Modeling of Protonation Processes in Acetohydroxamic Acid

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · FEBRUARY 2000

Impact Factor: 4.72 · DOI: 10.1021/jo991251x · Source: PubMed

5 AUTHORS, INCLUDING:

Camelia Muñoz-Caro
University of Castilla-La Mancha
100 PUBLICATIONS **828** CITATIONS
SEE PROFILE

Alfonso Niño
University of Castilla-La Mancha
104 PUBLICATIONS **843** CITATIONS
SEE PROFILE

Maria L Senent
Spanish National Research Council
152 PUBLICATIONS **1,623** CITATIONS
SEE PROFILE

Modeling of Protonation Processes in Acetohydroxamic Acid

C. Muñoz-Caro* and A. Niño

Grupo de Química Computacional, Escuela Superior de Informática, Universidad de Castilla-La Mancha, Ronda de Calatrava 5, 13071 Ciudad Real, Spain

M. L. Senent

Departamento de Química y Física Teóricas, Instituto de Estructura de la Materia, C.S.I.C. Serrano 113, 28006 Madrid, Spain

J. M. Leal and S. Ibeas

Departamento de Química, Facultad de CyTA y Ciencias Químicas, Universidad de Burgos, Misael Bañuelos, 09001 Burgos, Spain

Received August 6, 1999

This work presents a theoretical study of acetohydroxamic acid and its protonation processes using ab initio methodology at the MP2(FC)/cc-pdVZ level. We find the amide form more stable than the imidic tautomer by less than 1.0 kcal mol^{-1}. For comparison with the experimental data, a three-dimensional conformational study is performed on the most stable tautomer (amide). From this study, the different barriers to rotation and inversion are determined and the intramolecular hydrogen bond between the OH group and the carbonyl oxygen is characterized. The electrostatic potential distribution shows three possible sites for electrophilic attack, but it is shown that only two of them, the carbonyl oxygen and the nitrogen atoms, are actual protonation sites. The protonation energy (proton affinity) is obtained from the results of the neutral and charged species. Proton affinities for the species charged on the carbonyl oxygen and the nitrogen atoms are estimated to be 203.4 and 194.5 kcal mol^{-1}, respectively. The development of a statistical model permits the quantification of ΔG (gas-phase basicity) for the two protonation processes. In this way, the carbonyl oxygen protonated form is found to be more stable than that of the nitrogen atoms by 8.3 kcal mol^{-1} at 1 atm and 298.15 K, due to the enthalpic contribution. As temperature increases, the proportion of the nitrogen protonated form increases slightly.

Introduction

Hydroxamic acids (*N*-acylhydroxylamines) are naturally occurring compounds that follow the formula RCON-R′OH (R, R′=H, aryl or alkyl) and usually exhibit biological activity. Some of them are antibacterial, antifungal, anticancer agents, antibiotic agents, and specific enzyme inhibitors.[1−3] As iron chelators, siderophores, they have applications for iron-related diseases. In most of the metal chelates formed by hydroxamic acids, coordination occurs by the deprotonation of the hydroxyl group and the subsequent coordination of the deprotonated OH and the carbonyl oxygen.[2,4a] The metal complexing character of hydroxamic acids makes them useful for analytical applications as well.[5] Hydroxamic acids act as weak acids (p$K \approx 8-9$) and can also act as weak bases.[1,6] The mechanism of these processes is not yet fully understood.

It was initially assumed that the deprotonation of hydroxamic acids occurs at the OH group.[7] However, deprotonation on the nitrogen is, in principle, also possible. The structure of the anion had been a matter of controversy until XPS studies, in the solid state,[8] and ^{17}O NMR studies, in methanol,[9] confirmed the N-deprotonation. At present, the theoretical and experimental evidence shows the existence of both O and N deprotonation,[10−15] depending on the system and which solvent is used.

The basicity of hydroxamic acids has received less study. In theory, protonation can occur at the nitrogen, the carbonyl oxygen, or the oxygen in the OH group. By similarity with the chemical behavior of amides, it is usually accepted that the protonation site is the carbonyl

