The Gas-Phase Acidity and the Acidic Site of Acetohydroxamic Acid: A FT-ICR Study

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Summary: Gas-phase acidities of acetohydroxamic acid and its *O*-methyl and *N*-methyl derivatives have been measured by Fourier transform ion cyclotron resonance and compared to those of acetamide and *N*-methylacetamide. These results together with the analysis of collision-induced dissociation spectra of the corresponding deprotonated species lead to the conclusion that acetohydroxamic acid behaves essentially as a NH acid in the gas phase.

The structural chemistry of hydroxamic acids contains still unresolved problems, like the reason for their relatively high acidity and the structure of the corresponding anions.[1] In principle, two possible tautomeric structures of the acid, **1a** and **1b**, can produce three anions, **2a–c**.

While **1a** seems to be the only form detected under various conditions,[1] the structure of the anion has been subject of controversy. Older reviews[2] and even recent data collections[3] assume that the bearer of the acidic properties is the OH hydrogen leading to **2a**. The same structure was inferred from many experimental studies in the crystalline state[4,5] or in solution;[6-11] sometimes the presence of another form in smaller amount was admitted.[6-8] This view was challenged by one of the authors in favor of **2b** as the predominant form.[12-15] Original proofs based on IR,[12,13] UV,[12,14] and pK values[15] were later confirmed by ^{17}O NMR in solution,[16] and XPS in the solid state.[17]

Recently, equilibrium acidities in dimethyl sulfoxide were reported.[18] *N*- and *O*-alkyl effects on pK_{HA}'s and on oxidation potentials of hydroxamate anions indicate NH ionization. Nevertheless, oxidation potential measurements in methanol admit OH ionization in addition.

In order to understand the conflicting results one must consider that the equilibrium **2a** ⇌ **2b** depends both on solvent and on the structure of R, i.e. electron-attracting substituents R influence more the NH than the OH hydrogen and favor[15,17] **2b** against **2a**. Moreover, some structural proofs are open to criticism. Particularly, comparisons of acidities of hydroxamic acids **1** with that of *O*-alkyl and *N*-alkyl derivatives[7-11,18] neglect the substituent effect of the alkyl group. An attempt to account for this effect[15] was based only on its polar character. The effect of intramolecular hydrogen bonding[1,18-20] in **2b** and **1a** was often neglected.

We report in Table I the gas-phase acidities of acetohydroxamic acid **3**, *O*-methylacetohydroxamic acid **4**, and *N*-methylacetohydroxamic acid **5**, together with those of simple model compounds acetamide **6** and *N*-methylacetamide **7**.

Proton transfer equilibria were monitored by Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry,[21] using the electromagnet spectrometer built at the University of Nice–Sophia Antipolis, and according to an experimental procedure already described.[21b]

Our major goal was to assign the structure of the deprotonated acetohydroxamic acid under conditions corresponding to the unsolvated species by comparing the acidities of compounds **3–7** and by comparing the collision induced dissociation (CID) spectra of the pertinent ions.

Scheme I

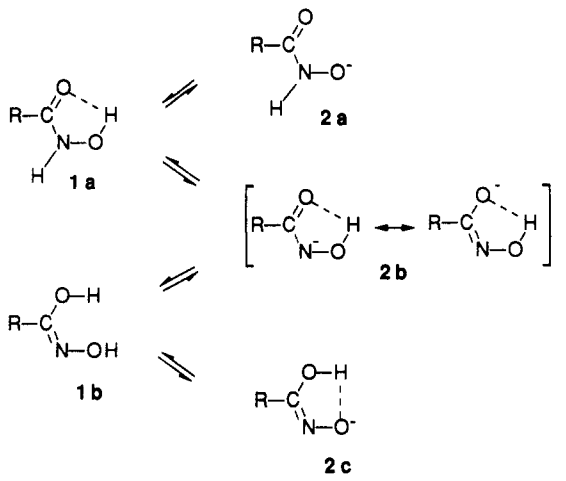

Table I. Gas-Phase Acidities of Acetohydroxamic Acid, Acetamide, and Their Methyl Derivatives (kcal mol^{-1})

entry	compounds[a]	$\Delta G°_{acid}$[b]
3	MeCONHOH	339.1
4	MeCONHOMe	343.7
5	MeCONMeOH	346.9
6	$MeCONH_2$	355.0[c]
7	MeCONHMe	354.5

[a] All chemicals used were commercially available except *O*-methylacetohydroxamic acid[23] and *N*-methylacetohydroxamic acid[24] prepared according to the literature. [b] Within this range the *relative* values are accurate to ±0.2 kcal mol^{-1}. An uncertainty of up to ±2 kcal mol^{-1} on the absolute $\Delta G°_{acid}$'s is inherent to the reference scale.[22] Bayard-Alpert gauge readings of the partial pressures have been corrected according to ref 25. [c] Taft, R. W.; Gal, J.-F. Unpublished result. The value given in ref 22 was misprinted.

