On pK_a Matching as a Requirement To Form a Low-Barrier Hydrogen Bond. A Theoretical Study in Gas Phase

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Theoretical calculations in the gas phase on a series of intermolecular complexes formed between 1-methylimidazole (1-MeIm) and four carboxylic acids R−COOH, where R = CF_3, $CHCl_2$, $C(CH_3)Cl_2$, and CH_2Cl, have been carried out. Results from NMR and FTIR spectroscopy, in previous experimental studies, have been used by Frey and co-workers, trying to characterize the hydrogen bond between those carboxylic acids and 1-methylimidazole in aprotic organic solvents. Our energetic results for the proton transfer through the hydrogen bond indicate that only one of the carboxylic acids is able to form a low-barrier hydrogen bond (LBHB) with 1-MeIm in gas phase. However, there is not equalization between the pK_as of R−COOH and 1-MeImH^+ (the conjugate acid of 1-MeIm). We suggest that, for short hydrogen bonds, a requirement for forming a LBHB is energy degeneration (or nearly degeneration) of the two minima in a double-well hydrogen bond. This energy degeneration in the double well is determined by a thermodynamic cycle where the pK_a difference of the conjugate acids of the interacting groups is one of the factors taken into account. We have also shown that a delocalized LBHB is not necessarily stronger than a localized hydrogen bond. Along with the thermodynamic results, an analysis of the electronic wave function at several stationary points of the different complexes is presented.

Introduction

It is becoming clear that the catalytic power is mainly due to transition state stabilization,[1] but there is yet to be a consensus on how the stabilization is provided. Recently several authors have attributed differential stabilization of high-energy transition states and intermediates of enzymatic processes to the formation of "short strong" or "low-barrier" hydrogen bonds (LBHBs).[2−8] Although short strong or LBHBs have long been considered as possible features of transition states for acid−base-catalyzed reactions, the potential scope of the role they play in enzymatic catalysis has revived interest in them and is now being debated by several groups. The first way to denominate those hydrogen bonds refers to the short distance between hydrogen bond donor and acceptor atoms (<2.55 Å for O−H−O and <2.65 Å for O−H−N) experimentally measured by X-ray diffraction techniques.[3,4] The bond strength seems to be correlated with the bond distance, the shortest bonds being the strongest. Nevertheless, the direct relationship between hydrogen bond strength and length, particularly for very short hydrogen bonds, has been considerably discussed, and more recently it was remarked that there is no direct experimental evidence for it.[9]

Theoretical calculations as well as experimental measurements in the gas phase indicate that the hydrogen bond strength of an LBHB can be greater than 30 kcal/mol in comparison to "normal" hydrogen bonds that have strengths of only a few kilocalories per mole.[10] The strengths of LBHBs have also been associated with the fact that the energy barrier for proton transfer between donor and acceptor atoms is less than the zero-point energy level at the two hydrogen bond wells (hence, the term low barrier).[11] In such a situation the proton can freely move in the space between the heteroatoms. In a weak hydrogen bond the hydrogen is attached to one heteroatom by a covalent bond, whereas the interaction with the other heteroatom is largely electrostatic. Recently, all cases of strong and very strong O−H···O hydrogen bonds whose geometries are known from accurate neutron and X-ray diffraction studies have been reviewed by Gilli et al.[9] The authors classify short strong hydrogen bonds in three fundamental types: (1) −O−H···O^-−, or negative charge-assisted hydrogen bonding; (2) ═O···H^+···O═, or positive charge-assisted hydrogen bonding; (3) −O−H···O═, or resonance-assisted hydrogen bonding. They have postulated that while the O···O distance is shortened the hydrogen bond is transformed from an asymmetrical O−H···O electrostatic interaction to a symmetrical and covalent O···H···O bond. Although hydrogen bonds in systems where the two heteroatoms are different may also be the low-barrier type, they are probably not as strong as O···H···O bonds.[3]