* Fax: 34-926-295354. E-mail: cmunoz@inf-cr.uclm.es

(1) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.
(2) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563.
(3) Stewart, A. O.; Martin, G. J. *J. Org. Chem.* **1989**, *54*, 1221.
(4) (a) Brown, D. A.; Coogan, R. A.; Fitzpatrick, N. J.; Glass, W. K.; Abukshima, D. E.; Shiels, L.; Ahlgren, M.; Smolander, K.; Pakkanen, T. T.; Pakkanen, T. A.; Perakyla, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2673. (b) Ertl, P.; Exner, O. *Struct. Chem.* **1992**, *3*, 305.
(5) (a) King, T. J.; Harrison, P. G. *J. Chem. Soc., Chem. Commun.* **1972**, *13*, 815. (b) Michaelson, R. C.; Palermo, R. E.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 1990.
(6) Buglass, A. J.; Hudson, K.; Tillet, J. G. *J. Chem. Soc. B* **1971**, 123.
(7) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209.
(8) Lindberg, B.; Berndtsson, A.; Nilsson, R.; Nyholm, R.; Exner, O. *Acta Chem. Scand.* **1978**, *32*, 353.
(9) Lipczyńska-Kochany, E.; Iwamura, H. *J. Org. Chem.* **1982**, *47*, 527.
(10) Exner, O.; Hradil, M.; Mollin, J. *Collect. Czech. Chem. Commun.* **1993**, *58*, 1109.
(11) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Org. Chem.* **1990**, *55*, 3980.
(12) Remko, M.; Mach, P.; Schleyer, P. V. R.; Exner, O. *J. Mol. Struct.* **1993**, *279*, 139.
(13) Ventura, O.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 5754.
(14) Bagno, A.; Comuzzi, C.; Scorrano, G. *J. Am. Chem. Soc.* **1994**, *116*, 916.
(15) Yamin, L. J.; Ponce, C. A.; Estrada, M. R.; Tomas Vert, F. *J. Mol. Struct.* **1996**, *360*, 109.

10.1021/jo991251x CCC: $19.00
Published on Web 12/21/1999

oxygen[6,16,17] rather than the nitrogen or the OH group. However, Fourier transform ion cyclotron resonance (FT-ICR) studies of gas-phase basicities on the acetohydroxamic acid and its *N*-methyl and *O*-methyl derivatives[18] do not provide conclusive results. In this context, ^{14}N NMR measurements on acetohydroxamic acid in aqueous solution seem to support protonation on the oxygen.[14]

Another long-standing problem is the relative stability of the amide and imidic (RCOH═NOH) tautomeric forms.[1] Both forms can be present in either the *E* or the *Z* orientation about the C−N bond. However, only the amide form seems to be experimentally found.[1,10] On the other hand, several high level ab initio studies on formohydroxamic acid have yielded small energy differences between the tautomers.[12,19] These energetic stabilities contrast with the experimental data. Until now, no definitive explanation of these results has been provided.

Several theoretical studies at the semiempirical, INDO,[20] AM1,[4] and ab initio level[4,13−15,21−23] have been reported on hydroxamic acids. Most of these studies focused on conformational stabilities, especially in formohydroxamic acid. In addition, it is usually the energetic stability of the different anions and cations and the stability of the amide and imidic tautomers that are considered. These studies suggest that deprotonation occurs at the nitrogen, whereas protonation takes place at the carbonyl oxygen. However, thermodynamic considerations have not yet been taken into account.

As a prototype for more complex cases, this paper presents a detailed theoretical study of protonation processes in the acetohydroxamic acid in gas phase. The neutral form is considered in its different tautomeric and conformational isomers. In addition, the possible protonation sites are identified from the electrostatic potential distribution. For the first time, statistical models are developed for these protonation processes. We analyze the thermodynamic properties associated with protonation and the thermodynamic stability of the protonated species. In this way, we determine the proton affinities and the gas-phase basicities. Our aim is to use this work as a starting point for the theoretical and experimental study of more complex hydroxamic systems of biological interest in solution.

Computational Details

Molecular structures, potential electrostatic maps, and atoms in molecules properties are obtained using ab initio methodology at the MP2(frozen core)/cc-pVDZ level. This double-ζ correlation consistent basis set includes, by definition, polarization functions on hydrogen and heavy atoms. This basis set has been selected because it was developed on a rational basis for working at the MP2 (FC) level.[24] All the calculations are carried out using the GAUSSIAN 94 package.[25] Enthalpy, entropy, and Gibbs energy values are computed statistically with the PARTI program,[26] using the semiclassical model for rotation and the harmonic model for vibration.[26b,27]

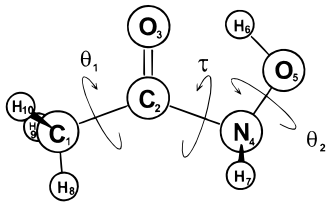

Figure 1. Numbering convention and C1 equilibrium structure of the amide tautomer of acetohydroxamic acid. The methyl torsional, θ_1, OH torsional, θ_2, and C−N bond torsional, τ, angles are also shown.

