 14 possible neutral allopurinol tautomers were calculated at the DFT level with the Becke−Perdew (BP86) exchange-correlation functional[13, 14] and the DZVP basis set[15] by using the standard procedure in Gaussian 94.[16] For the three energetically most stable tautomers (Fig. 2) this protocol was extended by employing the B3LYP functional with the DZVP basis set and the BP86 functional with the 6−31G** basis set.

The allopurinol crystalline structure[17] in its N(1)-H/N(5)-H (K15) form was used as starting
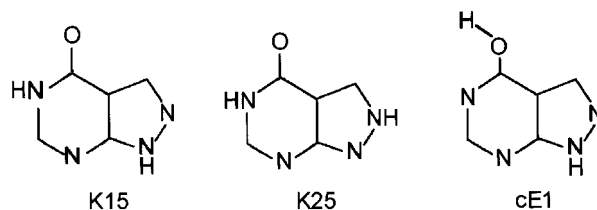
FIGURE 2. Schematic drawing of the three energetically most stable (this study) neutral allopurinol tautomers. K15, K25, and cE1 are the N(1)-H / N(5)-H, N(2)-H / N(5)-H, and cis-enolic / N(1)-H tautomers, respectively.

data for its geometry optimization. The resulting structure was used to construct the other tautomeric initial geometries. For the ketonic forms, the corresponding interchangeable H atoms were systematically located either on or out of the molecular plane; all propositions converged to the respective same structure. For the enolic tautomers, several OH group initial configurations were proposed, and the respective cis and trans configurations always converged to the same corresponding structure.

The criteria for the geometry optimization and self-consistent field (SCF) convergence were 10^{-7} Hartree/bohr and 10^{-9} Hartree, respectively. Frequency calculations showed that all the tautomers were stationary points in the geometry optimization procedure, and none showed imaginary frequencies in the vibrational analysis.

The optimized geometries corresponding to the three energetically most stable tautomers were used to perform single point calculations with Gaussian 92[18] (with the same functional and basis set) to obtain several of their properties. The difference in the SCF energy with respect to the value obtained with Gaussian 94 was 10^{-8} Hartree in all cases. Visualization of these properties was done with the Unichem program.[19a] Single point calculations with the DGauss program[20] for the Gaussian 94 optimized geometries were also done to obtain the Mayer valence indices.

Due to the very good confidence level previously found for the hypoxanthine properties by employing the BP86/DZVP level[12] and the fact that other protocols like BP86/6−31G** and B3LYP/DZVP give the same behavior, the BP86 functional and the DZVP basis set were chosen to calculate the properties for the three most stable allopurinol tautomers.

The IR vibrational absorptions' calculated frequencies were corrected with a scaling factor of 1.0054, which was obtained by comparing the theoretical IR $\nu(C=O)$ vibrational mode wave number (1725.6988 cm^{-1}) for the $\underline{N}$(1)-H/$\underline{N}$(7)-H hypoxanthine tautomer in the gas phase with the experimental one (1735 cm^{-1}).[21] Vibrational normal modes assignment was done by visualizing them with the XMol 1.3.1 program.[19b] Frequency calculations were done at 298.15 and 480.15 K to obtain the molar Gibbs free energy thermal corrections; the contributions to these corrections were calculated within the rigid rotor-harmonic oscillator-ideal gas approximation with the rotational constants and harmonic frequencies by using the standard methods of statistical mechanics.[22] From

these $\overline{G}$ values the tautomeric equilibrium constants at those temperatures were calculated. First vertical ionization potentials (IPs) and electron affinities (EAs) were obtained from SCF energy calculations of the resulting radicals (with the optimized structures of the respective neutral tautomers).

The calculations were done on an SGI Origin 2000 and Cray YMP4/464 supercomputers (at DGSCA-UNAM), an SGI Power Challenge R8000-18 computer (at UAM-Iztapalapa), and a R4400 SGI workstation (at FQ-UNAM).

Results and Discussion

RELATIVE ENERGETIC STABILITY

Table I shows the relative energetic stability of the $\underline{N}$(2)-H/$\underline{N}$(5)-H (K25) and the *cis*-enolic/$\underline{N}$(1)-H (cE1) tautomers with respect to the most stable $\underline{N}$(1)-H/$\underline{N}$(5)-H (K15) form. This order is independent of the functionals and basis sets explored here. The remaining 11 tautomers show energetic differences higher than 12 kcal/mol.