The FT-ICR CID spectra were obtained as described elsewhere.[21a,c] Ions of significant intensity obtained by

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Table II. Ions Obtained by Collision-Induced Dissociation of Deprotonated Acetohydroxamic Acid, Acetamide, and Methyl Derivatives[a]

	formation (relative abundance)[b]						
precursor	CH_2N^-	CH_3O^-	$C_2H_2N^-$	CNO^-	$C_2H_2NO^-$	$C_2H_2O_2^-$	$C_2H_3O_2^-$
MeCONHOH				100			
MeCONHOMe		35	10	100			
MeCONMeOH						42	100
$MeCONH_2$			7	100			
MeCONHMe[c]	25			100	46		

[a] Parent ion kinetic energy, 50 eV; collision gas, argon; total pressure, ca. 2×10^{-4} Pa; proton abstraction by *t*-BuO^- generated by dissociative electron capture of *tert*-butyl nitrite. [b] Ions signals of intensity at least 2-fold compared to the background noise are reported. Composition of ions is deduced from exact mass measurements. [c] At a kinetic energy of 50 eV, only a weak fragmentation is observed; reported results correspond to 120 eV.

dissociation of deprotonated acids **3**–**7** are given in Table II.

A salient feature of Table I is that the two methyl derivatives **4** and **5** are weaker acids (Gibbs energies of deprotonation, $\Delta G°_{acid}$, are larger) than unsubstituted acetohydroxamic acid **3**; the *N*-methyl derivative is weaker by 7.8 kcal mol^{-1}, the *O*-methyl derivative only by 4.6 kcal mol^{-1}. The same acidity order was observed for these compounds in dimethyl sulfoxide[18] with smaller differences (1.4 and 4.9 kcal mol^{-1}, respectively) and for substituted benzohydroxamic acids in 80% methyl cellosolve[15] (e.g. 0.1 and 1.8 kcal mol^{-1} for 4-nitrobenzohydroxamic acid; the corresponding figures for benzohydroxamic acid are less reliable due to a weak acidity). These results indicate that the anions from **3** and **4** have similar structures. This means that parent hydroxamic acids behave also as NH acids.[15,17] The difference between **3** and **4** can be attributed to the hydrogen bond which is certainly stronger in the anion **2b** than in the neutral form **1a**.[1,18] This explanation is corroborated by a comparison to amides. The differences of 11.3 kcal mol^{-1} between **4** and **6** and of 10.8 kcal mol^{-1} between **4** and **7**, which are due to the polarizability[26,27] of the methyl group are almost the same as in dimethyl sulfoxide.[18] This expresses essentially the field/inductive effect of the methoxy group. The difference between **3** and **4** in the gas phase (4.6 kcal mol^{-1}) is reduced to one-third in dimethyl sulfoxide,[18] since the hydrogen bond is supressed in solution. The above reasoning is only qualitative in character. A semiquantitative estimation might be attempted as follows: the behavior of hydroxamic acids as NH acids or OH acids may be expressed by the equilibria **1a** ⇌ **2b** and **1a** ⇌ **2a**, respectively. We can estimate the Gibbs energy corresponding to the latter equilibrium referring to the dissociation of **5**: the effect of the methyl group is essentially an acidity strengthening due to enhanced polarizability,[26,27] and should be similar to the methyl effect on alcohols acidity.[28] For the OH acidity of **3** we thus estimate: $\Delta G°_{acid}$ = 347.4 ± 0.5 kcal mol^{-1}, much lower than the experimental value. Of course, a better reference model should refer to the effect of α-methylation of NH acids but this effect is less well known than for OH acids.

For instance, α-methylation of *N*-methylaniline giving *N*-ethylaniline induces an acidity weakening[22] (6.5 kcal mol^{-1}). The α-methylation of the NH function in **3** giving **4** corresponds also to an acidity decrease (4.6 kcal mol^{-1}). This acidity decrease may also be attributed to the loss of the hydrogen-bond stabilization in **2b** (vide supra). Our whole reasoning is in favour of NH acidity of **3**.

The above results are essentially confirmed from the CID experiments. In the high energy (7 keV) CID spectra of deprotonated acetamide and *N*-methylacetamide[29] (NH acids) the principal fragmentations are the loss of H• or neutral molecules (methane). In the FT-ICR conditions (lower energies, multiple collisions) we do not observe significant H• loss, but methane and ethane losses represent the main fragmentations of $MeCONH^-$ and $MeCONMe^-$ ions (Table II), leading to CNO^- and $C_2H_2NO^-$. For both **6** and **7** the main fragment ion is CNO^-. This is also the case for **4** while for **5** no significant intensity at m/z = 42 is observed. This is in agreement with acetohydroxamic acid ionized essentially on the nitrogen atom under equilibrium conditions in the gas phase.

The acetohydroxamate ion is an α-effect nucleophile,[30] as are α-keto aldoximate ions.[31] For these two classes of compounds, quantum chemical calculations and further acidity measurements, in the gas phase and in solution are in progress.[32]

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Note added in proof: After this communication was submitted, Dr. John Bartmess provided us with a preprint reporting the CID spectrum of formylhydroxamate ion. The main fragment observed is m/z = 42, indicating that formylhydroxamic and acetohydroxamic acids behave similarly.

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