Results and Discussion

Our first concern is the stability of the amide and imidic tautomers of the acetohydroxamic acid. Therefore, we obtain the total molecular energy, on both systems, after full geometry optimization. The starting geometry for the amide form is taken from the HF/6-311G(d, p) data of Bagno et al.[14] The numbering convention, equilibrium geometry, methyl torsional angle θ_1 (H8C1C2O3), and OH torsional angle θ_2 (H6O5N4C2) are shown in Figure 1. The τ angle (O5N4C2O3) defines the rotation around the C−N bond. These three coordinates suffice to describe all of the conformational isomers. The equilibrium structure is found in a C1, non-planar, $\theta_1 = 65.7°$, $\theta_2 = 7.0°$, $\tau = -13.6°$ conformation. See Figure 1 and Table 1. The application of the atoms in molecules theory[28] show a bond path linking O_3 and H_6. A bond path is a line connecting the nuclei, along which the charge density is a maximum. The existence of such a line implies that the two nuclei are bonded to one another. In short, this *Z* isomer exhibits an intramolecular hydrogen bond, $O_5-H_6\cdots O_3$. This fact has been suggested, although not conclusively, by previous experimental[1,29] data and calculations at the AM1 level.[4b] Also, the methyl group is antieclipsed with respect to the O_3. This situation contrasts with the behavior of acetaldehyde, in which the methyl group eclipses the carbonyl oxygen. In acetaldehyde, evidence has been found that the eclipsed conformation is due to hyperconjugative interactions between the in-plane and out-of-plane methyl hydrogens and the carbonyl oxygen.[30] In the present case, the carbonyl oxygen is involved in the hydrogen bond. Therefore, its interaction with the methyl hydrogens is weakened. As a consequence, steric hindrance prevails over bonding interactions, and the methyl group adopts

(16) Berndt, D. C.; Fuller, R. L. *J. Org. Chem.* **1966**, *31*, 3312.
(17) Levi, A.; Modena, G.; Scorrano, G. *J. Am. Chem. Soc.* **1974**, *96*, 6585.
(18) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Org. Chem.* **1992**, *57*, 1621.
(19) Turi, L.; Dannenberg, J. J.; Rama, J.; Ventura, O. N. *J. Phys. Chem.* **1992**, *96*, 3709.
(20) Hilal, R.; Moustafa, H. *Int. J. Quantum Chem.* **1984**, *26*, 183.
(21) Nguyen, M. T.; Ha, T.-K. *THEOCHEM* **1982**, *88*, 127.
(22) Fitzpatrick, N. J.; Mageswaran, R. *Polyhedron* **1989**, *8*, 2255.
(23) Wu, D.-H.; Ho, J-.J. *J. Phys. Chem.* **1998**, *102*, 3582.
(24) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90(2)*, 1007.
(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94, Revision E.2*, Gaussian, Inc., Pittsburgh, PA, 1995.
(26) (a) Niño, A.; Muñoz-Caro, C. *QCPE Bull.* **1997**, *17*, 1. (b) Niño, A.; Muñoz-Caro, C. *Comput. Chem.* **1997**, *21*, 143.
(27) Lucas, K. *Applied Statistical Thermodynamics*; Springer-Verlag: New York, 1991.
(28) (a) Bader, R. F. W.; Nguyen-Dang, T. T. *Adv. Quantum Chem.* 1981, *14*, 63. (b) Bader, R. F. W. *Chem. Rev.* 1991, *91*, 893. (c) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, 1994.
(29) Hadži, D.; Peevoršek, D. *Spectrochim. Acta* **1957**, *10*, 38.
(30) Muñoz-Caro, C.; Niño, A.; Moule, D. C. *Theor. Chim. Acta* **1994**, *88*, 299.

Table 1. Structural Parameters for the Neutral and Protonated Forms of the Acetohydroxamic Acid Obtained at the MP2(FC)/cc-pVDZ Level[a]