The stability order found is the same as that obtained in previous DFT and *ab initio* calculations.[10] Our preliminary DFT study[11] is also in agreement with the suggestion of K15 and K25 as the two most stable ketonic forms. Considering the theoretical results for hypoxanthine[12] and those obtained here for allopurinol, the two energetically most stable forms in both isomers are ketonic tautomers that show protonation of the $\underline{N}$ atom nearest to the carbonyl group. This led us to suggest the higher relative basicity for that endocyclic electron donor site in both isomers. This property was also inferred from theoretical studies on anionic hypoxanthine[23] and from the coordination mode experimentally shown by monoanionic al-

TABLE I.

Total Molecular Energy Differences (kcal / mol) for $\underline{N}$(2)-H / $\underline{N}$(5)-H (K25) and cis-Enolic / $\underline{N}$(1)-H (cE1) Allopurinol Tautomers Relative to $\underline{N}$(1)-H / $\underline{N}$(5)-H (K15) Form.

Tautomer	BP86 / DZVP	BP86 / 6-31G**	B3LYP / DZVP
K25	3.38	3.45	3.67
cE1	6.87	6.28	6.33

The values were calculated by employing different functionals and basis sets. Zero-point energies are included in the respective total molecular energies.

lopurinol.[5] The two ketonic tautomers of both isomers were also experimentally detected as the respective preponderant species in solutions of neutral hypoxanthine[1, 3] and allopurinol.[2, 4, 6] For both isomers, the correspondent third tautomer (an enolic form) following in energetic stability was not detected experimentally.

## STRUCTURAL PARAMETERS AND TOTAL ELECTRONIC CHARGE DENSITY (TECD)

The theoretical internuclear distances for the two most stable allopurinol $\underline{N}$(5)-H species are strongly dependent on their tautomeric form. In particular, the deprotonated $\underline{N}$ atoms are involved in lower relative distances, which let us invoke a comparatively higher internuclear electronic charge density localization between those atoms and their nearest neighbors. In both tautomers, a double-bond character for the $\underline{C}$(4)-O group is also suggested. These propositions are also in concordance with the TECD contour maps and the Mayer valence indices [e.g., in K15 the indices are $\underline{N}$(1), 3.35; $\underline{N}$(2), 2.98; $\underline{C}$(3), 3.92; $\underline{C}$(4), 4.19; $\underline{N}$(5), 3.30; $\underline{C}$(6), 3.96; $\underline{N}$(7), 3.18; $\underline{C}$(8), 3.91; $\underline{C}$(9), 3.88; $\underline{O}$, 2.22]. The CNC and CNN groups also show theoretical angle values strongly associated with the tautomerism: comparatively lower values are obtained when the central $\underline{N}$ atom in such groups is deprotonated.

These features were also found in theoretical studies on the two most stable hypoxanthine $\underline{N}$(1)-H tautomers.[12] For the two most stable tautomers of both isomers, the theoretical properties are in full agreement with the respective experimental tautomeric structural parameters obtained from solid sample X-ray diffraction studies.[5, 12, 17] As for hypoxanthine,[12] the two most stable allopurinol $\underline{N}$(5)-H tautomers show total planarity.

MOLECULAR ELECTROSTATIC POTENTIAL (MEP) AND ELECTRIC DIPOLE MOMENT (EDM).

Figure 3 shows the MEP contour maps (considering a positive charge as the probe) together with the EDM vector (the arrow head points to the positive end) for the tautomers under discussion. Table II shows the respective EDM values.

The highest negative MEP level lies on two regions near the $\underline{O}$ atom and a region near each one of the deprotonated $\underline{N}$ atoms. In both tautomers, the protonated regions are associated with positive (repulsive) MEP. The EDM properties are in full agreement with the MEP distribution around
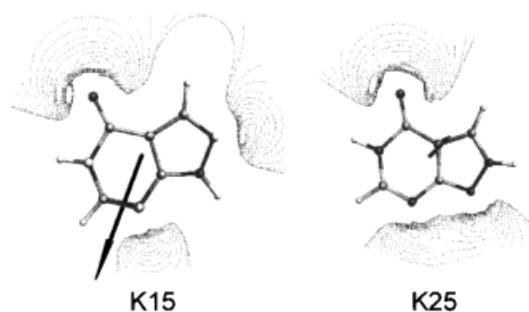
FIGURE 3. MEP contour maps (0 to -50 kcal / mol range, changes in -5 units) and the EDM vector at the optimized molecular plane for the $\underline{N}$(1)-H / $\underline{N}$(5)-H (K15) and the $\underline{N}$(2)-H / $\underline{N}$(5)-H (K25) neutral allopurinol tautomeric forms.

the heterocycles. The deprotonated atoms could be suggested as Lewis acids−attractive interactions potential sites, being characterized or initially mediated by electrostatic contributions.

