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# Protonation Thermochemistry of Selected Hydroxy- and Methoxycarbonyl Molecules

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The gas-phase basicities of a representative set of hydroxy- and methoxycarbonyl compounds (hydroxyacetone, **1**, 3-hydroxybutanone, **2**, 3-hydroxy-3-methylbutanone, **3**, 1-hydroxy-2-butanone, **4**, 4-hydroxy-2-butanone, **5**, 5-hydroxy-2-pentanone, **6**, methoxyacetone, **7**, 3-methoxy-2-butanone, **8**, 4-methoxy-2-butanone, **9**, and 5-methoxy-2-pentanone, **10**) were experimentally determined by the equilibrium method using Fourier transform ion cyclotron resonance and high-pressure mass spectrometry techniques. The latter method allows the measurement of proton transfer equilibrium constants at various temperatures and thus the estimate of both the proton affinities and the protonation entropies of the relevant species. Quantum chemical calculations at the G3 and the B3LYP/6-311+G(3df,2p)//6-31G(d) levels of theory were undertaken in order to find the most stable structures of the neutrals **1**−**10** and their protonated forms. Conformational and vibrational analyses have been done with the aim of obtaining a theoretical estimate of the protonation entropies.

## 1. Introduction

Protonation thermochemistry is a subject of importance in fundamental and applied chemistry and biochemistry due to the role of the protonation process in preparative chemistry, in living processes, and in analysis by mass spectrometry.[1] In recent years we have been interested in the intrinsic basicity of various carbonyl bases (ketones, acids, anhydrides, lactams, lactones) and bifunctional aliphatic compounds.[2] In the same vein, the present work reports the results of an experimental and computational investigation on a series of hydroxy- and methoxycarbonyl molecules. The simplest member of this class of compounds, glycolaldehyde ($HCOCH_2OH$), has been identified in the interstellar medium,[3] and its protonation thermochemistry as well as the reactivity of its protonated form has been recently elucidated.[4] Higher homologues are involved in tropospheric chemistry since they may be formed by OH radical initiated reactions with alkanes, alkenes, or diols.[5] Moreover, their reactivity with OH, $NO_3$, and $O_3$ radicals has been investigated in order to understand the mechanism of atmospheric loss processes initiated by volatile organic compounds.[6,7] Hydroxycarbonyls are also of interest in biochemical events since they provide direct routes to a vast number of biologically significant compounds including carbohydrates, antibiotics, alkaloids, ands terpenes[8] and they may be present in clinically detected metabolites.[9]

Despite this significant role in both gas- and condensed-phase chemistry, most of the physicochemical properties of hydroxycarbonyls and their derivatives are not fully documented.[10] The goal of the present study is to convey detailed information on the structures and energetics of neutral and protonated representative hydroxy- and methoxycarbonyl molecules, M. A primary objective is the experimental determination of accurate gas-phase basicities, GB(M), and proton affinities, PA(M), i.e., the Gibbs free energy and standard enthalpy, respectively, of reaction 1:

$$MH^+ \rightarrow M + H^+ \qquad (1)$$

As a corollary, protonation entropies, $\Delta_p S°(M) = S°(MH^+) - S°(M)$, could then also be deduced in several cases. Further, these results can be analyzed with the aid of high-level quantum chemistry calculations. The experimental data were obtained through the use of Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry and high-pressure mass spectrometry (HPMS). The selected compounds M include hydroxyacetone, **1**, 3-hydroxybutanone, **2**, 3-hydroxy-3-methylbutanone, **3**, 1-hydroxybutanone, **4**, 4-hydroxy-2-butanone, **5**, 5-hydroxy-2-pentanone, **6**, methoxyacetone, **7**, 3-methoxy-2-butanone, **8**, 4-methoxy-2-butanone, **9**, and 5-methoxy-2-pentanone, **10** (Scheme 1).

## 2. Experimental and Theoretical Section

**Experiments.** The experimental studies of proton exchange equilibria involving molecules M and reference bases B

$$MH^+ + B \rightarrow M + BH^+$$

were performed using either an ion cyclotron resonance mass spectrometer or a pulsed electron beam, variable-temperature, high-pressure mass spectrometer. The equilibrium constant for the exchange reaction is given by

$$K = I_{BH^+}[M]/I_{AH^+}[B]$$

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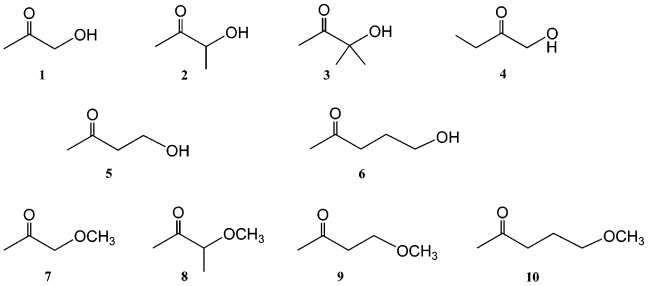
**SCHEME 1**



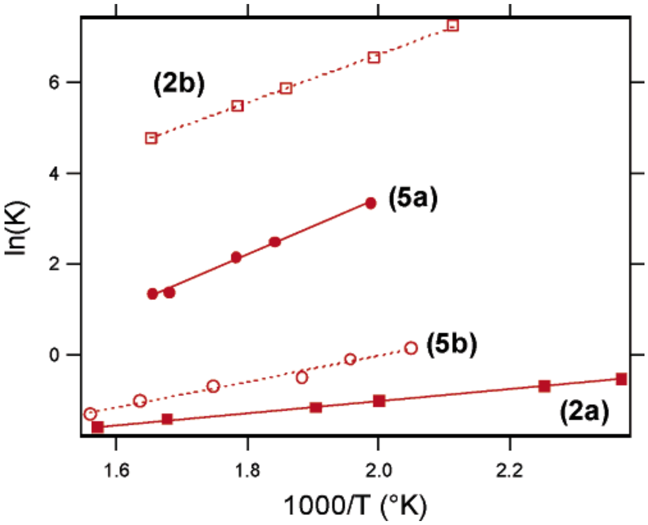


**Figure 1.** Example of van't Hoff plots for proton transfer equilibria involving 3-hydroxybutanone, **2** (with mesitylene and isobutene as reference bases for (2a) and (2b), respectively), and 4-hydroxy-2-butanone, **5** (with mesitylene and cyclopropyl methyl ketone as reference bases for (5a) and (5b), respectively).

where $I_x$ are ionic abundances and [M] and [B] represent the relative proportions of neutrals M and B.

Ion cyclotron resonance mass spectrometry experiments have been performed on a Bruker Spectrospin CMS 47X FT-ICR mass spectrometer.[11] Ions arising from dissociative ionization of either M or B were produced by electron ionization in the cell located inside the 4.7 T superconducting magnet. $MH^+$ or $BH^+$ species were then selected by ejection of unwanted ions by a combination of chirp and soft radio frequency pulses and were subsequently relaxed to thermal energy ($T \sim 300$ K) using a relaxation delay of 2−6 s after the selection of reacting ions. The ions were then allowed to react for a variable time with neutral bases B and M until a constant ratio of peak intensities was reached. Experiments were conducted at a constant pressure in the range of $10^{-8}-10^{-7}$ mbar as indicated by the ionization gauge (Balzers-IMR-132) located between the high vacuum pump and the cell housing. The intensities of the peaks were determined in the frequency domain after Fourier transformation of the corresponding time domain signal. Relative pressures of the neutral molecules were corrected by taking into consideration the sensitivity of the ionization gauge relative to $N_2$. Relative sensitivities $S_r$ were estimated according to the method of Bartmess and Georgiadis:[12] $S_r = 0.36[\alpha(\text{ahc})] + 0.30$, where $\alpha$(ahc) is the average molecular polarizability based on atomic hybrid components calculated using the additivity scheme of Miller.[13]

Pulsed ionization, high-pressure mass spectrometry (HPMS) experiments were conducted on a spectrometer constructed at the University of Waterloo. The apparatus and its capabilities have been described in detail previously.[14] Several compounds were tested as proton exchange partners in the experiments. The selection criteria were based on the requirement that exchange partners do not participate in competing reactions, such as proton-bound dimer formation or dissociation, to any significant extent. Thus only compounds M = **2**, **5**, **7**, **9**, and **10** have been found to fulfill these requirements and provide meaningful results. Typically, the proton exchange equilibria were measured over a 150−300 °C temperature range. van't Hoff plots of the data allowed the determination of the enthalpy and entropy changes associated with the proton exchange reaction and thus with the proton affinity and protonation entropy of the unknown M. Figure 1 shows two examples of van't Hoff plots obtained for the two isomeric hydroxybutanones **2** and **5**.