parameter	neutral	O3 protonated	N4 protonated
C1C2	1.511	1.488	1.488
C2O3	1.231	1.320	1.188
C2N4	1.380	1.303	1.619
N4O5	1.405	1.361	1.390
H6O5	0.983	0.978	0.986
H7N4	1.020	1.021	1.036
H8C1	1.101	1.102	1.103
H9C1	1.100	1.099	1.103
$O_3\cdots H_6$	1.924	2.123	1.931
H10C1	1.100	1.103	1.099
H^+O3		0.974	
H^+N4			1.036
C1C2O3	124.7	123.9	134.5
N4C2O3	120.1	114.2	113.0
O5N4C2	113.8	125.3	111.4
H6O5N4	99.5	105.7	103.1
H7N4C2	116.9	122.8	110.5
H8C1C2	108.9	109.2	110.0
H9C1C2	112.5	111.4	109.9
H10C1C2	108.7	109.2	108.5
H^+O3C2		111.4	
H^+N4C2			110.5
N4C2O3C1	183.5	180.0	180.0
H8C1C2O3 (θ_1)	65.7	59.4	120.6
H6O5N4C2 (θ_2)	7.0	0.0	−0.6
O5N4C2O3 (τ)	−13.6	0.0	0.5
H7N4C2O3	216.5	180.0	240.1
H9C1C2H8	121.8	120.5	119.7
H10C1C2H8	−117.0	−118.9	−120.2
$H^+O3C2N4$		180.1	
$H^+N4C2H7$			−119.4

[a] Distances in angstroms and angles in degrees.

the antieclipsed conformation. The nitrogen is pyramidal, with a O5N4C2H7 angle of −129.9°. To assess the existence of conjugation with C_2, we locate the transition state for the C−N bond (τ angle). The resulting structure is 4983 cm^{-1} (14.2 kcal mol^{-1}) higher in energy than the equilibrium value. Consequently, the torsion about the C−N bond is highly restricted. This result contrasts with the torsional barrier for the C−N rotation found in methylamine,[31] 708.6 cm^{-1} (2.0 kcal mol^{-1}), and dimethylamine,[32] 1201.2 cm^{-1} (3.4 kcal mol^{-1}). This large difference cannot be attributed solely to conjugation. It must also be attributed to the existence of hydrogen bonding. The C−N distances for the equilibrium and the twisted structure are found to be 1.3800 and 1.4706 Å, respectively. This increase in the C−N distance is in agreement with a loss of conjugation. This fact is also supported by the increase, in absolute terms, of the pyramidalization angle (O5N4C2H7) from 129.9° to 111.2°. The conjugation can be visualized using a map of the Laplacian of the charge density(Figure 2).The negative values of the Laplacian correspond to zones of locally concentrated charge. Accordingly, the positive values correspond to zones of locally depleted charge density. In Figure 2, we observe a negative zone involving the O3, C2, and N4 atoms, which reveals the existence of conjugation among these atoms. The existence of conjugation is translated into a smaller conformational flexibility that contributes to stabilize the intramolecular hydrogen-bonded structure.

The most probable imidic structures,[13] see Figure 3, would be built from the previous geometric results of the amide form. At each considered conformation, the geometry is fully relaxed at the MP2(FC)/cc-pVDZ level. The energy differences refer to the most stable form (amide) and are shown in Figure 3. We observe that the imidic tautomer II is the most stable tautomer. The energy difference between the most stable form and this imidic structure is smaller than 1.0 kcal mol^{-1}. These results agree with the small difference in energy (even 1.3 kcal mol^{-1}) found in the formohydroxamic acid at different levels of theory.[12,19] However, the experimental findings[1] show only the amide tautomer. Clearly, these questions deserve further attention. Because only the amide tautomer is found experimentally, the present study will focus on this system.

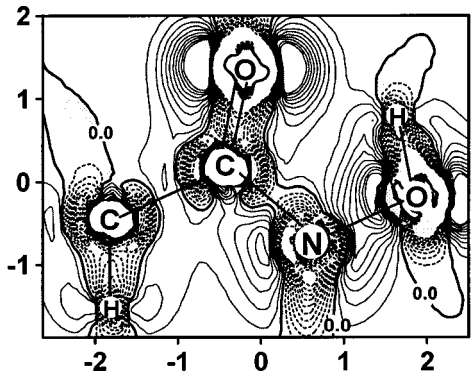

Figure 2. Laplacian of the charge density ($\nabla^2\rho$) for acetohydroxamic acid at the equilibrium position. The map corresponds to the O3C2N4 plane. Only the atoms closest to the plane are represented. Laplacian in atomic units (au) and distances in Angstroms. Interval between isolaplacian lines is 0.1 au. Shadowed zones correspond to $\nabla^2\rho<0$ values.

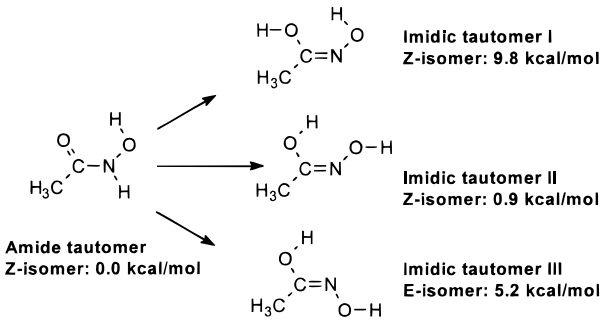

Figure 3. Most stable amide and imidic conformers of acetohydroxamic acid. Relative energies to the most stable tautomer are included.