According to several authors, a requirement for LBHB formation seems to be that the pK_as of the conjugate acids of the interacting groups must be matched within their microenvironment.[2−5,8,12] Gerlt and Gassman[2] proposed that the mechanisms of several enzyme-catalyzed reactions that involve abstraction of the α-proton of a carbon acid go through an enolic intermediate stabilized by the formation of an LBHB. This LBHB is formed between the uncharged active site general acidic catalyst and the substrate. The authors state that the pK_a of the acidic catalyst is approximately equal to that of the OH group of the enol tautomer of the substrate carbon acid. On the basis of the matching of these pK_as, they propose that the transition states for enzyme-catalyzed enolization reactions resemble the enolic intermediates formed in the concerted mechanism. The H-bond between enzyme and substrate may be initially weak then due to a mismatch in the pK_a of the donor and acceptor, while the equalization of pK_as in the transition state permits the strengthening of the H-bond. However, the analysis of this pK_a balance in enzyme active sites has been done with values of pK_as measured in aqueous solution because no unequivocal measurements are available for pK_as within the active sites of enzymes. The pK_as perturbation introduced by the enzymatic medium is then mainly inferred by analogy between several reactions or relying on chemical intuition.

Much of the recent discussion concerning the detection and

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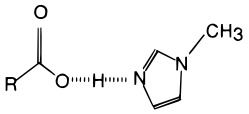


characterization of low-barrier hydrogen bonds has focused on the use of NMR chemical shifts.[13−16] Frey and co-workers have applied NMR and FTIR spectroscopies to study a series of intermolecular complexes formed between carboxylic acids and 1-methylimidazole in aprotic organic solvents (see Scheme 1).[17] Those complexes were taken as models of the hydrogen bond between His^{57} and Asp^{102} in the active site triad of chymotrypsin. In this enzymatic site, the hydrogen bond was described as an LBHB by the same authors[4] because the bridging proton resonates at an unusually low field in the NMR spectrum. Working with the complexes of Scheme 1, Frey and co-workers[17] measure downfield chemical shifts values (around 18 ppm) similar to the values observed in the enzymatic system. The largest chemical shift value corresponds to that complex that seems to present pK_a balance between the carboxylic acid and 1-methylimidazolium ion (the conjugate acid of 1-methylimidazole) in chloroform. However, there is a difference of 4.9 units between the corresponding pK_as in aqueous solution. Those NMR results, along with the values of antisymmetric C═O stretching frequencies and the shape of O−H stretching bands, support the assignment by Frey and co-workers of LBHBs in complexes of carboxylic acids with 1-methylimidazole when acidities are supposed to be matched. However, they do not reveal the strengths of those hydrogen bonds.

As stated above, the existence of LBHBs and their role in enzymatic processes have encountered opposing viewpoints in the literature. Guthrie and Kluger,[18] for example, argue in the general and specific case of mandelate racemase that electrostatic stabilization of the enolate could supply the required energy to allow rapid reactions of carbon acids, without recourse to any particular strong H-bonds. Warshel[19,20] suggests that in most cases enzymes need simply to align and provide an appropiate electrostatic potential to affect the catalysis they do; no pK_a balance or LBHBs need be invoked.[21] Warshel et al. also indicate that analyzing the energetics of hydrogen bond formation using the empirical valence bond method, one leads to the conclusion that LBHBs destabilize ionic transition states relative to asymmetric hydrogen bonds in enzymes as well as the corresponding case in water and thus leads to "anticatalysis".[1,22,23] Scheiner and Kar have recently carried out gas-phase ab initio calculations on several neutral and charged hydrogen-bonded complexes.[24] They concluded that interactions between neutral partners seldom exceed 10 kcal/mol and cannot be made stronger by compressing the H-bond to be shorter than its equilibrium length. Interactions between and ion and a neutral molecule are found to be much stronger, shorter, and without a significant barrier for proton transfer in gas-phase. The authors claim however than in enzymatic active sites the LBHBs hypothesis may only be valid if we think of a mechanism where two partners, one of them charged, are first held further apart than their equilibrium separation by the enzyme and, later, by releasing the constraint, the two groups approach one another, thus magnifying the H-bond energy and lowering the proton transfer potential energy barrier. This mechanism, though, would require an extra amount of energy to hold the two partners apart in the initial configuration. On the other hand, Scheiner et al. indicate that equalization of pK_as seems not to be associated with any special stabilization.

