The Gas-Phase Acidities of Substituted Hydroxamic and Silahydroxamic Acids: A Comparative ab Initio Study

Milan Remko[†]

Department of Pharmaceutical Chemistry, Comenius University, Odbojárov 10, SK-832 32 Bratislava, Slovakia

Received: January 30, 2002; In Final Form: March 28, 2002

The structure and gas-phase acidities of formohydroxamic and silaformohydroxamic acid derivatives R−M(═O)NHOH (R = H, CH_3, CF_3, and phenyl; M = C and Si) have been studied using the Becke3LYP functional of DFT theory and the two-layered ONIOM (B3LYP/6-311+G(d,p): AM1) method. The calculations showed that the thermodynamic stability of the neutral species and their anions depends on both the type of substituent R and the possibility for competitive existence of *O*- and *N*-anions resulting from the monodeprotonation of the hydroxamate and silahydroxamate moieties. The molecules of neutral acids should exist in several forms very close in energy. Thus formohydroxamic, acetohydroxamic, trifluoroacetohydroxamic, benzohydroxamic, trifluorosilaacetohydroxamic, and silabenzohydroxamic acids in the gas phase are *N*-acids. On the other hand, the $N(H)O^-$ anion is more stable in silaacetohydroxamic and silabenzohydroxamic acids, hence these acids in the gas phase are *O*-acids. The acidity increases in the order: RSi(═O)NHOH < RC(═O)NHOH (R = H, CH_3, CF_3, and phenyl). Their acidity order is CH_3M(═O)NHOH < HM(═O)-NHOH < Phe-M(═O)NHOH < CF_3M(═O)NHOH (M = C and Si). The highest gas-phase acidity (1336 kJ mol^{-1}) has been calculated for trifluoroacetohydroxamic acid. The acidities of phenyl-substituted derivatives computed using the hybrid ONIOM (B3LYP/6-311+G(d,p):AM1) method are in very good agreement with the full DFT ones and this method can be adopted to model large substituted hydroxamic acids.

1. Introduction

The structure and deprotonation of hydroxamic acid derivatives has been the subject of several theoretical investigations.[1−11] Because of the ease of formation of metal complexes, these compounds are important in analytical chemistry[3] and −CON-HO− grouping occurs in numerous biologically active compounds.[12] Many hydroxamates exhibit metalloproteinase inhibition activity[13,14] and some of them also act as efficient carbonic anhydrase inhibitors.[15−17] The hydroxamic moiety of these enzymatic inhibitors is present in the active site of metalloenzymes in the form of anion.[13−17] The existence of the silicon analogues of hydroxamic acids, silahydroxamic acids, has not been proved experimentally and therefore no structural details are available. Previous high-level theoretical calculations have been shown that the substitution of the central carbon atom with the silicon in the formohydroxamic acid significantly influences the structure and acidity by comparison with the parent compound.[10]

The aim of the present work is to provide a consistent and reliable set of gas-phase acidities for formohydroxamic and silaformohydroxamic acid derivatives R−M(═O)NHOH (R = H, CH_3, CF_3, and phenyl; M = C and Si) using a high-level model chemistry. Of particular interest are the molecular geometries, acidities, and how these properties change upon isosteric substitution of carbon atom in carbonyl compounds by silicon.

2. Computational Details

The geometries of formohydroxamic and silaformohydroxamic acid derivatives R−M(═O)NHOH (R = H, CH_3, CF_3 and Phenyl; M = C, Si) (Figure 1) were completely optimized with the Gaussian 98 program,[18] using the Becke3LYP/6-311+G-(d,p) method. For reason of comparison of two theoretical methods, the calculations of benzohydroxamic and silabenzohydroxamic acids have also been performed by means of the two-layered ONIOM[19,20] method. The ONIOM approach can be used to model very large substituents of substituted hydroxamic acids. The model system and real molecule (R) used for the two-layer ONIOM calculations are shown in Figure 1. The real systems consist of the entire benzohydroxamic and silabenzohydroxamic acid molecules. The model systems (MS) are formohydroxamic and silaformohydroxamic acids, respectively