**Computational Details.** Molecules **1**−**10** and their protonated forms were first examined at the HF/6-31G(d) level in order to locate the most favorable conformations and to determine the rotational barriers used in the entropy calculations (see below). This was followed by a search of the most stable conformation whose HF geometry was refined using the density functional theory at the B3LYP/6-31G(d) level. Zero point vibrational energies, ZPVE, and thermal contributions to the enthalpy at 298 K, $H_{298}(M) - H_0(M)$, were estimated at this level of theory. No scaling of these latter quantities has been applied since its influence on the calculation of proton affinities is negligible (for example, Scott and Radom[15] suggest an empirical factor of 1.0126 to correct ZPVE values when using the B3LYP/6-31G(d) basis set, which leads to insignificant $\text{ZPVE}(M) - \text{ZPVE}(MH^+)$ differences of less than 0.5 kJ·mol$^{-1}$).

Proton affinities are computed, according to reaction 1, from the standard enthalpy change given by

$$PA_{calc}(M) = E_{tot}(M) - E_{tot}(MH^+) + \Delta_1 ZPVE + \Delta_1 H_{0\rightarrow 298}$$

with $E_{tot}$ being the calculated total energy of the considered species, $\Delta_1$ZPVE the zero point vibrational energy difference $\text{ZPVE}(M) - \text{ZPVE}(MH^+)$, and $\Delta_1 H_{0\rightarrow 298}$ the thermal correction to enthalpy including the 298 K enthalpy contribution of the proton (i.e., $\Delta_1 H_{0\rightarrow 298} = [H_{298}(M) - H_0(M)] - [H_{298}(MH^+) - H_0(MH^+)] + 6.2$ kJ·mol$^{-1}$). It has been demonstrated that, to obtain accurate (±1−5 kJ·mol$^{-1}$) proton affinities by this procedure, very high levels of correlation and very large basis sets must be used.[16] Various protocols are available, ranging from W1, W2,[17] G2, and G3[18] to CBS-Q[19] procedures. In the present study, we have adopted the method of highest accuracy practicable owing to the size of the investigated systems, i.e., the G3 method. Only for compound **10**, which is too large for our computational capacity, have we used the more economical G3MP2 scheme. These G3 calculated values have been compared with those obtained at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) level, which usually lead to satisfactory proton affinities and acidities.[20] All calculations have been undertaken using the Gaussian98 and Gaussian03 suites of programs.[21]

To compare experimental and computed gas-phase basicities, GB(M), it is necessary to know the entropy change associated with reaction 1 since, at a temperature $T$, $GB(M) = PA(M) - T\Delta_1 S°$. As noted in the Introduction, the entropy difference $\Delta_1 S°$ may be expressed by $[S°(H^+) - \Delta_p S°(M)]$, where $\Delta_p S°(M) = S°(MH^+) - S°(M)$ is defined as the protonation (or "half-reaction") entropy. At 298 K the entropy of the proton $S°(H^+)$ is equal to 108.8 J·K$^{-1}$·mol$^{-1}$ and the protonation entropy $\Delta_p S°(M)$ can be estimated by calculating the absolute third law entropy of both M and $MH^+$. The calculation of entropies in the Gaussian suites of programs uses standard statistical thermodynamic formulas to obtain the electronic, translational,

**TABLE 1: FT-ICR Data for Reactions $BH^+ + M \rightarrow B + MH^+$**

| M | B | $\Delta G_{300}°$ [a] | GB(B)[a,b] | GB(M)[a] |
|---|---|---|---|---|
| hydroxyacetone, **1** | butanone | 2.3 | 795.8 | 793.5 |
| | methyl vinyl ketone | 4.6 | 797.9[c] | 793.3 |
| | | | | 793.4 ± 0.1 |
| 3-hydroxy-2-butanone, **2** | 2-methoxyethanol | −6.0 | 797.9[d] | 803.9 |
| | diethyl ether | −2.1 | 801.0 | 803.1 |
| | | | | 803.5 ± 0.4 |
| 3-hydroxy-3-methylbutanone, **3** | cyclopropyl methyl ketone | 3.2 | 823.2 | 820.0 |
| | diisopropyl ketone | 2.0 | 820.5 | 818.5 |
| | | | | 819.2 ± 0.8 |
| 1-hydroxybutanone, **4** | 3-pentanone | 4.7 | 805.6 | 800.9 |
| | butanone | −3.4 | 795.8 | 799.2 |
| | cyclopentanone | −4.0 | 794.0 | 798.0 |
| | | | | 799.4 ± 1.5 |
| 4-hydroxy-2-butanone, **5** | pyrolle | 6.0 | 844.0 | 838.0 |
| | | | | 838.0 |
| methoxyacetone, **7** | cyclopropyl methyl ketone | 4.4 | 823.2 | 818.8 |
| | diisopropyl ketone | 3.9 | 820.5 | 816.6 |
| | methylbenzoate | 1.7 | 819.5 | 817.8 |
| | | | | 817.7 ± 1.1 |
| 3-methoxy-2-butanone, **8** | cyclopropyl methyl ketone | −3.1 | 823.2 | 826.3 |
| | diisopropyl ketone | −2.8 | 820.5 | 823.3 |
| | | | | 824.8 ± 1.5 |
| 4-methoxy-2-butanone, **9** | pyrolle | −1.6 | 844.0 | 845.6 |
| | aniline | 4.0 | 850.6 | 846.6 |
| | | | | 846.1 ± 0.5 |
| 5-methoxy-2-pentanone, **10** | methylamine | −5.7 | 864.5 | 870.2 |
| | ethylamine | 4.8 | 878.0 | 873.2 |
| | | | | 871.7 ± 1.5 |

[a] In kJ·mol$^{-1}$. [b] From ref 1 (reconsidered from the original data) except when otherwise indicated. [c] T. B. McMahon, unpublished results. [d] From ref 2k.

rotational, and vibrational contributions to entropy. The latter terms are estimated using the harmonic oscillator approximation. However, it is well-known that the lowest frequencies are generally highly anharmonic and thus poorly described by the harmonic oscillator approximation. This is particularly true for internal rotations. It should also be noted that the lowest frequencies are those that give the largest contributions to the vibrational entropy. In the systems considered, the possibility of intramolecular hydrogen bonds will change the barrier for internal rotation considerably between M and $MH^+$ and consequently strongly affect the corresponding vibrational frequencies. To correctly estimate the protonation entropy $\Delta_p S°(M) = S°(MH^+) - S°(M)$, it is thus essential to circumvent this problem. We consequently treat separately each internal rotation as hindered rotor by using a model developed by Pitzer[22] and applied to monofunctional molecules containing one, two, or three internal rotations by East and Radom[23] and to the protonation of bifunctional bases by us.[2l−n] Briefly, this procedure involves calculation of the rotational energy barrier, $V_0$, appearing in the variation of the potential energy with the dihedral angle $\phi$: $V_0(\phi) = V_0/2(1 - \cos n\phi)$. The reduced moment of inertia, $I_{red}$, of the two rotating groups around the axis containing the bond is also required. In the present study, the rotational potential energy barriers, $V_0$, were obtained at the HF/6-31G(d) level using a relaxed rotation approach without symmetry constraint (i.e., all geometric parameters were optimized except the dihedral angle considered). A complete scan of the dihedral angle, between 0 and 360° by steps of 5°, was explored for each torsional mode. The $V_0$ values used in the entropy calculations were equated with the difference between maxima and minima of the smoothed potential energy curves.[2l−n,23] This procedure has been applied to the six simplest representative hydroxy- and methoxycarbonyls **1**, **5**, **6**, **7**, **9**, and **10**.