To assess the importance of the different conformational isomers, a conformational analysis on the methyl torsional angle, θ_1, and the OH torsional angle, θ_2, is carried out in the amide form. We use a grid of points from 0° to 360° in θ_1 and θ_2, with increments of 90°. The result is shown in Figure 4. There, we observe the 3-fold periodicity of the methyl group with a barrier of ∼200 cm^{-1}. On this torsional coordinate, three minima appear (60°, −60°, and 180°). The OH torsion reaches a maximum near 180°, which is much higher in energy than the torsional barrier. Analysis of the geometry changes show that the nitrogen inverts as the OH group rotates. However, no inversion appears upon rotation of the methyl group. This fact can be understood from the values of the barriers to rotation and inversion.

To obtain the barriers to rotation and inversion, the corresponding transition states are determined. There-

(31) Smeyers, Y. G.; Villa, M.; Senent, M. L. *J. Mol. Spectrosc.* **1996**, *177*, 66.
(32) Senent, M. L.; Smeyers, Y. G. *J. Chem. Phys.* **1996**, *105*, 2789.

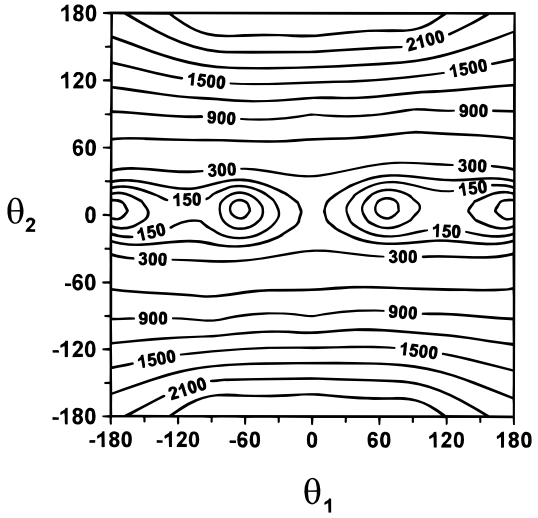

Figure 4. Potential energy surface for the methyl, θ_1, and OH torsion, θ_2, of acetohydroxamic acid. The interval between isopotential lines is 50 cm^{-1} in the range 0−200 cm^{-1} and 300 cm^{-1} from the 300 cm^{-1} line.

fore, we find the first-order saddle points corresponding to maxima for the methyl rotation, OH rotation, and nitrogen inversion coordinates. The maximum for the methyl rotation appears in an almost eclipsed conformation, $\theta_1 = 5.6°$, $\theta_2 = 7.4°$, and $\tau = -14.1°$. The barrier to methyl rotation is 190 cm^{-1}. This value contrasts with the larger barrier to methyl torsion (408.4 cm^{-1}) found in acetaldehyde.[33] As previously shown, the difference can be attributed to the lack of the stabilizing hyperconjugative interactions, between the methyl group and the carbonyl oxygen, in the acetohydroxamic acid. On the other hand, the transition state for the OH rotation appears for $\theta_1 = 77.0°$, $\theta_2 = 221.2°$, and $\tau = -15.4°$ where the hydroxyl hydrogen is located in a conformation opposite to that of equilibrium. The barrier is found to be 3819 cm^{-1} (10.9 kcal mol^{-1}). As previously shown, the transition state for the C−N rotation gives an energy barrier of 14.2 kcal mol^{-1}. These data include the hydrogen bond energy, and they show a very stable equilibrium structure. Finally, the transition state for the inversion of nitrogen appears in a planar conformation, $\theta_1 = 58.6°$, $\theta_2 = 0.0°$, $\tau = 0.0°$. The barrier to inversion is 442 cm^{-1} (1.3 kcal mol^{-1}). The difference in zero point energies (ZPE), 0.4 kcal mol^{-1} (the difference between the 49.3 kcal mol^{-1} ZPE for the equilibrium and the 48.9 kcal mol^{-1} ZPE for the transition state), is much smaller than the barrier. Thus, we can expect to find the pyramidal structure experimentally. These data explain the inversion of nitrogen upon rotation of the OH group. In this case, the variation of energy is much higher than the barrier to inversion, and therefore, the molecule inverts. However, the barrier to methyl rotation is much smaller than the inversion barrier. Consequently, the nitrogen does not invert.