Also, it is important to point out the EDM vector influence on the relative tautomeric population by changes in the solvent dielectric constant. Those most stable tautomers that in isolated form show the higher EDM values will be comparatively more favorable in solvents with an increasing dielectric constant. For allopurinol and hypoxanthine the tautomers with the higher EDM [$\underline{N}$(1)-H/$\underline{N}$(5)-H (K15) for allopurinol and $\underline{N}$(1)-H/$\underline{N}$(9)-H (K19) for hypoxanthine[12]] are suggested to be the respective most favorable ones with the solvent dielectric constant increase. These predictions have been strongly corroborated in experimental studies on neutral hypoxanthine[1, 3] and allopurinol[2, 4] solutions. For allopurinol, K15 is the predominant free species in aqueous solution, and it was also found to be the preponderant one in allopurinol−metallic center compounds.[5] In these the most favorable heterocyclic metallic coordination site found is the $\underline{N}$(2) atom, which is the comparatively more favorable endocyclic deprotonated site theoretically suggested here to be involved in attractive interactions with Lewis acids from a electrostatic point of view.

ENERGY AND SYMMETRY PROPERTIES OF WAVE FUNCTIONS ASSOCIATED WITH HOMOs AND LUMOs

Table II shows the HOMO and LUMO wave functions energies for the tautomers discussed. For these the respective 3-dimensional isosurfaces show that the HOMOs properties are the same; the

TABLE II.
Electric Dipole Moment (μ), HOMO and LUMO Energies, and First Vertical Ionization Potential (IP) and Electron Affinity (EA) for $\underline{N}$(1)-H / $\underline{N}$(5)-H (K15) and $\underline{N}$(2)-H / $\underline{N}$(5)-H (K25) Neutral Allopurinol Tautomeric Forms.

Tautomer	μ (D)	HOMO Energy (eV)	LUMO Energy (eV)	IP (eV)	EA (eV)
K15	3.65	−6.139	−2.351	7.49	0.25
K25	0.93	−6.072	−2.288	7.43	0.26

π type potential electron donor properties are independent of the tautomeric form. When comparing these HOMOs wave functions properties with those corresponding to the HOMOs of the two most stable hypoxanthine tautomers,[12] it is observed that they all show the same characteristics (i.e., the isomeric and tautomeric features in these species have no influence on the HOMOs wave functions symmetry properties and thus on their potential electron donor properties). These results let us suggest that in the formation or dissociation of an N—H chemical bond, other molecular orbitals (MOs) (σ type) of lower energy would be involved. Indeed, the analysis of all the occupied MOs for these isomers and their tautomers supports this proposition.

On the other hand, the π type potential electron acceptor properties for the two most stable tautomers of both allopurinol and hypoxanthine show a relative dependence on both the isomeric and the tautomeric forms.

IP AND EA

Table II shows the first vertical IP and EA for our tautomers. These values belong to the energetic difference for the processes: neutral species → monocationic radical species, and neutral species → monoanionic radical species.

The MOs involved in the first IP appear to be mainly the π type HOMOs. When comparing these IPs with the correspondent ones for the hypoxanthine forms,[12] the allopurinol tautomers appear to be comparatively stronger reductor agents; they are stronger π type Lewis bases. The concordance between the theoretical and the experimental IP values for hypoxanthine[12] gave us confidence in our allopurinol IP values.

With respect to the MOs involved in the EA, these appear to be mainly the π type LUMOs.

When comparing the EA values for the two most stable allopurinol tautomers with those of hypoxanthine,[12] the allopurinol tautomers appear now to be comparatively more favorable oxidant agents; they are stronger π type Lewis acids. These properties for the most stable allopurinol tautomers could convert them in heterocycles comparatively more accessible for being involved in redox processes.

It is possible to suspect that these features for allopurinol could contribute partially to the comparatively higher reactivity shown by this heterocycle in competitive isomeric reactions with a common metallic center.[5] In this problem, the metal-ligand backbonding would be postulated as a more favorable potential property to be shown by allopurinol.

TAUTOMERIC EQUILIBRIUM CONSTANTS (K_{eq}) IN GAS PHASE AS FUNCTION OF TEMPERATURE

We calculated the K_{eq} corresponding to the equilibrium: $\underline{N}$(1)-H / $\underline{N}$(5)-H (K15) ⇔ $\underline{N}$(2)-H/$\underline{N}$(5)-H (K25), for which

$$K_{eq} = \frac{[K25]}{[K15]} = e^{-\Delta \overline{G}/RT},$$

where $\Delta \overline{G}$ is the molar Gibbs free energy difference between K25 and K15. The K_{eq} values are 3.07×10^{-3} (298.15 K) and 3.05×10^{-2} (500 K).

The K_{eq} (or $\Delta \overline{G}$) values strongly favor the K15 predominance in the allopurinol tautomeric population in the gas phase. This property for K15 joined to its higher EDM vector support the predominance of this species in the neutral allopurinol aqueous solutions commented on before.