The bonding characteristics of both neutral and protonated species were analyzed by means of the atoms-in-molecules (AIM) theory.[24] For this purpose we have located the bond critical points (bcp's) and the ring critical points (rcp's) for the particular case of cyclic systems using a B3LYP/6-31G(d) formalism, and we have obtained the corresponding molecular graphs defined by the network of bond paths. It has been shown[25] that the charge densities at both the bcp's and the rcp's are a good measure of the relative stability of intramolecular hydrogen bonds.

## 3. Results and Discussion

**General Considerations.** Experimental FT-ICR and HPMS results are given in Tables 1 and 2. Comparison of the two sets of data is satisfactory since the mean deviation in gas-phase basicity GB(M) (for molecules M = **2**, **5**, **7**, **9**, **10**) is only 3.0 kJ·mol$^{-1}$ with a maximum deviation of 5.4 kJ·mol$^{-1}$.

It may be noted that, unfortunately, no meaningful experimental data have been obtained for 5-hydroxy-2-pentanone, **6**, by either FT-ICR or HPMS techniques. It has been observed that protonation of this molecule leads rapidly to a dehydration process, leading to an intense peak at $m/z$ 85 and thus rendering the determination of a correct equilibrium constant impossible. Consequently, examination of the influence of the distance between the two basic sites on the thermodynamic properties of hydroxycarbonyls could only be done on theoretical grounds. In contrast, a complete set of experimental data has been obtained for the methoxycarbonyls **7**, **9**, and **10** as discussed below.

Both FT-ICR (Table 1) and HPMS (Table 2) measurements provide GB values that demonstrate a nearly identical increase (∼26 kJ·mol$^{-1}$) when passing from **7** to **9** and from **9** to **10**. An examination of the enthalpic and entropic contributions shows clearly that this increase in basicity is associated with a large increase in proton affinity (34 and 31 kJ·mol$^{-1}$, respectively, Table 2) counterbalanced by a significant decrease in protonation entropy (−29 and −11 J·K$^{-1}$·mol$^{-1}$, respectively,

**TABLE 2: Summary of HPMS Data for Reactions $BH^+ + M \rightarrow B + MH^+$**

| M | B | $\Delta G_{300}°$ [a] | $\Delta H°$ [a] | $\Delta S°$ [b] | GB(B)[a,c] | GB(M)[a,d] | PA(B)[a] | PA(M)[a,d] | $\Delta_p S°(B)$ [b] | $\Delta_p S(M)°$ [b,d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 3-hydroxy-2-butanone, **2** | isobutene | −31.4 | −40.2 | −29 | 776.6 | 808.0 | 801.9[d] | 842.1 | 24[d] | −6 |
| | mesitylene | −1.1 | −10.0 | −30 | 808.3 | 809.4 | 833.9[e] | 843.9 | 23[e] | −7 |
| | | | | | | 808.7 ± 0.7 | | 843.0 ± 0.9 | | −6 ± 1 |
| 4-hydroxy-2-butanone, **5** | mesitylene | −25.8 | −46.9 | −70 | 808.3 | 834.1 | 833.9[e] | 880.8 | 23[e] | −47 |
| | cyclopropyl methyl ketone | −8.1 | −21.8 | −46 | 822.9 | 831.0 | 854.4[f] | 876.2 | 3[f] | −43 |
| | | | | | | 832.6 ± 1.6 | | 878.5 ± 2.3 | | −45 ± 3 |
| methoxyacetone, **7** | mesitylene | −11.4 | −23.8 | −41 | 808.3 | 819.7 | 833.9[e] | 857.7 | 23[e] | −18 |
| | | | | | | 819.7 | | 857.7 | | −18 |
| 4-methoxy-2-butanone, **9** | pyrolle | −4.1 | −16.3 | −41 | 844.0 | 848.1 | 875.3[f] | 891.6 | 4[f] | −37 |
| | | | | | | 848.1 | | 891.6 | | −37 |
| 5-methoxy-2-pentanone, **10** | pyrolle | −32.3 | −48.1 | −53 | 844.0 | 876.3 | 875.3[f] | 923.4 | 4[f] | −49 |
| | 1-methoxy-4-butanol | 1.1 | −3.8 | 16 | 866.8 | 867.9 | 918.0[g] | 921.8 | −63[g] | −47 |
| | | | | | | 872.1 ± 4.2 | | 922.6 ± 0.8 | | −48 ± 1 |

[a] In $kJ \cdot mol^{-1}$. [b] In $J \cdot K^{-1} \cdot mol^{-1}$. [c] $GB(B) = PA(B) - 298(108.8 - \Delta_p S°(B))$. [d] $GB(M) = GB(B) + \Delta G_{300}°$; $PA(M) = PA(B) - \Delta H°$; $\Delta_p S(M)° = \Delta_p S° + \Delta_p S(B)°$. [e] From ref 1 (reconsidered from the original data). [f] From ref 30. [g] From ref 2k.

Table 2). These observations are obviously related to the formation of a strong intramolecular ionic hydrogen bond in the protonated species and to the influence of the basic site separation upon its strength.[26] Intramolecular ionic hydrogen bond stabilizes the $MH^+$ ions and consequently increases the PA of the molecule M. Similarly, it constrains the $MH^+$ structure by hindering several internal rotations, thus leading to an entropy value lower than that of the neutral molecule and consequently to a negative protonation entropy $\Delta_p S°(M)$. It is noteworthy that the effects observed for methoxycarbonyls **7** and **9** are also apparent for the hydroxy derivatives, although to a different extent. For example, the GB loss noted when passing from **7** to **9** (~26 $kJ \cdot mol^{-1}$) is increased to 45 $kJ \cdot mol^{-1}$ (FT-ICR, Table 1) for the pair **1** and **5**.

The experimental thermochemical data reported in Tables 1 and 2 and their interpretation based on the formation of an intramolecular hydrogen bond are in fair agreement with quantum chemical calculations (Tables 3−5).

Entropy calculations have been limited to the six representatives compounds **1**, **5**, **6**, **7**, **9**, and **10**. Details on the contribution of each internal hindered rotation to entropy together with the resulting calculated protonation entropies, $\Delta_p S°(M) = S°(MH^+) - S°(M)$, are given in Table 3. Satisfactorily enough, the increase in entropy loss calculated when passing from the 1,2- to 1,3- and 1,3-hydroxy- or methoxycarbonyls parallels the observations quoted in Table 2. Comparison with experiment reveals, however, a systematic underestimate in the absolute value of $\Delta_p S°(M)$ of ca. 13 $J \cdot K^{-1} \cdot mol^{-1}$ as given by theory.