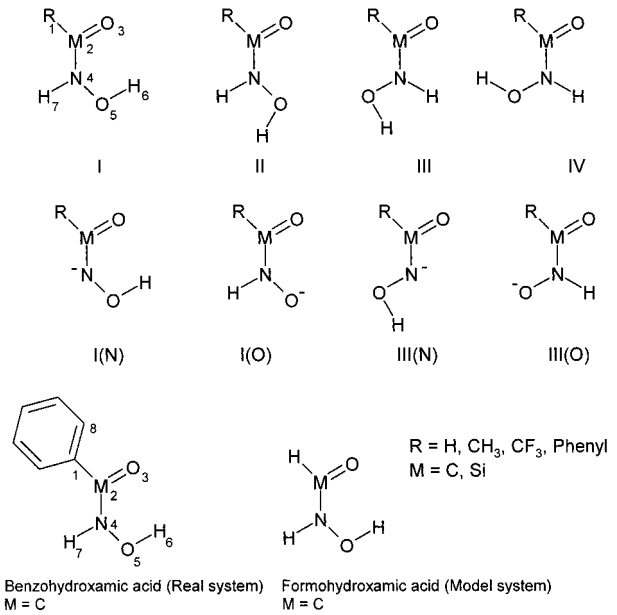

Figure 1. Structure and atom numbering of the species studied

[†] E-mail: remko@fpharm.uniba.sk.

10.1021/jp020300y CCC: $22.00
Published on Web 04/24/2002

TABLE 1: B3LYP/6-311+G(d,p) Optimized Geometries of Most Stable Conformers of Substituted Hydroxamic Acid Species and Their Silicon Derivatives

parameter[a]	HC(=O) NHOH	exptl[b]	$CH_3C(=O)$ NHOH	exptl[c]	$CF_3C(=O)$ NHOH	Phe-C(=O) NHOH	exptl[d]	HSi(=O) NHOH	$CH_3Si(=O)$ NHOH	$CF_3Si(=O)$ NHOH	Phe-Si(=O) NHOH
d[M(2)−R(1)]	1.101		1.508	1.505	1.543	1.489	1.498	1.472	1.856	1.946	1.841
d[M(2)−O(3)]	1.220	1.217	1.226	1.245	1.219	1.228	1.223	1.529	1.532	1.523	1.534
d[M(2)−N(4)]	1.355	1.312	1.365	1.333	1.340	1.374	1.316	1.707	1.714	1.694	1.713
d[N(4)−O(5)]	1.397	1.388	1.399	1.400	1.384	1.400	1.402	1.419	1.422	1.409	1.419
d[O(5)−H(6)]	0.977		0.979	0.75	0.977	0.980		0.966	0.966	0.967	0.966
d[N(4)−H(7)]	1.010		1.009	0.90	1.007	1.011		1.013	1.013	1.013	1.013
d[H(6)···O(3)]	2.080		1.998		2.107	1.963			3.711		
Θ[R(1)−M(2)−O(3)]	124.8	121.0	124.3	122.4	122.1	124.2	120.1	128.5	128.8	125.0	125.1
Θ [R(1)−M(2)−N(4)]	112.9	113.0	116.0	114.3	114.8	116.4	115.7	107.1	110.2	103.7	115.3
Θ [O(3)−M(2)−N(4)]	122.2	125.3	119.7	123.3	123.1	119.4	124.2	124.3	121.0	131.1	119.5
Θ [M(2)−N(4)−O(5)]	117.5	118.3	116.4	120.6	118.5	115.2		119.6	120.7	121.6	124.2
Θ [N(4)−O(5)−H(6)]	102.1	111.0	101.6	94	102.7	101.8		104.8	104.7	105.3	104.6
Θ [M(2)−N(4)−H(7)]	122.9	123.0	122.1	125	127.6	119.7		124.4	122.8	124.5	120.9
Φ[O(5)−N(4)−M(2)−R(1)]	−172.8		172.1		−179.4	−172.7	−176.6	14.9	15.7	−170.8	−10.2
Φ [O(5)−N(4)−O(2)−O(3)]	9.8		−10.5		0.9	8.8	3.8	−168.2	−167.3	13.9	172.8
Φ [H(7)−N(4)−M(2)−O(3)]	156.5		−152.2		177.9	143.8		−15.1	−16.5	174.0	17.3
Φ [H(7)−N(4)−M(2)−R(1)]	−26.0		30.4		−2.5	−37.6		168.0	166.4	−10.7	−165.7
Φ [H(6)−O(5)−N(4)−M(2)]	−5.5		6.0		−0.7	−3.5		−109.3	−111.9	−95.6	109.9
Φ [H(7)−N(4)−O(5)−H(6)]	−155.8		151.9		−178.1	−142.7		94.3	94.2	101.9	−92.5
Φ [O(3)−M(2)−C(1)−C(8)]						−23.2	−19.0		10.6		

[a] R=H or C; M=C or Si [b] Experimental values for formohydroxamic acid, ref 32. [c] Experimental values for acetohydroxamic acid hemihydrate, ref 33. [d] Experimental values for benzohydroxamic acid, ref 38.