In this paper we intend to discuss some aspects of this complex subject. Concretely, we have done research on whether the pK_a equivalence is a requirement for forming an LBHB and whether an LBHB necessarily involves a strong hydrogen bond. To this aim we have theoretically studied in gas phase four of the complexes formed between carboxylic acids and 1-methylimidazole, which have previously been experimentally studied by Frey and co-workers in aprotic organic solvents.[17]

Method of Calculation

Ab initio restricted Hartree−Fock calculations have been carried out using the split valence 6-31+G basis set, which includes a diffuse sp shell on heavy atoms.[25] Full geometry optimization and direct location of stationary points have been done with the Schlegel gradient optimization algorithm.[26] The characterization of both kinds of stationary points, minima or transition state structures, has been carried out by diagonalizing their Hessian matrices and looking for zero or one negative eigenvalues, respectively.[27] In addition, some single-point calculations have been done with the 6-31+G(d,p) basis set, which also includes d and p polarization functions on heavy and hydrogen atoms, respectively. We have to underline that the systems studied in this work are quite sizeable. Thus, the 6-31+G basis set used for those electronic calculations presents an important number of basis functions: from 165 in the smallest system to 197 in the greatest complex. In the single-point calculations with the 6-31+G(d,p) basis set, the number of basis functions involved increases up to 305. Analysis of the electronic wave function has been performed by means of the theory of molecular structure proposed by Bader and co-workers.[28−31] According to this methodology, the total electronic charge density $\rho(\vec{r})$ and its Laplacian $\nabla^2\rho(\vec{r})$ are considered. The Laplacian of the charge density is defined as the sum of the three principal curvatures of the ρ function at each point in space. That is

$$\nabla^2\rho(\vec{r}) = \frac{\delta^2\rho}{\delta x^2} + \frac{\delta^2\rho}{\delta y^2} + \frac{\delta^2\rho}{\delta z^2}$$

When two neighboring atoms are chemically bonded to each other, a bond critical point ($\vec{r}_c$) in the charge density appears between them. At the bond critical point $\vec{\nabla}\rho(\vec{r}_c) = 0$, the charge density is a minimum at $\vec{r}_c$ along the bond path but a maximum along any orthogonal displacement. In turn, the Laplacian of the charge density at a point $\vec{r}$ in space determines where the electronic charge is locally concentrated ($\nabla^2\rho(\vec{r}) < 0$) or depleted ($\nabla^2\rho(\vec{r}) < 0$). So, when $\nabla^2\rho(\vec{r}_c)$ is negative, the electronic charge is locally concentrated in the internuclear region. This occurs due to shared (covalent) interactions. Conversely, for closed-shell (electrostatic) interactions $\nabla^2\rho(\vec{r}_c)$ is positive. This last kind of interaction is dominated by the contraction of charge away from the interatomic surface toward each of the nuclei. In a closed-shell interaction the atoms are bonded as a consequence of the charge that is concentrated within the basin of each atom. Taking all this into account, in a normal hydrogen bond the hydrogen atom is bound to the acid fragment by a shared interaction and to the base by a closed-shell interaction.[31]

δ_H NMR chemical shifts relative to hydrogen atoms in Si$(CH_3)_4$ have been obtained from nuclear magnetic shielding tensors calculated through the IGAIM[32] (individual gauges for atoms in molecules) method, which uses the coupled perturbed Hartree−Fock formalism.

Thermodynamic magnitudes have been computed by using the statistical thermodynamic formulation of partition functions within the ideal gas, rigid rotor, and harmonic oscillator models. A pressure of 1 atm and a temperature of 298.15 K have been

TABLE 1: Deprotonation Classical Energy,[a] Deprotonation Gibbs Free Energy[a] and Relative pK_as in Gas Phase Referred to the Corresponding Value of 1-MeImH$^+$ (Conjugated Acid of 1-Methylimidazole)

	ΔV	ΔG	ΔpK_a
1-MeImH$^+$	249.09	226.75	0
1	321.16	305.48	306.28
2	329.77	314.28	340.51
3	331.92	316.45	348.95
4	338.72	323.30	375.60

[a] In kcal/mol.

assumed in the calculations. The analytical second derivatives of the energy with respect to the Cartesian coordinates were used for the determination of vibrational frequencies.[33] The imaginary frequency is neglected in the thermodynamic evaluation for transition state structures.