Total energies and corrections to enthalpy at 298 K calculated at the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) levels are given in Table 4. At this level of theory, the resulting proton affinities $PA_{calc}(M)$ exhibit a systematic overestimate. For example, the proton affinity of acetone is calculated to be 819.6 $kJ \cdot mol^{-1}$ since its experimental value is only 812.0 $kJ \cdot mol^{-1}$.[1] Although the difference probably lies within the accuracy of the experimental values, the $PA_{calc}(M)$ reported in the second column of Table 5 has been corrected by calculating the enthalpy variation $\Delta H_{298}°$(homo) of the homodesmic process, $MH^+ + \text{acetone} \rightarrow M + \text{acetone}H^+$, and using $PA_{calc}(M) = 812.0\ kJ \cdot mol^{-1} + \Delta H_{298}°(\text{homo})$. This procedure gives an excellent agreement with the values calculated at the more sophisticated G3 level as shown in Table 5. It may be noted that the G3 method provides proton affinity values in agreement within ±2 $kJ \cdot mol^{-1}$ with the tabulated values for simple ketones such as acetone, butanone, and 3-pentanone. Thus, no homodesmic correction has been considered at this level. Where comparison of $PA_{calc}(M)$ with experimental proton affinity values is possible (HPMS, Table 2), it reveals a correct agreement although with a systematic underestimate of ca. 9 $kJ \cdot mol^{-1}$ obtained by theory.

Finally, the gas-phase basicities of **1**−**10**, calculated from $PA_{calc}(M)$ and the theoretical protonation entropy, are given in the last column of Table 5. The agreement with experiment is excellent since a mean absolute deviation of only 4.8 $kJ \cdot mol^{-1}$ is observed.

The role of the intramolecular hydrogen bond in proton affinity and entropy may be understood by examination of the most stable conformations of M and $MH^+$. The molecular graphs corresponding to the most stable conformers of hydroxycarbonyls and their protonated forms are presented in Figure 2. Similar information is provided for methoxycarbonyls in Figure 3. Their optimized geometries are available upon request. The existence of both a bond critical point and a ring critical point unequivocally shows that both the neutral and the protonated forms of hydroxycarbonyl compounds are stabilized by an intramolecular hydrogen bond, while this is obviously only possible for protonated methoxycarbonyls. It can be observed that protonation of all the molecules investigated occurs preferentially on the carbonyl oxygen. Thus, for hydroxycarbonyl neutral molecules the carbonyl oxygen acts as a hydrogen bond acceptor while in the protonated form it behaves as a hydrogen bond donor with the hydroxyl group behaving as hydrogen bond acceptor. In other words, in the protonated species the intramolecular hydrogen bond is oriented in the direction opposite that in the neutral system. More importantly, in all cases the intramolecular hydrogen bonds are systematically stronger in the protonated species than in the neutral species, as indicated by the charge densities at the bcp's and at the ring critical points. This will be obviously reflected in a basicity enhancement of all these species. Similarly, the formation of an intramolecular hydrogen bond in protonated methoxycarbonyl molecules will also lead to an even larger basicity enhancement.

There is not an unbiased way of measuring the strength of an intramolecular hydrogen bond.[25] In particular, the internal hydrogen bond effect cannot be disclosed from other effects such as that involving the electron-withdrawing effect of the hydroxyl or methoxy group and, in the latter case, involving interaction of the methyl group with the carbonyl moiety. However, different indexes such as (i) the charge density at the bcp, (ii) the charge density at the rcp, (iii) the hydrogen bond length ($d_{O \cdots H}$), and (iv) the O···HO bond angle $\alpha_{OHO}$ are good indicators of its relative strength, if a similar intermolecular system is used as a suitable reference. The values of these geometric parameters are given in Table 6 and compared with the equivalent quantities in the analogous intermolecular systems acetone/methanol and acetone/dimethyl ether. For the first terms

**TABLE 3: Summary of Entropy Calculations for Neutral and Protonated Species M = 1, 7, 5, 9, 6, and 10**

| species | bond | $V_0$[a] | $S°$ [b] | $S°_{hr}$[c] (Pitzer) | $\Delta_pS°$ |
|---|---|---|---|---|---|
| 1 | C2−C3 | 17.8 | 335.1 | 20.6 | |
| | C3−O4 | 27.5 | | 9.2 | |
| **1H**$^+$ | C2−C3 | 47.0 | 324.7 | 19.33 | −10.4 |
| | C3−O4 | 78.3 | | 2.57 | |
| 7 | C2−C3 | 21.6 | 368.6 | 24.2 | |
| | C3−O4 | 37.3 | | 21.4 | |
| **7H**$^+$ | C2−C3 | 47.3 | 362.1 | 20.2 | −6.5 |
| | C3−O4 | 95.5 | | 14.3 | |
| 5 | C2−C3 | 22.5 | 373.3 | 25.1 | |
| | C3−C4 | 19.6 | | 10.6 | |
| | C4−O5 | 28.5 | | 22.9 | |
| **5H**$^+$ | C2−C3 | 42.9 | 353.6 | 22.3 | −19.7 |
| | C3−C4 | 65.0 | | 16.4 | |
| | C4−O5 | 86.2 | | 2.4 | |
| 9 | C2−C3 | 17.2 | 415.6 | 26.6 | |
| | C3−C4 | 24.4 | | 25.7 | |
| | C4−O5 | 34.4 | | 21.9 | |
| **9H**$^+$ | C2−C3 | 95.16 | 389.1 | 16.4 | −26.5 |
| | C3−C4 | 69.08 | | 18.8 | |
| | C4−O5 | 57.69 | | 17.0 | |
| **6**[d] | C2−C3 | 23.3 | 420.8 | 25.5 | |
| | C3−C4 | 12.7 | | 31.8 | |
| | C4−C5 | 25.5 | | 24.0 | |
| | C5−O6 | 15.3 | | 12.1 | |
| **6H**$^+$ | C2−C3 | 57.3 | 380.8 | 18.5 | −40.0 |
| | C3−C4 | 70.0 | | 19.8 | |
| | C4−C5 | 89.5 | | 15.5 | |
| | C5−O6 | 102.1 | | 2.0 | |
| 10 | C2−C3 | 14.0 | 465.9 | 27.6 | |
| | C3−C4 | 20.0 | | 30.1 | |
| | C4−C5 | 20.7 | | 27.0 | |
| | C5−O6 | 41.5 | | 18.5 | |
| **10H**$^+$ | C2−C3 | 126.2 | 422.6 | 15.4 | −43.3 |
| | C3−C4 | 92.6 | | 20.1 | |
| | C4−C5 | 77.1 | | 19.1 | |
| | C5−O6 | 80.9 | | 15.3 | |

[a] Potential energy barrier of the internal rotation around the "bond"; value in kJ·mol$^{-1}$, calculated at the HF/6-31G(d) level. [b] Total calculated entropy (J·mol$^{-1}$·K$^{-1}$) of the species considered. [c] Contribution to entropy of the hindered rotation around the bond, calculated using the Pitzer method (see text). [d] Absolute entropies of the cyclized structure **6R** and its protonated forms **6RH**$^+$ and **6R′H**$^+$, as given by Gaussian, are 344.6, 359.2, and 397.7 J·mol$^{-1}$·K$^{-1}$; i.e., 76 J·mol$^{-1}$·K$^{-1}$. This leads to protonation entropy values $\Delta_pS°$ of +15 and +53 J·mol$^{-1}$·K$^{-1}$ for the processes **6R** → **6RH**$^+$ and **6R** → **6R′H**$^+$.

of the series, **1** and **5** and the protonated species **1H**$^+$, **5H**$^+$, **7H**$^+$, and **9H**$^+$, all indexes predict the corresponding intramolecular hydrogen bond to be weaker than in the model systems $(CH_3)_2CO\cdots HOCH_3$, $(CH_3)_2COH^+\cdots O(H)CH_3$, and $(CH_3)_2COH^+\cdots O(CH_3)_2$. However for species **6**, **6H**$^+$, and **10H**$^+$, due to a greater flexibility of the system the other way, geometric parameters point to intramolecular hydrogen bonds comparable to that of the model systems. This parallels the observations concerning the proton affinities and the protononation entropies discussed above. It may also be noted that the protonated forms of homologue hydroxy- or methoxycarbonyl molecules present almost identical $\alpha_{OHO}$ angles, but the distances $d_{H+\cdots O}$ are slightly shorter for the methoxy derivative and the charge density at the bcp is larger, due to the higher basicity of a methoxy oxygen relative to a hydroxy oxygen.