(Figure 1). Because previous theoretical studies have been shown that the molecules of neutral formohydroxamic and silaformohydroxamic acids exist in more stable keto form,[10] the calculations of acidities were only performed for keto tautomers of the parent acids and their model systems (Figure 1). The geometric parameters of the model systems were taken from the values of the real system, except for the terminal hydrogen which is assumed to replace the carbon (silicon) of the C−C (Si−C) bond with a C−H (Si−H) distance of 1.1 (1.4) Å. The two levels of theory used for energy calculations were density functional theory[21,22] (DFT) at the Becke3LYP level[23−25] in conjunction with a polarized triple split valence 6-311+G(d,p) basis set for the high level (H) of theory and the semiempirical AM1 method[26] for the low level (L).

The integrated energy for the two-layered ONIOM approach is defined as[19]

$$E(\text{ONIOM2}) = E(\text{High, Model}) + E(\text{Low, Real}) - E(\text{Low, Model}) = E(\text{High, Model}) + \Delta E(\text{Low, Real} \leftarrow \text{Model}) \quad (1)$$

The gas-phase acidity $\Delta E(\text{A})$ was defined as the energy of deprotonation ΔE for reaction (A).

$$\text{AH(g)} \rightarrow \text{A}^-\text{(g)} + \text{H}^+\text{(g)} \quad \text{(A)}$$

The energy of deprotonation, ΔE, at $T = 0$ K, was computed using eq 2,

$$\Delta E(\text{A}) = E(\text{A}^-) - E(\text{AH}) \quad (2)$$

where E stands for the total energies of the stable conformations of the acid and its anion. For calculation of the deprotonation energies by means of the ONIOM method, the values of oniom extrapolated energies (E_{ONIOM}) were used.

The enthalpy of deprotonation, ΔH,[298] was computed using eq 3 and 4,

$$\Delta H^{298}(\text{A}) = \Delta E^{298}(\text{A}) + \Delta(pV) \quad (3)$$

$$\Delta E^{298} = [E^{298}(\text{A}^-) + {}^3/_2 RT] - E^{298}\,(\text{AH}) \quad (4)$$

where E^{298} stands for the total energies of the stable conformations of the acids and their anions (including the thermal energy correction at $T = 298.15$ K). In eq 3 we substituted $\Delta(pV) = RT$ (one mol of gas is obtained in the reaction (A)). The gas-phase Gibbs energy, ΔG^{298}, of the proton abstraction reaction may be calculated from

$$\Delta G^{298} = \Delta H^{298} - T\Delta S^{298} \quad (5)$$

The enthalpy of deprotonation was calculated using expression 3. The entropy contribution is given by

$$-T\Delta S^{298} = -T[S(\text{A}^-) + S(\text{H}^+) - S(\text{AH})] \quad (6)$$

For $T = 298$ K at the standard pressure, the second term $TS(\text{H}^+) = 32.5$ kJ mol^{-1}.[27] Thus,

$$\Delta G^{298} = \Delta H^{298} - T[S(\text{A}^-) - S(\text{AH})] - 32.5 \quad (7)$$

Notice that there is an inverse relationship between the magnitude of ΔG and the strength of the acid. The more positive the value of the ΔG, the weaker the acid. It has been shown[28−31] that the integrated MO approach, ONIOM, provides an ideal method for accurate calculations for large systems. For such molecules accurate calculations are often too expensive and out of reach.

3. Results and Discussion

Relative Energies and Molecular Structures. The selected structural parameters of the fully optimized hydroxamic and silahydroxamic acids under study are given in Table 1. An analysis of the harmonic vibrational frequencies of the optimized molecules at the two model levels applied revealed that these systems are minima (zero number of imaginary frequencies). To our knowledge no hydroximic tautomer of any hydroxamic acid has been observed. Experimental evidence[32,33] and previous theoretical calculations[1−11] of the molecular structure of hydroxamate and silahydroxamate moieties have been shown that these functional groups exist in the more stable keto form. Therefore all calculations in this work were carried out for this tautomer only. The neutral molecules [R−M(=O)NHOH (R = H, CH_3, CF_3; M = C, Si)] were considered in one set of

TABLE 2: Relative Ethalpies and Gibbs Energies (kJ mol^{-1}) of Studied Rotamers of Substituted Hydroxamic Acids and Their Silicon Derivatives

	HC(═O)NHOH		CH_3C(═O)NHOH		CF_3C(═O)NHOH		Phe-C(═O)NHOH	
species	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}
neutral molecules								
I	0	0	0	0	0	0	0	0
							0[a]	0[a]
III	3.5	3.6	6.3	6.2	12.7	17.8	19.6	18.5
							13.4[a]	13.5[a]
anions								
I(N$^-$)	0	0	0	0	0	0	0	0
							0[a]	0[a]
I(O$^-$)	46.6	45.6	56.5	55.3	53.4	52.3	60.3	59.3
							51.5[a]	52.0[a]
III(O$^-$)	33.9	33.1	32.4	28.5	60.0	59.7	38.2	38.4
							39.1[a]	39.2[a]
III(N$^-$)	34.2	31.0	45.5	40.7	55.2	53.3	65.8	61.9
							42.9[a]	41.2[a]