Protonation of the neutral molecule can be analyzed from the molecular electrostatic potential. The electrostatic potential has proven to be useful in rationalizing interactions between molecules and in molecular recognition processes.[34,35] This is due to the fact that electrostatic

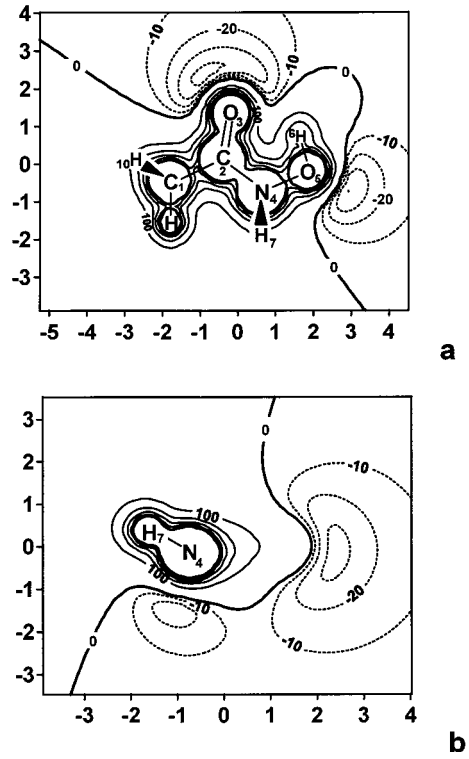

Figure 5. Electrostatic potential maps, in kcal mol^{-1} per unit electron charge, for the acetohydroxamic acid. Case a: XY plane. Case b: YZ plane. The interval between isopotential lines is 10 kcal mol^{-1} e^{-1} in the negative zone and 100 kcal mol^{-1} e^{-1} in the positive region. Distances in angstroms.

forces are primarily responsible for long-range interactions. Therefore, an electrostatic potential map is obtained at the equilibrium conformation. Figure 5a shows the map on the XY, $C_1C_2O_3$ plane. The map shows two electronegative zones around O3 and O5. These zones are appropriate for electrophilic attack and correspond to the lone pair of electrons of the oxygens. Figure 5b shows the electrostatic potential in the YZ plane passing through N4 and H7. We observe an electronegative zone corresponding to the lone pair of electrons of nitrogen and directed opposite to H7. Figure 5 shows that the electronegative zones created by the oxygens are further extended in space and deeper than the one created by the nitrogen. In short, the oxygens seem best suited for electrophilic attack. Consequently, there are three possible sites for protonation. However, because the molecular electrostatic potential is a static reactivity index,[34] it changes in the process. It is therefore not possible to affirm that these three sites are actually protonation points. Therefore, we simulate protonation by placing in each site an H^+ at an initial distance of 1 Å and at angles defined by the maximum of the electrostatic potential in Figure 5. After full geometry optimization, we find protonated structures in O3 and N4, but the optimization process is unable to converge in the case of O5. The problem is traced back to the nonpositive definitiveness of the Hessian in this zone. As would be expected, no stable protonated structure seems to exist on O5.

The molecular frame of the O3 protonated form is fully planar, giving rise to a C_s structure (Table 1). In this structure, we still find the intramolecular hydrogen bond

(33) Muñoz-Caro, C.; Niño, A.; Moule, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 399.

(34) Scrocco, E.; Tomasi, J. *Adv. Quantum Chem.* **1978**, *11*, 115.

(35) Leach, A. R. *Molecular Modelling*, 1st ed; Addison-Wesley Longman Limited: Reading, 1996.

and the antieclipsed conformation of the methyl group. The proton is placed at 0.974 Å of O3 with an H^+O3C2 angle of 111.4°. In the N4 protonated form, the structure is also planar with H7 and the proton found symmetrically in an out-of-plane position (Table 1). The H^+N4 distance, H^+N4C2 angle, and $H^+N4C2H7$ dihedral are found to be 1.036 Å, 110.5°, and −119.4°, respectively. These angle values show N4 in an sp^3-like structure. This fact favors a loss of conjugation and a pyramidal structure.