**α-Hydroxy- and Methoxycarbonyls (1−4 and 7, 8).** For the four hydroxycarbonyl molecules **1**−**4**, the formation of the intramolecular hydrogen bond imposes a quasi planar arrangement of the OCCOH atoms. A similar situation arises for the corresponding protonated forms although, as mentioned before, the intramolecular ionic hydrogen bond is established between the protonating hydrogen located on the oxygen of the carbonyl group and the oxygen atom of the hydroxyl. For the typical case of hydroxyacetone, **1**, rotations around the C−C and C−O bonds are associated with energy barriers of 18 and 28 kJ·mol$^{-1}$ in the neutral, and 47 and 78 kJ·mol$^{-1}$ for the protonated form (HF/6-31G* level, Table 4), in agreement with the fact that the intramolecular hydrogen bond is stronger in the latter. This change in barrier height leads to a noticeable change in entropy for the C−O rotor alone and finally, after inclusion of all the contributions to $S°$, to a modest protonation entropy $\Delta_pS°$(**1**) of −10 J·K$^{-1}$·mol$^{-1}$. Experimentally, among the 1,2-hydroxycarbonyls, only the protonation entropy of 3-hydroxybutanone, **2**, has been determined. The value, −2 J·K$^{-1}$·mol$^{-1}$, confirms that a small negative protonation entropy is associated with protonation of 1,2-hydroxycarbonyl molecules.

Another point of interest is the comparable increase in gas-phase basicity observed when passing from **1** to either **2** or **4** (8 or 4 kJ·mol$^{-1}$, respectively, Table 1). By contrast, the gas-phase basicity of **3** is higher than that of **1** by a larger amount (24 kJ·mol$^{-1}$, Table 1). These observations are readily explained by the reinforcement of stability of the protonated forms due to the increase in polarizability afforded by the presence of additional $CH_2$ groups in **2**, **3**, and **4** with respect to **1**. Another conspicuous fact is that the basicity increase clearly parallels a similar increase of the strength of the hydrogen bond in the protonated forms, as reflected by the values of the charge densities at the corresponding bcp's (see Figure 2). The smallest increases in the strength of this intramolecular hydrogen bond occur on going from **1H**$^+$ to **4H**$^+$ and **2H**$^+$, respectively, and this is reflected in changes in the basicity by 4 and 8 kJ·mol$^{-1}$, respectively. The largest change in charge density is observed

**TABLE 4: Total Energies, Zero Point Vibrational Energies, and 298 K Corrections to Enthalpy (hartrees)**[a]

| M | $E_{tot}$(B3LYP/6-31G(d)) | ZPVE | $H°_{298} - H°_0$ | $E_{tot}$(B3LYP/6-311+G(3df,2p)) | G3 enthalpy |
|---|---|---|---|---|---|
| **1** | −268.363 12 | 0.089 393 | 0.007 022 | −268.476 23 | −268.179 18 |
| **1H**$^+$ | −268.692 14 | 0.101 507 | 0.007 151 | −268.802 60 | −268.490 87 |
| **2** | −307.681 74 | 0.118 043 | 0.008 153 | −307.806 72 | −307.455 66 |
| **2H**$^+$ | −308.015 54 | 0.129 888 | 0.008 467 | −308.137 88 | −307.771 69 |
| **3** | −346.998 49 | 0.145 711 | 0.009 661 | −347.135 62 | −346.733 08 |
| **3H**$^+$ | −347.336 97 | 0.157 833 | 0.009 793 | −347.471 35 | −347.053 20 |
| **4** | −307.677 68 | 0.118 214 | 0.008 310 | −307.803 04 | −307.450 06 |
| **4H**$^+$ | −308.009 57 | 0.130 466 | 0.008 397 | −308.132 80 | −307.764 60 |
| **5** | −307.679 51 | 0.118 909 | 0.007 994 | −307.803 65 | −307.451 09 |
| **5H**$^+$ | −308.023 57 | 0.131 011 | 0.007 861 | −308.144 75 | −307.777 33 |
| **6** | −346.992 222 | 0.147 700 | 0.009 188 | −347.129 05 | −346.719 92 |
| **6R** | −346.994 494 | 0.149 605 | 0.008 144 | −347.128 83 | −346.727 73 |
| **6H**$^+$ | −347.349 33 | 0.159 012 | 0.009 029 | −347.483 69 | −347.060 74 |
| **6RH**$^+$ | −347.333 371 | 0.160 906 | 0.009 0033 | −347.467 638 | |
| **6′H**$^+$ | −347.307 617 | 0.158 304 | 0.010 346 | −347.441 804 | |
| **6R′H**$^+$ | −347.345 084 | 0.157 787 | 0.010 70 | −347.482 523 | |
| **7** | −307.666 47 | 0.117 589 | 0.008 570 | −307.785 60 | −307.430 52 |
| **7H**$^+$ | −308.004 37 | 0.130 145 | 0.008 602 | −308.121 63 | −307.750 88 |
| **8** | −346.983 89 | 0.146 113 | 0.009 789 | −347.114 52 | −346.704 80 |
| **8H**$^+$ | −347.326 58 | 0.158 540 | 0.009 878 | −347.455 39 | −347.031 17 |
| **9** | −346.983 84 | 0.146 380 | 0.009 930 | −347.115 50 | −346.704 29 |
| **9H**$^+$ | −347.335 71 | 0.158 979 | 0.009 430 | −347.463 83 | −347.038 61 |
| **10** | −386.298 77 | 0.175 138 | 0.011 139 | −386.443 06 | −385.681 13 |
| **10H**$^+$ | −386.661 46 | 0.186 346 | 0.010 588 | −386.802 84 | −386.027 48 |

[a] Geometries optimized at the B3LYP/6-31G(d) level, uncorrected ZPVE, and $H°_{298} - H°_0$ terms.

**TABLE 5: Summary of Computed Proton Affinities, Protonation Entropies, and Gas-Phase Basicities at 298 K**

| M | PA(M)[a,c] | | $\Delta_pS°$ [b] | GB(M)[a,d] |
|---|---|---|---|---|
| | B3LYP(homodesmic) | G3 | | |
| hydroxyacetone, **1** | 823 | 824 | −10 | 789 |
| 3-hydroxybutanone, **2** | 836 | 838 | −10 | 803 |
| 3-hydroxy-3-methylbutanone, **3** | 848 | 846 | −10 | 811 |
| 1-hydroxybutanone, **4** | 832 | 832 | −10 | 797 |
| 4-hydroxy-2-butanone, **5** | 863 | 863 | −20 | 825 |
| 5-hydroxy-2-pentanone, **6** | 900 | 901 | −40 | 857 |
| **6R** (→**6RH**$^+$) | 850 | | +15 | |
| **6R** (→**6R′H**$^+$) | 893 | | +53 | |
| methoxyacetone, **7** | 848 | 847 | −6 | 813 |
| 3-methoxy-2-butanone, **8** | 861 | 863 | −6 | 829 |
| 4-methoxy-2-butanone, **9** | 881 | 884 | −26 | 844 |
| 5-methoxy-2-pentanone, **10** | 915 | 915 | −43 | 870 |

[a] In kJ·mol$^{-1}$; see Table 4. [b] In J·mol$^{-1}$·K$^{-1}$; $\Delta_pS$ values in italics assumed by comparison with the simplest homologue compound. [c] Calculated PA(M) = $E_{tot}$(M) − $E_{tot}$(MH$^+$) + [ZPVE(M) − ZPVE(MH$^+$)] + [$H°_{298}$(M) − $H°_0$(M)] − [$H°_{298}$(MH$^+$) − $H°_0$(MH$^+$)] + 6.2 kJ·mol$^{-1}$. Based on B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) total energies $E_{tot}$ and ZPVE and $H°_{298} - H°_0$ terms calculated at the B3LYP/6-31G(d) level without scaling corrections. [d] GB(M) = [PA(M) − 298(108.8 − $\Delta_pS$)] × $10^{-3}$ kJ·mol$^{-1}$.

in going from **1H**$^+$ to **3H**$^+$, with the basicity of the latter being 24 kJ·mol$^{-1}$ greater than that of the former. Also interesting, the effect of methyl substitution seems to be nonadditive, since the second methyl group leads to a basicity enhancement twice that found for the first methyl substitution.