Quantum-mechanical calculations have been done with the GAUSSIAN 94 package[34] and the Bader's analysis has been performed with the AIMPAC code.

Results and Discussion

The theoretical discussion on gas-phase LBHBs presented in this work focuses on four of the complexes experimentally studied by Frey and co-workers[17] in aprotic organic solvents. In particular we have analyzed the features of a series of intermolecular complexes formed between 1-methylimidazole (1-MeIm) and four carboxylic acids R−COOH, where R = CF_3 (**1**), $CHCl_2$ (**2**), $C(CH_3)Cl_2$ (**3**), and CH_2Cl (**4**).

Firstly, we have studied the deprotonation process of the four carboxylic acids and 1-methylimidazolium cation (1-MeImH$^+$), the conjugated acid of 1-MeIm. Classical energies (that is, not zero-point energy corrected) and Gibbs free energies (including zero-point correction, thermal contributions, and the entropic term) corresponding to those deprotonation reactions are given in Table 1, along with the pK_as of each acid in gas phase relative to the pK_a of 1-MeImH$^+$. The deprotonation is easier in terms of Gibbs free energy than in terms of classical energy due to the entropic contribution. Anyway, the variation of ΔG values along the set of acids parallels the corresponding variation of ΔV values. pK_a values are directly calculated from deprotonation Gibbs free energies. Since 1-MeImH$^+$ turns out to be the strongest acid in the gas phase, its pK_a was taken as origin of the relative pK_a scale. The adopted numeration for the carboxylic acids reflects the acidity ordering, from the most acidic (**1**) to the least acidic (**4**). Note that the pK_as values are unusually high because in our gas-phase calculation there is not any base to capture the lost proton.

Each carboxylic acid can give several complexes with 1-MeIm, depending on the number and type of intermolecular hydrogen bonds that are formed between the partners. To begin with, minimum energy structures corresponding to neutral, singly hydrogen-bonded complexes are displayed in Figure 1. In these structures the bridging proton is mainly bonded to the carboxylic acid, and, therefore, the partners in the complexes are essentially neutral. Although each complex involves just one hydrogen bond, there are also a number of secondary longer-distance interactions that contribute to their stabilization.

Classical energies (ΔV_n) and Gibbs free energies (ΔG_n) for the formation of the neutral complexes displayed in Figure 1 are given in Table 2. The values are relative to the neutral partners separated at infinite distance. Again, the values of ΔG_n parallel the ΔV_n values, although here the entropic term destabilizes the formation of the complexes, in such a way that for the carboxylic acids **2** and **4** dissociation of the complexes is thermodynamically favored. It is noteworthy that the shorter