	HSi(═O)NHOH		CH_3Si(═O)NHOH		CF_3Si(═O)NHOH		Phe-Si(═O)NHOH	
species	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}	ΔH^{298}	ΔG^{298}
neutral molecules								
I	3.4	2.8	6.7	4.5	0	0	3.5	6.1
							0[a]	0[a]
III	0	0	0	0	0.5	2.5	0	0
							−0.9[a]	4.3[a]
anions								
I(N$^-$)	0	0	5.6	6.8	0	0	7.6	10.8
							7.7[a]	3.5[a]
I(O$^-$)	3.1	4.0	14.3	15.3	9.8	14.1	18.6	21.1
							12.1[a]	7.3[a]
III(N$^-$)	12.4	12.3	15.7	15.3	17.3	18.2	24.1	21.3
							19.3[a]	14.1[a]
III(O$^-$)	2.2	3.5	0	0	23.1	21.8	0	0
							0[a]	0[a]

[a] ONIOM (Becke3LYP/6-311+G(d,p):AM1) method

hydroxamic structures (**I**−**IV**), and the anions in four sets [**I(N)**, **I(O)**, **III(N)**, and **III(O)**], Figure 1. The relative enthalpies and Gibbs energies of stable isomers and anions of the compounds studied with respect to the most stable species are reported in Table 2. The relative free energies of hydroxamic acid species and their siladerivatives follow the enthalpy changes and conformational entropy contribution for isomerization reactions is small.

Derivatives of Hydroxamic Acid. Four planar conformations (**I**−**IV**) of the hydroxamic acid derivatives were used as initial structures for geometry optimization. Two distinct final nonplanar conformers were obtained (Table 2). Structure **II** optimized to **I** conformer and conformer **IV** upon optimalization became **III**. These nonplanar structures deviate from planarity in two ways. The more important is the nonplanar conformation around the N−O bond displacing the OH hydrogen atom out of the plane of N−C═O heavy atoms. In conformer **I** this displacement is very small (the values of about 6° to −7° were found, Table 1), which is due to the mutual electrostatic attraction of hydrogen and oxygen atoms via intramolecular hydrogen bond.

The inspection of the distances between nonbonding H···O atoms in the most stable conformer **I** of acids studied shows that these lengths are within the range of 1.99−2.11 Å, which is substantially less than the sum of the van der Waals radii[34] of oxygen and hydrogen (2.6 Å) (Table 1). The relative stability of hydrogen-bonded structure **I** in the compounds studied increase as follows: HC(═O)NHOH < CH_3C(═O)NHOH < CF_3C(═O)NHOH < Phe-C(═O)NHOH.

In the absence of this intramolecular stabilization in conformer **III** of formohydroxamic acid and its substituted derivatives studied the hydroxy group is oriented perpendicularly to the plane of the N−C═O group. The dihedral angle H(6)−O(5)−N(4)−C(2) is for conformer **III** in the range 90−120°.

Less important is a nonplanar configuration on the nitrogen atom. For both stable conformers (**I** and **III**) of hydroxamic acid derivatives the structures with pyramidal nitrogen conformation were found. Only exception is the conformer **I** of trifluoroacetohydroxamic acid with practically planar arrangement of the −N(H)OH moiety stabilized via intramolecular hydrogen bond N(4)−H(7)···F with the length of 2.29 Å which is less than the sum of the van der Waals radii[34] of hydrogen and fluorine atoms (2.55 Å). In the benzohydroxamic acid the C(1)−C(2) bond length of 1.489 Å is a single bond length between sp^2 hybridized carbon atoms since the dihedral angle Φ [O(3)−C(2)−C(1)−C(8)] between the hydroxamate group and the benzyl ring is −23.2°. Slightly lower value of −32.8° for this dihedral angle was found by the ONIOM2 method. However, the calculations of the individual conformers of benzohydroxamic acid using the ONIOM method gave the same order of their relative stability (Table 2).