Methoxycarbonyl molecules **7** and **8** are most stable in a conformation that places the two oxygen atoms in an anti conformation (Figure 3). Calculation of the protonation entropy of methoxyacetone, **7**, has been done by considering internal rotations as hindered rotations. The results given in Table 4 show trends similar to those observed with hydroxyacetone since a small and negative protonation entropy, $\Delta_pS°$(**7**), is calculated (−6.5 J·K$^{-1}$·mol$^{-1}$) and nicely reproduces the experimental value ($\Delta_pS°$(**7**) = −8 J·K$^{-1}$·mol$^{-1}$, Table 2). Satisfactory agreement is found between calculated and experimental proton affinity and gas-phase basicity values for methoxyacetone as summarized in Table 5. Note that a uniform value of $\Delta_pS°$(M) = −10 J·K$^{-1}$·mol$^{-1}$ has been assumed in Table 5 for the estimate of the basicities of molecules **2**, **3**, **4**, and **8**.

The increase in basicity in bifunctional compounds due to the formation of a strong ionic hydrogen bond in the protonated form can be seen from a comparison of the results obtained for **1**, **2**, **7**, and **8** and their monofunctional homologues acetone and butanone. These two latter molecules have gas-phase basicities equal to 782 and 795 kJ·mol$^{-1}$, respectively.[1] Examination of the data quoted in Tables 1, 2, and 5 shows an enhancement of GB (or PA) values of ca. 10 kJ·mol$^{-1}$ for hydroxycarbonyl molecules **1** and **2**, and a more dramatic increase of ca. 35 kJ·mol$^{-1}$ in the case of the methoxycarbonyl molecules **7** and **8**. The difference in chelating abilities between the hydroxy and methoxy substituents parallels the known basicity differences between an alcohol and an ether (for example, GB(ethanol) = 746 kJ·mol$^{-1}$ and GB(ethyl methyl ether) = 781 kJ·mol$^{-1}$; ref 1). This was indeed expected in view of the structure of the protonated species, where the oxygen atom of the hydroxyl or methoxy group acts as acceptor in the ionic hydrogen bond, and it is clearly mirrored in the values of the charge densities at the bcp's (Figures 1 and 2).

***β*-Hydroxy- and Methoxycarbonyls (5 and 9).** Neutral 4-hydroxy-2-butanone, **5**, and protonated structures **5H**$^+$ and **9H**$^+$ are more stable in their pseudo-chair conformations (Figures 2 and 3). This favorable arrangement allows a strong

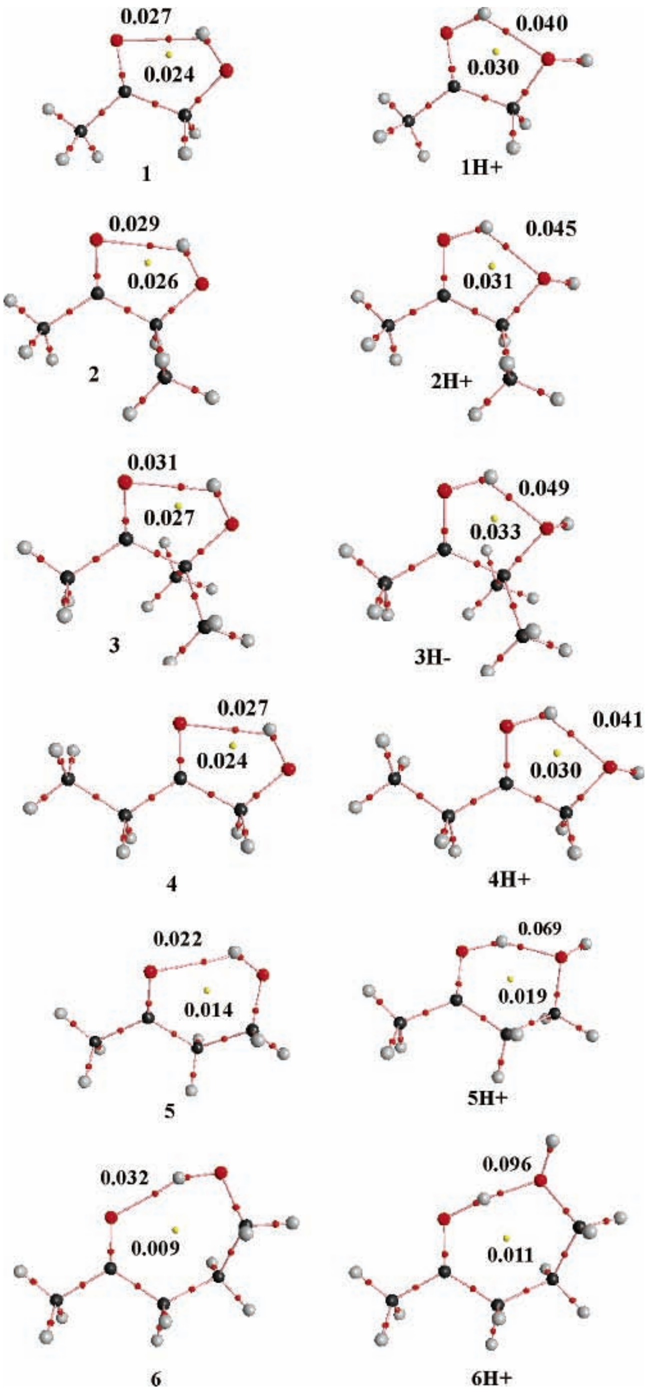


**Figure 2.** Molecular graphs of hydroxycarbonyl compounds and their protonated species. The charge densities at the bond critical points (red) and ring critical points (yellow) are in e au$^{-3}$.

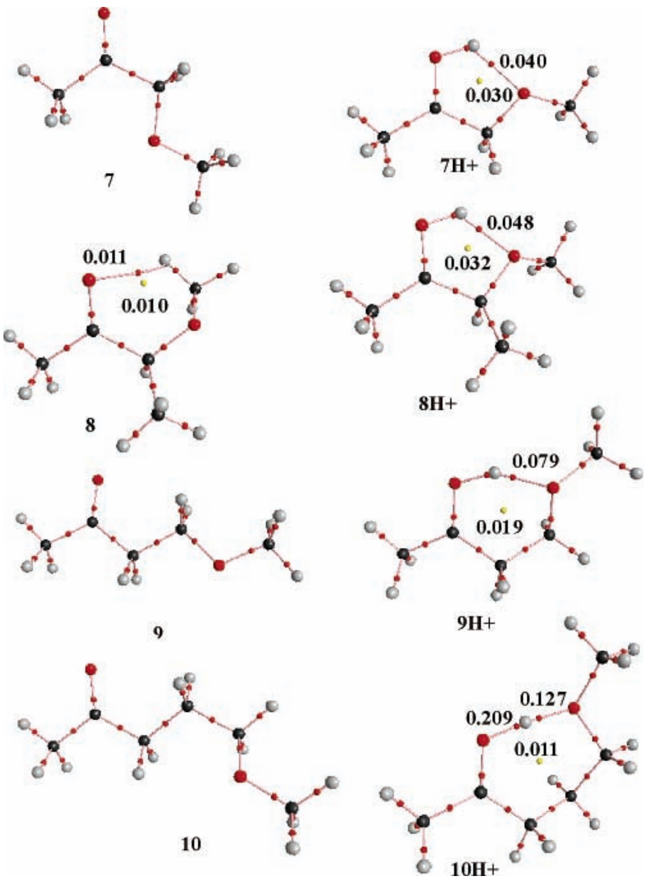


**Figure 3.** Molecular graphs of methoxycarbonyl compounds and their protonated species. The charge densities at the bond critical points (red) and ring critical points (yellow) are in e au$^{-3}$.