The dissociation energies computed from the bottom of the potential well (D_e) are determined as the energy difference between the neutral and charged species. For the O3 and the N4 protonated forms, the dissociation energies are 211.5 and 202.2 kcal mol^{-1}, respectively. We calculate the protonation energies, that is, proton affinities, correcting energy origins with zero point energies (49.3 kcal mol^{-1} (neutral), 57.4 kcal mol^{-1} (proton on O3), and 57.0 kcal mol^{-1} (proton on N_4)). The results are 203.4 and 194.5 kcal mol^{-1} for the O3 and N4, respectively. These data show that, on energetic (enthalpic) grounds, protonation on O3 is favored over protonation on N4 by 8.9 kcal mol^{-1}. This value for hydroxamic acid is smaller than the 14.8 kcal mol^{-1} obtained by Bagno et al.[14] for the formohydroxamic acid at the MP2(FC)/6-311++G(d,p)//HF/6-311G(d,p) level. The present result agrees with the conclusion of Decouzon et al.,[18] obtained by comparison of FT-ICR results for acetohydroxamic acids and alkyl-substituted amides, regarding preferred protonation on oxygen.

However, only at low temperatures, with the population of levels almost restricted to the ground state, are the energetic (enthalpic) considerations fully determinant of stability. To analyze the behavior of our systems on population of the energy levels we consider the ideal, pure protonation equilibria

$$ACO_3 + H^+ \rightleftharpoons ACO_3H^+$$
$$ACN_4 + H^+ \rightleftharpoons ACN_4H^+ \qquad (1)$$

where ACN_4 H^+ and ACO_3 H^+ represent the acetohydroxamic acid forms protonated at N4 and O3, respectively. The behavior will be analyzed considering the increments of enthalpy, entropy, and Gibbs energy for the reaction in eq 1. For the calculation of the different partition functions, the *A*, *B*, and *C* rotation constants are obtained at the equilibrium geometries. In turn, the vibration frequencies are determined from a normal mode analysis at the equilibrium structures. All of these data are collected in Table 2. The thermodynamic properties (ΔS, ΔH, and ΔG) corresponding to eq 1 are calculated as the difference between the corresponding property for the protonated and neutral species. The contribution from the proton is obtained by applying a monoatomic ideal gas model. All of the considered properties are computed at 1 atm and at a temperature of 298.15 K. The results are collected in Table 3. The ΔG (gas-phase basicities) data show that the O3 protonated form is the most stable species by 8.3 kcal mol^{-1}. In addition, it is clear that the stability arises from energetic (enthalpic) rather than from entropic contributions.

Our thermodynamic data have been obtained using a harmonic model for the vibrations. Thus, it is interesting to determine if the existence of low-frequency vibrations (Table 2) could significantly modify our results. As shown in previous studies,[36,37] the increase in the density of states arising from anharmonicity translates to an increase of entropy and a decrease of enthalpy and Gibbs energy. However, the results obtained on the effect of low-frequency vibrations in malondialdehyde[37] show that the difference is small (0.4%, 0.4%, and 1% for enthalpy, entropy, and Gibbs energy, respectively).

The variation of the relative stability between the protonated forms with changes in temperature can be determined by considering an equilibrium between the protonated forms

$$ACN_4H^+ \rightleftharpoons ACO_3H^+ \qquad (2)$$

For this process we compute the $\Delta\Delta S$, $\Delta\Delta H$, and $\Delta\Delta G$ values as the difference of the ΔS, ΔH, and ΔG values corresponding to the protonation equilibria from eq 1. In these calculations, ΔH and ΔG refer to the same energy origin, using the energy difference between both molecules, that is, 9.3 kcal mol^{-1}. The temperatures considered are 273.15, 298.15, 373.15, and 573.15 K, at a pressure of 1 atm. The results are shown in Table 4. We observe that the differences in enthalpy, entropy, and Gibbs energy decrease with temperature increases. In all the cases, the O3 protonated form is favored over the N4 form. As expected, this stability decreases slightly with

Table 2. *A*, *B*, and *C* Rotational Constants (GHz) and Harmonic Frequencies (ν in cm^{-1}) Obtained at the MP2(FC)/cc-pVDZ Level for the Neutral and Protonated Species of the Acetohydroxamic Acid[a]

	neutral	$O3H^+$	$N4H^+$		neutral	$O3H^+$	$N4H^+$
A	10.428	9.8327	9.6463	ν_{13}	1286.8	1117.5	1118.5
B	4.1041	3.9906	3.8022	ν_{14}	1387.2	1252.1	1303.4
C	3.0186	2.8912	2.8196	ν_{15}	1427.3	1339.6	1306.3
ν_1	81.7	92.3	38.9	ν_{16}	1469.7	1408.7	1395.8
ν_2	241.2	157.4	108.6	ν_{17}	1491.2	1461.5	1445.3
ν_3	293.5	270.9	277.9	ν_{18}	1559.6	1468.8	1464.0
ν_4	413.7	281.9	375.6	ν_{19}	1783.8	1500.3	1517.5
ν_5	433.2	399.1	381.9	ν_{20}	3102.0	1574.3	1624.1
ν_6	513.6	441.7	480.6	ν_{21}	3206.5	1799.3	1936.3
ν_7	637.7	586.8	535.2	ν_{22}	3214.8	3097.3	3092.6
ν_8	663.6	641.2	625.3	ν_{23}	3585.2	3197.9	3193.4
ν_9	956.1	701.8	844.3	ν_{24}	3608.5	3227.9	3235.4
ν_{10}	1016.0	951.8	983.2	ν_{25}		3607.2	3376.2
ν_{11}	1049.5	1009.5	1078.4	ν_{26}		3721.0	3458.2
ν_{12}	1092.0	1057.4	1081.1	ν_{27}		3778.0	3579.3