Some experimental studies on the structure of hydroxamic acid derivatives using X-ray[33] and ^{17}O NMR[35] concluded that the most stable structure was **I**. In the crystalline phase, conformations **II** and **III** are usually found,[32,36−38] but this is due to the additional stabilization derived from networks of intermolecular hydrogen bonds. In the absence of gas-phase data the geometry of the parent compounds only can be compared with X-ray data of formohydroxamic, acetohydroxamic, and benzenehydroxamic acids (Table 1). Disregarding the position of the hydrogen atoms, evidently unreliable in the X-ray work, the heavier atom bond lengths appear to be well reproduced by

TABLE 3: Gas-Phase Acidities (Enthalpies ΔH and Gibbs Energies ΔG) of the Substituted Hydroxamic Acids and Their Silicon Derivatives (at 298.15 K)

no.	reaction	ΔH/kJ mol^{-1}	ΔG/kJ mol^{-1}	ΔH^{exptl}/kJ mol^{-1}	ΔG^{exp}/kJ mol^{-1}
I	HC(═O)NHOH − H^+ → HC(═O)N(−)OH	1431.4	1401.9		
II	CH_3C(═O)NHOH − H^+ → CH_3C(═O)N(-)OH	1440.8	1412.1	1449 ± 9.6	1419 ± 8.4
III	CF_3C(═O)NHOH − H^+ → CF_3C(═O)N(-)OH	1361.4	1335.9		
IV	Phe-C(═O)NHOH − H^+ → Phe-C(═O)N(-)OH	1410.7	1380.3		
		1418.2[a]	1386.9[a]		
V	HSi(═O)NHOH − H^+ → HSi(═O)N(−)OH	1451.6	1419.2		
VI	CH_3Si(═O)NHOH − H^+ → CH_3Si(═O)NHO(−)	1467.7	1435.9		
VII	CF_3Si(═O)NHOH − H^+ → CF_3Si(═O)N(-)OH	1389.8	1356.7		
VIII	Phe-Si(═O)NHOH − H^+ → Phe-Si(═O)NHO(−)	1440.5	1411.1		
		1438.0[a]	1414.2[a]		

[a] ONIOM (Becke3LYP/6-311+G(d,p):AM1) method.

the most stable conformer **I** of these aids. However, the geometries of substituted hydroxamic acids in the crystalline phase are controlled by intermolecular hydrogen bonds and are not exactly comparable with those of the free molecules.

Derivatives of Silahydroxamic Acid. In the case of silicon species, the intramolecular electrostatic stabilization is in comparison with the parent hydroxamic acids less important. In the absence of intramolecular electrostatic stabilization the full optimization of four rotamers (**I**−**IV**) of silaacids lead to two geometrically different structures (**I** and **III**). **II** became upon optimization **I**, and **IV** became **III**. The most stable structure of silaformohydroxamic acid, its methyl and phenyl derivatives is nonplanar conformer **III**. For trifluromethyl derivative, the structure corresponding to the conformer **I** was found to be the most stable species. In the most stable rotamers of silahydroxamic acid derivatives the H···O distances are substantially higher than the sum of the van der Waals radii (Table 1) and intramolecular polarization by means of the H bond does not play any part. Upon the carbon-by-silicon substitution, the stability of hydroxamic tautomers in comparison with the hydroximic ones considerably increases.[10] However, there is no unambiguous enthalpy preference for two geometrically different silahydroxamic acid rotamers (Table 2). The substantial elongation of the M−N distance to about 1.7 Å in silaacids (Table 1) causes a considerable weakening of the stabilizing effect of intramolecular hydrogen bond in these species. In the absence of any conjugation between Si═O and NOH groups in silaformohydroxamic, silaacetohydroxamic and silabenzohydroxamic acids the most stable conformer is the nonplanar **III** form (Table 2) with the uniform distribution of the O(3)···H distances of about 3.1 Å. The equilibrium distribution of the two stable conformers of silaacids studied (at 298 K), based on the calculated Gibbs energies, is 76:24 [HSi(═O)NHOH], 86:14 [CH_3Si(═O)NHOH], 27:73 [CF_3Si(═O)NHOH], and 92:8 [Phe−Si(═O)NHOH]. According to the ONIOM2 calculations of phenyl derivative, the structure corresponding to the conformer **I** was found to be the most stable species. The H···O distance in this conformer is much lower than the sum of the van der Waals radii with d[H(6)−O(3)] = 2.58 Å, the distance of an intramolecular hydrogen bond. However, the energy differences computed between the two stable conformers are small (Table 2) and both rotamers can coexist.

In the silabenzohydroxamic acid, the computed C(1)−Si(2) bond length of 1.841 Å is close to the average value of that bond (1.868 Å) found in crystalline organic compounds.[39] Apeloig and Sklenak[40] computed for structurally related diphenylsilanone bond distance Car−Si = 1.853 Å (HF/6-31G** method). Thus this bond is a single bond between sp^2 hybridized carbon and silicon atoms since the dihedral angle Φ [O(3)−Si(2)−C(1)−C(8)] between the silahydroxamate group and the benzyl ring is 10.6°.