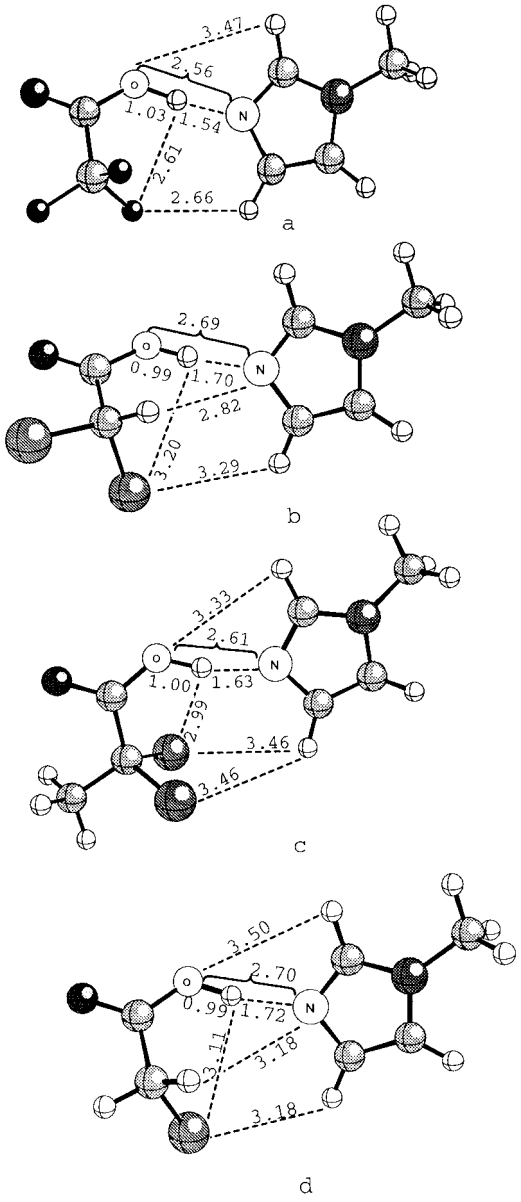


Figure 1. Minimum energy structures corresponding to the neutral complexes between 1-methylimidazole and the carboxylic acids R−COOH, where R is (a) CF_3 (**1**); (b) $CHCl_2$ (**2**); (c) $C(CH_3)Cl_2$ (**3**); and (d) CH_2Cl (**4**). Distances are given in Å.

TABLE 2: Classical Energy[a] and Gibbs Free Energy[a] for the Formation of the Neutral Complexes (Subscript n) and the Ionic Complexes (Subscript i) between the Corresponding Carboxylic Acid and 1-Methylimidazole[b]

	ΔV_n	ΔG_n	ΔV_i	ΔG_i	$\Delta V_i'$	$\Delta G_i'$
1	−15.34	−4.90	−18.79	−7.46	−90.86	−86.19
2	−10.29	0.85	−13.33	−4.41	−94.01	−91.94
3	−11.99	−1.22	−12.94	−2.28	−95.77	−91.98
4	−10.13	1.00	−9.13	1.84	−98.76	−94.71

[a] In kcal/mol. [b] ΔV_i and ΔG_i are relative to the neutral partners at infinite distance. $\Delta V_i'$ and $\Delta G_i'$ are relative to the ionic partners at infinite distance.

the hydrogen bond (see Figure 1), the more stable the complex. Conversely, there is no clear correlation between the strength of the hydrogen bond and the pK_a.

The bridging proton of the complexes shown in Figure 1 can be transferred to 1-MeIm through the hydrogen bond, so leading to the new four minimum energy structures displayed in Figure 2. These are ionic complexes coming from the formation of a single hydrogen bond between a carboxylate anion and 1-Me-

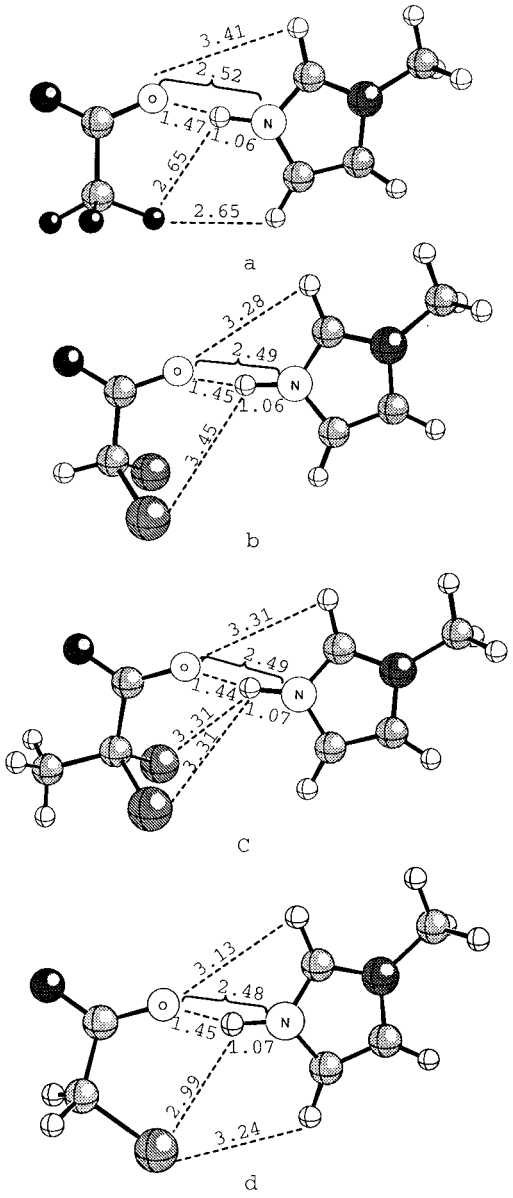
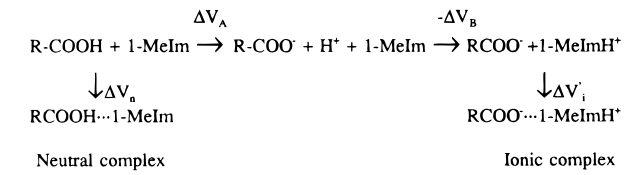