**TABLE 6: B3LYP/6-31G(d) Optimized Structural Parameters Relevant to Neutral and Protonated Molecules 1, 5, 6, 7, 9, and 10 and to Neutral or Protonated Acetone/Methanol Complexes**

| species | $d_{O\cdots H}$ (Å) | $\alpha_{OHO}$ (deg) | $d_{H^+\cdots O}$ (Å) |
|---|---|---|---|
| **1** | 2.008 | 119.8 | |
| **1H**$^+$ | | 120.6 | 1.758 |
| **7H**$^+$ | | 120.6 | 1.732 |
| **5** | 2.066 | 132.1 | |
| **5H**$^+$ | | 149.3 | 1.541 |
| **9H**$^+$ | | 151.4 | 1.488 |
| **6** | 1.871 | 157.1 | |
| **6H**$^+$ | | 171.2 | 1.401 |
| **10H**$^+$ | | 173.1 | 1.306 |
| $(CH_3)_2CO\cdots HOCH_3$ | 1.918 | 163.0 | |
| $(CH_3)_2COH^+\cdots O(H)CH_3$ | | 179.5 | 1.430 |
| $(CH_3)_2COH^+\cdots O(CH_3)_2$ | | 178.3 | 1.330 |

stabilization of the MH$^+$ ions and is consequently at the origin of a clear enhancement of the basicity of molecules **5** and **9** with respect to their monofunctional counterpart, butanone. Accordingly, a comparison of the proton affinities reveals an increase of ca. 50 kJ·mol$^{-1}$ for **5** and 65 kJ·mol$^{-1}$ for **9** (compare PA(butanone) = 827 kJ·mol$^{-1}$, ref 1, and the data reported in Tables 1 and 5). The formation of a strong intramolecular ionic hydrogen bond in MH$^+$ ions (see Figure 2) is also suggested by the protonation entropy. Experimentally, a common value of −40 J·K$^{-1}$·mol$^{-1}$ is measured for $\Delta_pS°$(**5**) and $\Delta_pS°$(**9**). Theoretical estimates are only in marginal agreement with calculated values of −20 and −30 J·K$^{-1}$·mol$^{-1}$ (Tables 4 and 5). The slightly lower absolute value calculated for **9** is in fact a reflection of a stronger ionic hydrogen bond in **9H**$^+$ with respect to **5H**$^+$ (see Figures 1 and 2) and of a floppy structure of the neutral.

**γ-Hydroxy- and Methoxycarbonyls (6 and 10).** Quantum chemical calculations indicate that 5-hydroxy-2-pentanone, **6**, and its hemiacetal isomer **6R**/**6S** (Figure 4) are of comparable stability. At the B3LYP/6-31G(d) level the two enantiomers **6R** and **6S** are 6.0 and 4.8 kJ·mol$^{-1}$ more stable than the classical structure **6**. These differences increase significantly at the G3 level and become 17.5 and 20.0 kJ·mol$^{-1}$, respectively. At the B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) level the situation is reversed and **6** becomes more stable than **6R** by 0.6 kJ·mol$^{-1}$. This latter difference becomes 2.3 kJ·mol$^{-1}$ at 298 K. In view of these results, protonation of both **6** and **6R** has been considered theoretically.

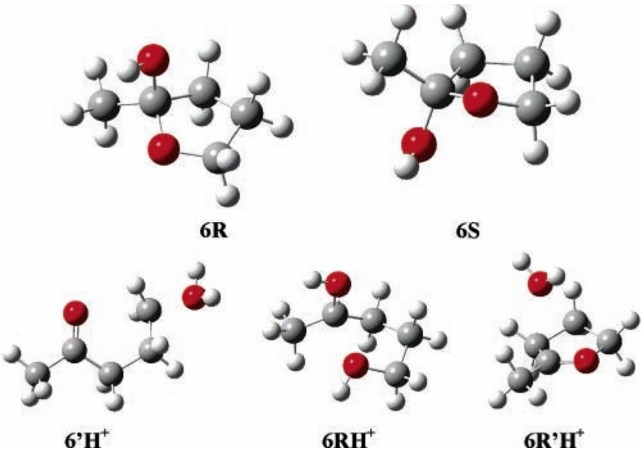


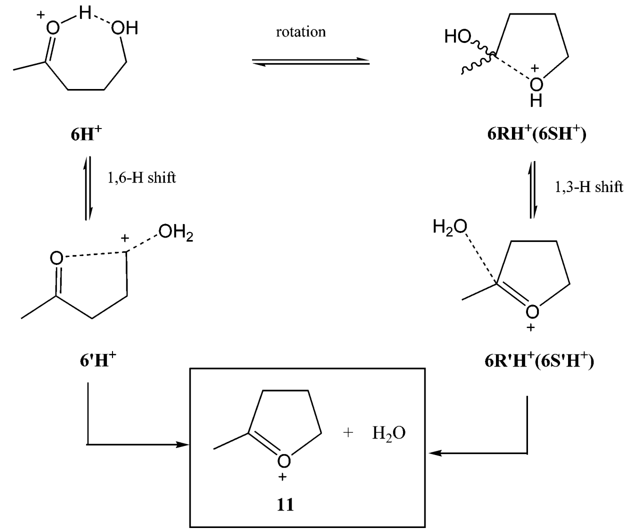
**Figure 4.** Structure of the two hemiacetal forms, **6R** and **6S**, of methoxyacetone and their protonated species.

By far the most stable protonated form of **6**, structure **6H**$^+$ (Figure 2), is characterized by an intramolecular ionic hydrogen bond, and thus direct protonation of **6** follows a trend similar to the previously described hydroxycarbonyl molecules. From this point of view, it is not surprising that a calculated proton affinity, PA(**6**), larger than that of 2-pentanone by 75 kJ•mol$^{-1}$ is obtained. Moreover, PA(**6**) is also larger than PA(**5**) by 38 kJ•mol$^{-1}$, as expected from the greater ability to assume a quasi linear arrangement of the OHO atoms in the ionic hydrogen bond, as discussed above. For the same reason, the protonation entropy is significantly negative ($\Delta_pS°$(**6**) = −40 J•K$^{-1}$•mol$^{-1}$, Tables 4 and 5) since the chelation involves the hindering of four internal rotations.