Gas-Phase Acidities. The deprotonation of substituted hydroxamic acids has been investigated experimentally,[35,41−43] more recently even in the gas phase.[44] However, no deprotonation and/or protonation of silahydroxamic acid derivatives has been studied. Table 3 contains acidities of formohydroxamic and silaformohydroxamic acid derivatives investigated. With respect to the possible existence of several stable rotational conformers (Table 2) the enthalpy of deprotonation may be computed between two arbitrary species, but only the differences between the most stable species can have physical meaning and can be compared with experiments. Of the four anions of hydroxamic acids studied [**I(N$^-$)**, **I(O$^-$)**, **III(O$^-$)**, and **III(N$^-$)**], the *N*-anion **I(N$^-$)** is most stable. This structure is stabilized by the five-membered intramolecular hydrogen bond O−H···$^-$O (the distance d[H(6)···O(3)] is in the range 1.86−1.93 Å). Hence, formohydroxamic acid and its methyl, trifluoromethyl, and phenyl derivatives behave as *N*-acids in the gas phase, which agrees with the results of theoretical calculations for formohydroxamic acid carried out at various levels of theory.[2,6,7,10] The acidities of phenyl-substituted derivatives computed using the hybrid ONIOM (B3LYP/6-311+G(d,p):AM1) method are in very good agreement with the full DFT ones (Table 3), and this method can be adopted to model large substituted hydroxamic acids.

For hydroxamic acids studied the acidities increase in the order: CH_3C(═O)NHOH < HC(═O)NHOH < Phe-C(═O)NHOH < CF_3C(═O)NHOH (Table 3). The same order of acidities was also experimentally observed for structurally related substituted carboxylic acids.[45] The electronegative trifluoromethyl substituent increases the acidity (by about 40 kJ mol^{-1}) in comparison with the parent formohydroxamic acid. The greater acidity of trifluoroacetohydroxamic acid can be attributed, in part, to the extra electron-attracting inductive effect of the electronegative fluorine atoms. It also stabilizes the trifluoroacetohydroxamate anion by dispersing its negative charge. The negative charge is more spread out in the trifluoroacetohydroxamate ion than in the parent formohydroxamate anion. Dispersal of charge always makes species more stable.[46−48] The increased stabilization of the conjugate base of trifluoroacetohydroxamic acid increases the strength of the acid (Table 3). Electron donation by the −CH_3 group in acetohydroxamic acid destabilizes the anion of this acid and reduces its acidity in comparison with the formohydroxamic acid. Phenyl group by means of its inductive effect disperses negative charge in the anions of benzohydroxamic acid less effectively than the −CF_3 substituent and benzohydroxamic acid is slightly more acidic than the formohydroxamic acid (Table 3). The increased acidity of trifluoroacetohydroxamic acid in comparison with the

acetohydroxamic acid well correlates with their inhibitory activity toward the human carbonic anhydrase II.[15] It is well-known that trifluoroacetohydroxamic acid is about 10 times more potent inhibitor[15] and that these hydroxamic acids bind to zinc of this enzyme through the coordination of ionized nitrogen directly to zinc.

Decouzon et al.[44] have experimentally examined acidity of acetohydroxamic acid. The computed enthalpy and Gibbs energy (1440.8 and 1412.1kJ mol^{-1}) correspond well to the experimentally estimated quantities (Table 3). The acidity of formohydroxamic and silaformohydroxamic acids was recently investigated at the high-level CBS-Q theory.[10] Enthalpies 1425.2 kJ mol^{-1} (formohydroxamic acid) and 1449.9 kJ mol^{-1} (silaformohydroxamic acid) are slightly lower than our B3LYP values (Table 3). The CBS-Q approximate a high-level calculation with a very large basis set. The comparison of the B3LYP results with this very accurate method shows that density functional theory performs quite well and should be used as a relatively inexpensive alternative for investigation of acidity of larger organic systems.

Of the four stable *O*- and *N*-anions of silaformohydroxamic acid investigated the HO−N^- anion **I(N^-)** is most stable (Table 2); hence, silaformohydroxamic acid is computed to be an *N*-acid in the gas phase. However, a recent comparative ab initio study[49] of thermodynamic stability of carbonyl and silacarbonyl anions has been shown that the unsubstituted silaformohydroxamic acid, with respect to the competitive existence of multiple deprotonation sites (*O*-, *N*-, and *Si*-anions), behaves in gas phase as *Si*-acid. In substituted silahydroxamic acids there are only two possible deprotonation sites (*O*- and *N*-anions). The deprotonation of trifluorosilaacetohydroxamic acid gives the *N*-anion as the most stable species. On the other hand, for methyl and phenyl substituted sila acids the *O*-anion represents the most stable form and these acids behave in the vapor phase as *O*-acids.