Figure 2. Minimum energy structures corresponding to the ionic complexes between 1-methylimidazole and the carboxylic acids R−COOH, where R is (a) CF_3 (**1**); (b) $CHCl_2$ (**2**); (c) $C(CH_3)Cl_2$ (**3**); (d) CH_2Cl (**4**). Distances are given in Å.

ImH^+. Classical energies and Gibbs free energies for the formation of these ion-paired complexes are given in Table 2. Values with respect to both carboxylic acid + 1-MeIm (ΔV_i and ΔG_i) and carboxylate anion + 1-$MeImH^+$ ($\Delta V_i'$ and $\Delta G_i'$) separated at infinite distance are presented. According to the deprotonation energies shown in Table 1, for the chemical systems in the gas phase studied in the present work, complex dissociation to give carboxylic acid + 1-MeIm is easier than fragmentation leading to carboxylate anion + 1-$MeImH^+$. Therefore we will use the ΔV_i and ΔG_i values to measure the hydrogen bond strength. As already seen above, Gibbs free energy values follow the same trends as classical energy values. As a consequence, our comments of results corresponding to ionic complexes exhibited in Table 2 will refer only to classical energy values.

In all these ionic structures the hydrogen bond is, as expected, clearly shorter than in the corresponding neutral complexes, while the relative position of the two fragments and the secondary interactions between them remain quite similar upon the proton transfer process. As for the hydrogen bond strength,

SCHEME 2



the ΔV_i values become more negative as the pK_a of the carboxylic acid decreases. That is, the hydrogen bond is stronger when the carboxylic acid is more acidic. Comparison with the ΔV_n reveals that the carboxylic acid **1** forms an ionic complex that is clearly more stable than the corresponding neutral one. The energy difference between the two types of hydrogen-bonded complexes gradually diminishes as the pK_a of the carboxylic acid increases, in such a way that for the complexes of the carboxylic acid **4**, the least acidic along the series, the neutral one is already the most stable.

The trends in formation energies of the different complexes from carboxylic acids and 1-MeIm at infinite distance can be better understood if we analyze the complexation process according to the formal thermodynamic steps outlined in Scheme 2. The formation of a neutral complex is done in just one step, which is associated with the classical energy difference ΔV_n. On the other hand, the formation of an ionic complex (ΔV_i) can be envisaged as the result of three successive steps: (1) deprotonation of the carboxylic acid, associated with the classical energy difference ΔV_A (ΔV_A stands for the deprotonation classical energy ΔV corresponding to the carboxylic acids **1**−**4** in Table 1); (2) protonation of 1-MeIm, which releases a classical energy ΔV_B (ΔV_B stands for the deprotonation classical energy ΔV of 1-$MeImH^+$ in Table 1); (3) formation of the ion-paired complex from the carboxylate anion and 1-$MeImH^+$ ($\Delta V_i'$ in Table 2). Then, assembling the three steps it can be seen that

$$\Delta V_i = \Delta V_A - \Delta V_B + \Delta V_i' \qquad (1)$$

$\Delta V_i'$ is much more negative than ΔV_n owing to the fact that it comes from bringing close two species of opposite charge in gas phase up to when the ion-paired complex is formed. Along the series of the carboxylic acids, ΔV_A and $\Delta V_i'$ evolve in opposite directions. As the carboxylic acid is less acidic, $\Delta V_i'$ becomes more negative (because of the more basic character of the corresponding carboxylate anion), but ΔV_A (involving positive values) grows faster, in such a way that ΔV_i gradually decreases.

In order to discuss whether the association of the carboxylic acids with 1-MeIm gives normal hydrogen bonds or LBHBs, we have studied the intramolecular proton transfer in the corresponding complexes. The neutral complexes (see Figure 1) and the ionic complexes (see Figure 2) are the reactants and products, respectively, of the proton transfer. The geometries of the transition states are displayed in Figure 3. In the four cases the proton is in flight from the carboxylic acid to 1-MeIm. The distances between the hydrogen-donor oxygen and the hydrogen-acceptor nitrogen atoms are compressed with respect to the situation at reactants and products, which facilitates the proton jump. As a consequence, the hydrogen bond and the secondary interactions between both fragments are shorter.