Also, and as shown below, these theoretical results could have important consequences on the experimental gas phase allopurinol physicochemical properties at temperatures lower than its thermal stability limit (sublimation temperature of ca. 500 K, vacuum higher than 10^{-6} torr).

IR VIBRATIONAL SPECTROSCOPY

In the absence of the experimental allopurinol IR vibrational spectrum, the theoretical one considering the tautomeric contributions could contribute to the heterocyclic properties' analysis. This can be suggested due to the excellent agreement between the theoretical[12] and the experimental[21] IR vibrational spectra for hypoxanthine.
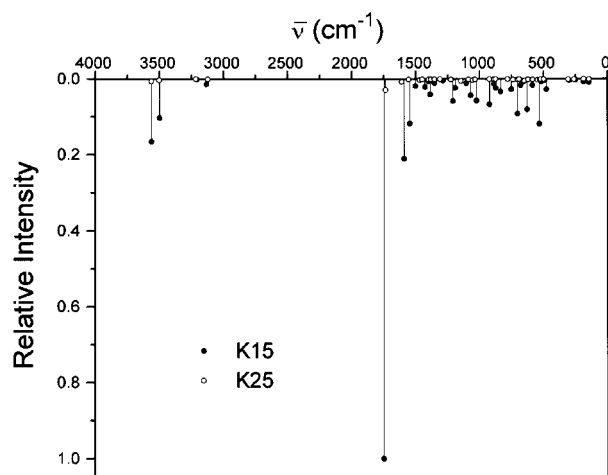
FIGURE 4. Theoretical IR vibrational spectrum of allopurinol in the gas phase, considering the relative contributions at 500 K of its two energetically most stable tautomers.

For the theoretical calculation of the allopurinol IR vibrational spectrum, the same considerations as those proposed for hypoxanthine[12] were made. We selected the approximate value of the experimental allopurinol sublimation temperature (ca. 500 K) as a more realistic one for which the analysis of the allopurinol tautomeric population in the gas phase should be done.

The respective mole fraction for K15 and K25 was obtained from the K_{eq} value. For each spectrum the theoretical intensities of the absorptions were weighted by the corresponding mole fraction. After this, all the intensities were scaled to make them relative to the highest intensity signal. The theoretical allopurinol IR vibrational spectrum when considering the relative contributions at 500 K of its two most stable tautomers is shown in Figure 4.

Figure 4 shows that the clearly observable absorptions correspond to the $\underline{N}(1)$-H/$\underline{N}(5)$-H (K15) tautomer. For the isomer hypoxanthine the theoretical[12] and the experimental[21] IR spectra are both a consequence of the $\underline{N}(1)$-H/$\underline{N}(7)$-H (K17) and $\underline{N}(1)$-H/$\underline{N}(9)$-H K(19) tautomeric contributions; this is attributed to their very similar energetic stability.

Concluding Remarks

Theoretical studies on purine derivatives are invaluable tools for the analysis and prediction of their experimental physicochemical properties. In this article and as part of our research program we selected the hypoxanthine isomer allopurinol to perform this type of study. All the theoretical calculations carried out suggest the higher K15 tautomer energetic stability followed by the K25 form. When the energetic stability results for both allopurinol and hypoxanthine are compared, the respective two most stable forms appear as prototropic tautomerism photographs in the correspondent five-membered rings, which is in agreement with the experimental results. The comparatively higher energetic stability of the N—H bond nearest to the carbonyl group here suggested for these isomers and tautomers is supported by experimental studies on monoanionic allopurinol bonded to Cu(II) and by theoretical studies recently carried out on anionic hypoxanthine. K15 is suggested to be the preponderant allopurinol tautomer in solvents with increasing dielectric constants, while for hypoxanthine this proposition is for the K19 form. This is in accord with the experimental studies. However, many other factors can modify the tautomeric relative stability; the hypoxanthine coordination chemistry is an example of this complexity.

The HOMOs wave functions symmetry properties are independent of the isomeric and tautomeric features considered in this study. This led us to suspect that in such heterocyclic forms the protonated $\underline{N}$ sites could be involved in additional electrophilic attacks by π type Lewis acids. This could be related to the great diversity in the coordination modes reported for allopurinol and hypoxanthine. Allopurinol is suggested to show stronger Lewis base−acid properties; this could be related to its higher reactivity that is experimentally shown in competitive allopurinol and hypoxanthine-Cu(II) reactions.

Allopurinol and hypoxanthine show different relative tautomeric populations in the gas phase, and thus different IR vibrational spectral features. In the analysis of the corresponding experimental physicochemical properties and chemical behavior, the relative tautomeric contributions in these isomers must also be included.

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