The higher acidity of silaacids in comparison with the parent carboxylic acid[50] has been explained on the basis of electronegativity and the concept of charge capacity introduced by Politzer et al., ref 51. The less electronegative silicon has a higher charge capacity than carbon, which results in a larger stabilization of silicon containing anions in comparison with carboxylate. The dispersion of charge is largest in the acids containing the Si═O double bond. For hydroxamic acids and their siladerivatives, the reverse order of acidity was found. The acidity increases in the order: RSi(═O)NHOH < RC(═O)-NHOH (R = H, CH_3, CF_3, and phenyl), Table 3. The reverse acidity order of hydroxamic and silahydroxamic acids by comparison with carboxylic acids could be explained by the extraordinary stabilization of hydroxamic acid anion by strong intramolecular hydrogen bond. This intramolecular hydrogen bond is even more important than in rotamers of neutral formohydroxamic acid. Higher charge capacity of the less electronegative silicon which results in a larger stabilization of silicon containing anions in comparison with parent carbon acids is not sufficient to overcome the hydrogen bond stabilization in the hydroxamate.

4. Conclusions

The density functional Becke3LYP/6-311+G(d,p) method has been applied to study the structure and acidity of eight substituted hydroxamic and silahydroxamic acids R−M(═O)-NHOH (R = H, CH_3, CF_3 and phenyl; M = C and Si). The calculations of benzohydroxamic acid and its sila-derivative were also carried out by means of two-layered ONIOM (B3LYP/6-311+G(d,p):AM1) method. Using the theoretical methods the following conclusions can be drawn.

(1) The thermodynamic stability of the neutral species and their anions depends on both the type of substituent R and the possibility for competitive existence of *O*- and *N*-anions resulting from the monodeprotonation of the hydroxamate and silahydroxamate moieties.

(2) The formohydroxamic, acetohydroxamic, trifluoroacetohydroxamic, benzohydroxamic, trifluorosilaacetohydroxamic, and silabenzohydroxamic acids in the gas-phase behave as *N*-acids. On the other hand, the N(H)O^- anion is more stable in silaacetohydroxamic and silabenzohydroxamic acids; hence, these acids in the gas phase are *O*-acids.

(3) The acidity increases in the order: RSi(═O)NHOH < RC(═O)NHOH (R = H, CH_3, CF_3, and phenyl). Their acidity order is CH_3M(═O)NHOH < HM(═O)NHOH < Phe-M(═O)-NHOH < CF_3M(═O)NHOH (M = C and Si).

(4) Changes in acidities upon carbon-by-silicon substitution are rationalized on the basis of different electronegativities, charge capacity (softnees) of these atoms and relative stability of individual species.

(5) The ONIOM (B3LYP/6-311+G(d,p):AM1) level of treatment can provide acidities in very good agreement with the results computed at the full Becke3LYP level, at a fraction of computational cost.

Acknowledgment. This work was supported by the Slovak Ministry of Education (Grant No. 1/7361/20).

References and Notes

(1) Turi, L.; Dannenberg, J. J.; Rama, J. B.; Ventura, O. N. *J. Phys. Chem.* **1992**, *96*, 131.
(2) Remko, M.; Mach, P.; Schleyer, P. v. R.; Exner, O. *J. Mol. Struct.* (*THEOCHEM*) **1993**, *279*, 139.
(3) Bagno, A.; Comuzzi, C.; Scorrano, G. *J. Am. Chem. Soc.* **1994**, *116*, 916.
(4) Stinchomb, D. M.; Pranata, J. *J. Mol. Struct.* (*THEOCHEM*) **1996**, *370*, 25.
(5) Yamin, L. J.; Ponce, C. A.; Estrada, M. R.; Vert, F. T. *J. Mol. Struct.* (*THEOCHEM*) **1996**, *360*, 109.
(6) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J. *J. Phys. Chem.* **1995**, *99*, 131.
(7) El Yazal, J.; Ping Pang, Y. *J. Phys. Chem.* **1999**, *A103*, 8346.
(8) Remko, M.; Lyne, P. D.; Richards, W. G. *Phys. Chem. Chem. Phys.* **1999**, *1*, 5353.
(9) Yen, S. J.; Lin, Ch. Y.; Ho, J. J. *J. Phys. Chem.* **2000**, *A104*, 11771.
(10) Remko, M.; Šefčíková, J. *J. Mol. Struct.* (*THEOCHEM*) **2000**, *528*, 287.
(11) Denis, P.; Ventura, O. N. *J. Mol. Struct.* (*THEOCHEM*) **2001**, *537*, 173.
(12) Wolff, M. E., Ed. *Burger's Medicinal Chemistry and Drug Discovery*, 5th ed.; John Wiley & Sons: New York, 1996, 1997; Vols. 3 and 5.
(13) Whittaker, M.; Floyd, C. D.; Brown, P.; Gearing, A. J. H. *Chem. Rev.* **1999**, *99*, 2735.
(14) Nagase, H.; Woessner, J. F., Jr. *J. Biol. Chem.* **1999**, *274*, 21491.
(15) Scolnick, L. R.; Clements, A. M.; Liao, J.; Crenshaw, L.; Hellberg, M.; May, J.; Dean, T. R.; Christianson, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 850.
(16) Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2000**, *43*, 3677.
(17) Kimura, E. *Acc. Chem. Res*. **2001**, *34*, 171.
(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
(19) Svensson, M.; Humbel, S.; Froese, R. D. J.; Matsubara, T.; Sieber, S.; Morokuma, K. *J. Phys. Chem.* **1996**, *100*, 19357.