Barriers imposed by the proton transfer transition states are collected in Table 3. The values are given regarding both reactants (neutral complexes, indicated by the subscript n accompanying the number of the carboxylic acid that forms each complex) and products (ionic complexes, indicated by the subscript i). In terms of classical energy, a double well with

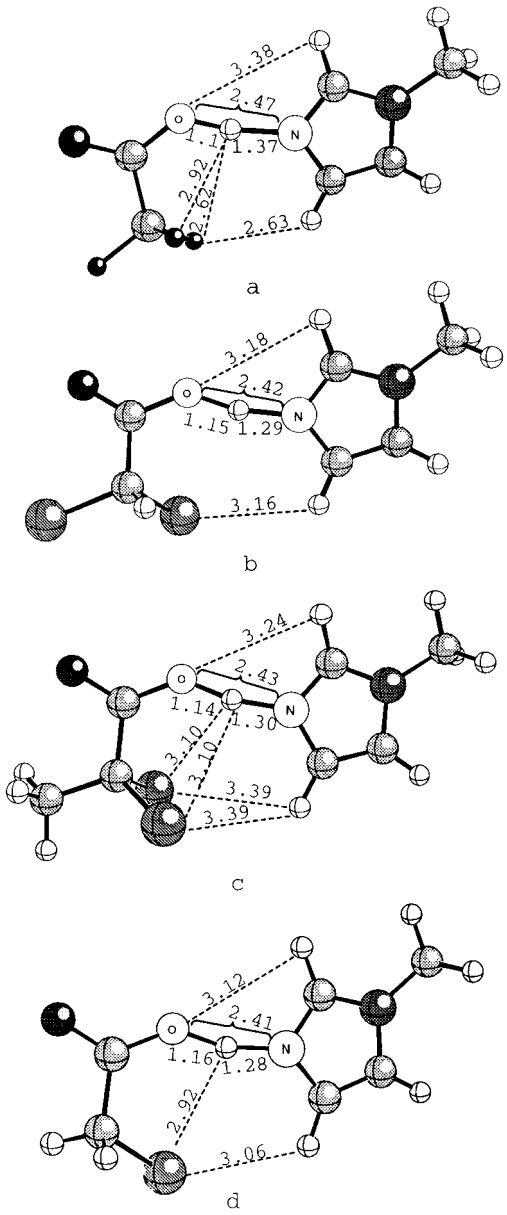


Figure 3. Transition states for the intramolecular proton transfer in the complexes between 1-methylimidazole and the carboxylic acids R−COOH, where R is (a) CF_3 (**1**); (b) $CHCl_2$ (**2**); (c) $C(CH_3)Cl_2$ (**3**); and (d) CH_2Cl (**4**). Distances are given in Å.

TABLE 3: Classical Energy Barrier,[a] Adiabatic Potential Energy Barrier,[a] Entropy Barrier,[b] and Gibbs Free Energy Barrier[a] for the Intramolecular Proton Transfer in the Complexes between the Corresponding Carboxylic Acid and 1-Methylimidazole[c]

	$\Delta V^{\ddagger}$	ΔE_0	$\Delta S^{0\ddagger}$	$\Delta G^{0\ddagger}$
$\mathbf{1}_n$	0.24	−1.62	−2.29	−1.25
$\mathbf{1}_i$	3.69	0.86	−2.42	1.31
$\mathbf{2}_n$	3.03	−0.01	−1.02	0.05
$\mathbf{2}_i$	6.07	3.04	−8.53	5.31
$\mathbf{3}_n$	1.29	−1.15	−2.61	−0.64
$\mathbf{3}_i$	2.24	−0.60	−4.28	0.42
$\mathbf{4}_n$	3.30	0.20	−1.64	0.47
$\mathbf{4}_i$	2.30	−0.60	−1.36	−0.37