Protonation of hemiacetal **6R** may occur a priori on either the ether or the hydroxyl oxygen atoms. Surprisingly, protonation on the latter is more favorable and leads to a structure, **6R′H**$^+$, that consists of an ion neutral complex between the 1-methyl-1-tetrahydrofuranyl cation, **11**, and a water molecule (Figure 4). The distance between the oxygen atom of the latter and the carbon atom bearing most of the positive charge in **11** is equal to 2.735 Å. Protonation of **6R** on the ether oxygen leads to a less stable structure, **6RH**$^+$ (Figure 4), with a difference in energy between **6RH**$^+$ and **6R′H**$^+$ equal to 43 kJ•mol$^{-1}$ at 298 K. As shown in Figure 4, **6RH**$^+$ has partly lost its cyclic character and the CO bond adjacent to the hydroxyl group has become elongated (to 2.070 Å) upon protonation of the ether oxygen. Thus, **6RH**$^+$ corresponds to an open structure which, like **6H**$^+$, derives its stability from an electrostatic interaction, in the present case between the oxygen of the hydroxyl group and the positively charged carbon of the protonated carbonyl. The calculated proton affinity and protonation entropy of **6R** are presented in Table 5 for the two possible protonation sites. Absolute third law entropies used in the $\Delta_pS°$ estimates are those given by Gaussian, with no special correction to low harmonic frequencies, and thus $S°$(**6RH**$^+$) and, particularly, $S°$(**6R′H**$^+$) may be underestimated. In either case, the protonation entropy $\Delta_pS°$(**6R**) should be positive because the protonation leads to protonated structures slightly less strained than the starting molecule. Accordingly, values of +15 and +53 J•K$^{-1}$•mol$^{-1}$ are calculated for the production of **6RH**$^+$ and **6R′H**$^+$, respectively (Table 5).

For 5-methoxy-2-pentanone, **10**, there is excellent agreement between the two sets of experiments (Tables 1 and 2) and these results are readily understandable from examination of the computational data. Upon protonation, the linear structure of the neutral **10** is constrained to adopt a chelated arrangement allowing an intramolecular ionic hydrogen bond (**10H**$^+$) which is the strongest of the whole series of protonated species considered in this work (see Figure 3). As a matter of fact, both the high value of the charge density at the bcp and the position of the proton involved in the hydrogen bond allow us to classify this as a proton share hydrogen bonded system. Accordingly, the proton affinity of **10** (PA(**10**) = 923 kJ•mol$^{-1}$) is significantly larger than that of 2-pentanone (PA(2-pentanone) = 833 kJ•mol$^{-1}$). Also, the protonation entropy $\Delta_pS°$(**10**) is negative and experiment and calculation are in excellent agreement, giving values of −43 and −48 J•K$^{-1}$•mol$^{-1}$, respectively (Table 5).

**SCHEME 2**



As noted above, we were unable to experimentally determine the protonation thermochemistry of **6** due to an exceedingly facile water loss from the protonated molecule. Fewer difficulties were encountered with 5-methoxy-2-pentanone, **10**, although some methanol loss does occur from MH$^+$. In fact, chemical ionization of **6** and **10** leads to *m*/*z* 85 fragment ions of identical structure as attested to by their mass analyzed ion kinetic energy (MIKE) and collisional activation spectra.[27] Moreover, these spectra are superimposable on those of the 1-methyl-1-tetrahydrofuranyl cation,[27] **11**, which is among the most stable cations of molecular formula $C_5H_9O$.[28] Formation of ions *m*/*z* 85, with the proposed structure **11**, has been also suggested to occur from reaction of **6** with acylium ions in the gas phase.[29] Formation of ion **11** from protonated 5-hydroxy-2-pentanone, **6**, or 5-methoxy-2-pentanone, **10**, may originate from an intramolecular nucleophilic substitution reaction in which the water (or methanol) loss is assisted by a cyclization process. Intramolecular nucleophilic substitution reactions have been experimentally demonstrated and their mechanisms theoretically detailed for protonated bifunctional molecules such as diols,[2j] diamines,[31] and amino alcohol.[2m] The situation should thus be comparable for protonated **6** and **10**. In the former case however, a second possibility of formation of the 1-methyl-1-tetrahydrofuranyl cation, **11**, is a direct water loss from the hydroxy protonated hemiacetal **6R**. Scheme 2 summarizes the two reaction routes of the hydroxy derivative **6** that have been investigated here at the B3LYP/6-31G(d) level.

The hydroxy protonated form of 5-hydroxy-2-pentanone, **6′H**$^+$, is found to be more stable in a conformation characterized by an elongated C−OH$_2$ bond (1.605 Å, Figure 4) associated with an incipient bonding interaction between the oxygen of the carbonyl and the C(5) methylene group (the O•••C distance is equal to 2.713 Å, Figure 4). The complete O···C ring closure accompanied by the $CH_2\cdots OH_2$ bond elongation would easily give the expected products **11** + $H_2O$. At the 298 K B3LYP/6-311+G(3df,2p)//B3LYP/6-31G(d) level, structure **6′H**$^+$ is situated 112 kJ·mol$^{-1}$ above **6H**$^+$ and 50 kJ·mol$^{-1}$ above the fragments **11** + $H_2O$. This means that the energy necessary for the cyclodehydration of **6H**$^+$ is at least equal to 112 kJ·mol$^{-1}$.

As noted above, protonation of the hemiacetal **6R** (or **6S**) occurs preferentially at the hydroxyl oxygen. Moreover, the resulting ion **6R′H**$^+$ may be seen as a complex between cation **11** and a water molecule. The simple bond cleavage of the components of this kind of complex is expected to occur without a reverse barrier, and consequently the critical energy of the fragmentation **6R′H**$^+$ → **11** + $H_2O$ should correspond exactly to its endothermicity. It should now be emphasized that the energy of **6R′H**$^+$ is only 12 kJ·mol$^{-1}$ above that of **6H**$^+$, and 50 kJ·mol$^{-1}$ below the separated products **11** + $H_2O$. Thus, it clearly appears that the process **6R′H**$^+$ → **11** + $H_2O$ is energetically more favorable than the intramolecular nucleophilic substitution reaction **6H**$^+$ → **6′H**$^+$ → **11** + $H_2O$ simply because **6′H**$^+$ is 112 kJ·mol$^{-1}$ above **6H**$^+$. It is therefore not impossible that the difficulties encountered during the experiments with 5-hydroxy-2-pentanone may be due to the existence of a mixture of structures **6** and **6R**/**6S** and to the facile water loss from the protonated form of the latter. Such a situation is not expected for the methoxy homologue since the hemiacetal formation is prevented by the absence of hydroxyl hydrogen.

## 4. Conclusion

The present study reports the first experimental investigation of the gas-phase basicity of an extensive set of hydroxyl- and methoxycarbonyl compounds. Experiments were carried out by equilibrium constant measurements at fixed (FT-ICR) or variable (HPMS) temperature. Enthalpic and entropic terms associated with the protonation process were examined by quantum chemistry calculations at the DFT B3LYP level using 6-31G(d) and 6-311+G(3df,2p) basis sets, as well as the G3 level of theory.

Basicities of the compounds studied are clearly affected by intramolecular hydrogen bonding, which is the cause of a dramatic enhancement of proton affinities and of a significant entropy effect. As expected from the geometric constraints on the arrangement of the atoms involved in the intramolecular hydrogen bonding, the increase in proton affinity parallels the number of carbon atoms separating the most favorable protonated site (the oxygen of the carbonyl group) and the second functionality (either a hydroxyl or methoxy group). Enhancement in proton affinity, with respect to the homologous ketone, lies between 10 and 90 kJ·mol$^{-1}$. Upon protonation, entropy losses as large as 50 J·mol$^{-1}$·K$^{-1}$ are detected and they are reasonably well reproduced via an analysis of intramolecular hindered rotations.

The strong basicity of hydroxy- and methoxycarbonyls is expected to have a profound influence on the reactivity of theses molecules in the gas phase, particularly in atmospheric and tropospheric chemistry where proton transfers are generally frequent. The reactivity of protonated 1,4-hydroxycarbonyl compounds, particularly by a dehydration process that leads to cyclic (furanoyl) cation, is also noteworthy.

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