(20) Humbel, S.; Sieber, S.; Morokuma, K. *J. Chem. Phys.* **1996**, *105*, 1959.
(21) Parr, R. G.; Yang, L. W. *Density-Functional Theory of Atoms and Molecules;* Oxford University Press: New York, 1994.
(22) Neumann, R.; Nobes, R. H.; Handy, N. C. *Mol. Phys*. **1996**, *98*, 1.
(23) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3038.
(24) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(25) Yang, L. W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785.
(26) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(27) Alberty, R. A.; Silbey, R. J. *Physical Chemistry*, 2nd ed.*;* J. Wiley & Sons: New York, 1997; p 878.
(28) Froese, R. D. J.; Morokuma, K. *Chem. Phys. Lett*. **1999**, *305*, 419.
(29) Vreven, T.; Morokuma, K. *J. Chem. Phys.* **1999**, *111*, 8799.
(30) Remko, M.; Lyne, P. D.; Richards, W. G. *Phys. Chem. Chem. Phys*. **2000**, *2*, 2511.
(31) Vreven, T.; Morokuma, K. *J. Comput. Chem.* **2000**, *21*, 1419.
(32) Larsen, I. K. *Acta Crystallogr., Sect. B,* **1988**, *44*, 527.
(33) Bracher, B. H.; Small, R. W. H. *Acta Crystallogr*. **1970**, *26*, 1705.
(34) Pauling, L. *The Nature of The Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p 260.
(35) Lipczynska-Kochany, F.; Iwamura, H. *J. Org. Chem.* **1982**, *47*, 5277.
(36) Nielsen, B. B.; Larsen, I. K. *Acta Crystallogr., Sect. C* **1993**, *49*, 810.
(37) Due, L.; Rasmussen, H.; Larsen, I. K. *Acta Crystallogr., Sect. C* **1987**, *43*, 582.
(38) Podlaha, J.; Cisarova, I.;. Soukupova, L.; Schraml, J. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1273.
(39) Lide, D. R., Ed. *CRC Handbook of Chemistry and Physics*, 77th ed.; CRC Press: New York, 1996; pp 9−10.
(40) Apeloig, Y.; Sklenak, S. *Can. J. Chem.* **2000**, *78*, 1496.
(41) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376.
(42) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T. Y.; Satish, A.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330.
(43) Decouzon, M.; Ertl, P.; Exner, O.; Gal, J. F.; Maria, P. C. *J. Am. Chem. Soc.*, **1993**, *115*, 12071.
(44) Decouzon, M.; Exner, O.; Gal, J. F.; Maria, P. C. *J. Org. Chem*. **1990**, *55*, 3980.
(45) Cumming, J. B.; Kebarle, P. *Can. J. Chem.* **1978**, *56*, 1.
(46) Remko, M.; Liedl, K. R.; Rode, B. M. *Chem Phys. Lett.* **1996**, *263*, 379.
(47) Remko, M.; Van Duijnen, P. T. *Chem Phys. Lett.* **1999**, *308*, 242.
(48) Remko, M.; Smieško, M.; Van Duijnen, P. T. *Mol. Phys.* **2000**, *98*, 709.
(49) Remko, M. *Phys. Chem. Chem. Phys*. **2000**, *2*, 1113.
(50) Remko, M. *Mol. Phys.* **1999**, *96*, 1677.
(51) Politzer, P.; Huheey, J. E.; Murray, J. S.; Grodzicki, M. *J. Mol. Struct.* (*THEOCHEM*) **1992**, *259*, 99.