[a] The frequencies are ordered by increasing value.

Table 3. Thermodynamic Properties for the Protonation Processes in the Acetohydroxamic Acid at a Temperature of 298.15 K and a Pressure of 1 Atm

property	$O3H^+$	$N4H^+$
ΔH (kcal mol^{-1})	−204.6	−195.7
ΔS (cal mol^{-1} K^{-1})	−23.8	−21.9
ΔG (kcal mol^{-1})	−197.5	−189.2

Table 4. Difference of Thermodynamic Properties for the Protonation Process in Acetohydroxamic Acid at a Pressure of 1 Atm[a]

property	273.15 K	298.15 K	373.15 K	573.15 K
$\Delta\Delta H$ (kcal mol^{-1})	−8.93	−8.91	−8.88	−8.81
$\Delta\Delta S$ (cal mol^{-1} K^{-1})	−1.94	−1.90	−1.80	−1.65
$\Delta\Delta G$ (kcal mol^{-1})	−8.40	−8.34	−8.21	−7.86

[a] The data have been computed with two decimal figures to show the small variation with temperature.

(36) Muñoz-Caro, C.; Niño, A.; Senent, M. L. *Chem. Phys. Lett.* **1997**, *273*, 135.
(37) Niño, A.; Muñoz-Caro, C. *J. Phys. Chem. A* **1998**, *102*, 1177.

temperature increases. This fact is a consequence of the higher density of vibrational states in the N4 protonated forms (a contribution to the molecular partition function of 0.6×10^{-40} against a value of 0.1×10^{-40} for the O3 protonated form). At low temperatures, energetic (enthalpic) factors dominate, and the O3 protonated form is favored. However, as temperature increases, the population of states in the N4 protonated form is translated to a higher contribution of this form to the equilibrium mixture. We can expect that these results are not affected by explicit consideration of the low frequency vibrations. As previously shown,[37] the effect is small, and it appears in both protonated forms. Therefore, we can expect a cancellation of errors when computing the $\Delta\Delta S$, $\Delta\Delta H$, and $\Delta\Delta G$ values.

Conclusions

In this work, we have presented a theoretical study of the protonation processes in acetohydroxamic acid in the gas phase, using ab initio methodology at the MP2(FC)/cc-pDVZ level. We have found that the most stable amide form exhibits a hydrogen bond that stabilizes the *Z* isomer. The most stable imidic tautomer is a *Z* isomer that is 0.9 kcal mol^{-1} higher in energy than the amide form.

A conformational analysis of the amide form, the only one found experimentally, yields a barrier to methyl rotation of 190 cm^{-1} and a barrier to nitrogen inversion of 442 cm^{-1}. Our results show that the nitrogen inverts upon rotation of the OH group, whereas no inversion occurs when the methyl group rotates. We found that these facts are a direct consequence of the energy changes involved in the corresponding motions.

Calculated molecular electrostatic potentials show that the two oxygens and the nitrogen are possible protonation sites. However, we only found stable protonated structures at the nitrogen and carbonyl oxygen. Both protonated forms exhibited a planar frame.

We determined the proton affinities for protonation on the carbonyl oxygen and on the nitrogen. Protonation on the carbonyl oxygen is favored, on energetic (enthalpic) grounds, by 8.9 kcal mol^{-1}. Consideration of entropic contributions does not modify this result because the difference in Gibbs energies is 8.3 kcal mol^{-1}.

The study of the variation of entropy, enthalpy, and Gibbs energy shows that the nitrogen protonated form stabilizes slightly with an increase in the temperature, as a consequence of a higher density of vibrational states.

Acknowledgment. The authors wish to thank the Universidad de Castilla-La Mancha, the Junta de Comunidades de Castilla y León (Grant No. BU07/97), and the Universidad de Burgos (Grant No. N066-541A-640.00) for supporting this work.

JO991251X