[a] In kcal/mol. [b] In cal mol^{-1} K^{-1}. [c] Values associated to subscripts n or i are relative to neutral or ionic complexes, respectively.

energy barriers rather low (due to the short O−N distance at both reactant and product) is obtained for each case. However, the analysis of the adiabatic energy barrier (that is, including the zero-point energy), ΔE_0, is the crux of the problem. It is clear that the ground vibrational level of the double well corresponding to the carboxylic acid **1** belongs to the ionic complex ($\Delta E_0 > 0$). That is, the proton is localized in the well associated with the ionic complex. The same thing occurs for the carboxylic acid **2**. Conversely, the proton is confined to the neutral complex in the case of carboxylic acid **4**. The scenario for the carboxylic acid **3** is noticeably different and, in some way, intermediate between the situation associated with the carboxylic acids **1** or **2** and the carboxylic acid **4**. In the case of **3**, the ground vibrational level of the double well is above the adiabatic energy barrier, the shifting proton being delocalized between the hydrogen-donor and the hydrogen-acceptor atoms. None of the two complexes (neutral or ionic) has a real individual existence. What exists is an unique complex between the carboxylic acid **3** and 1-MeIm, in which the proton freely moves along the hydrogen bond. So, only the carboxylic acid **3** forms properly an LBHB. Note that it is the adiabatic energy rather than the free energy that determines the height of the vibrational level and the shape of the nuclear wave function. Free energy is rather related with the statistical population of that vibrational level. We should emphasize that the analysis of the adiabatic energy barrier that we have performed in this paper has to be taken with caution because it comes from a harmonic model. When the classical energy barrier is small the harmonic model is rather unrealistic for the vibrational normal modes in which the proton transfer reaction coordinate has an important contribution. A more accurate treatment would involve the determination of the ground vibrational level corresponding to the motion of the proton along the entire reaction coordinate (that is, from the neutral to the ionic complexes). If this ground vibrational level appeared above the adiabatic barrier, the proton would be delocalized along the double well. Anyway, the harmonic treatment of this paper can be useful to justify the qualitative trends of the complexes between the corresponding carboxylic acids and 1-methylimidazole.

At this point we have to emphasize that the LBHB corresponds to a carboxylic acid whose pK_a in gas phase is very far from matching the pK_a of 1-MeImH$^+$. The following discussion will enable us to understand this important result. According to Warshel,[35,36] within the EVB formalism, a hydrogen bond can be described by mixing three resonance configurations: two covalent and one ionic valence bond structures. For short hydrogen bonds, the proton transfer energy barrier is low because of two reasons: the jump of the proton is short and the effective coupling among the resonance forms can be strong enough to stabilize significantly the transition state. Then, an LBHB may appear. That is true in a double well whose two minima (A−H···B and A$^-$···H−B$^+$) are degenerate in terms of classical energy. However, when the two minima are nondegenerate, the energy barrier relative to the lower well may be high (as a result of adding the absolute value of the energy difference between both minima to the energy barrier relative to the upper well). In this case, the ground vibrational wave function may be confined in the lower energy well, so leading to a normal hydrogen bond in which the shifting proton will be attached to one of the partners. To summarize, energy degeneration (or almost degeneration) of the two minima is probably a requirement for the existence of an LBHB. Matching of pK_as does not imply degeneration unless the interaction energy between fragments A−H and B (ΔV_n in Scheme 2) be similar to the interaction energy between A$^-$ and H−B$^+$ ($\Delta V_i'$ in Scheme 2). On the contrary, if these two interaction energies differ, a particular value of $\Delta pK_a \neq 0$ is required to reach degeneration and, as a consequence, an LBHB. Indeed this is

TABLE 4: Analysis of the 6-31+G Electronic Wave Function at Several Stationary Points[a]

	ρ(O−H)[b]	ρ(H−N)[b]	$\nabla^2\rho$(O−H)[c]	$\nabla^2\rho$(H−N)[c]	δ_H[d]
$\mathbf{1}_i$	0.07	0.26	0.24	−1.22	7.89
$\mathbf{2}_i$	0.08	0.26	0.24	−1.19	8.07
$\mathbf{3}_i$	0.08	0.26	0.24	−1.17	8.38
$\mathbf{3}_{TS}$	0.17	0.14	−0.41	−0.18	9.17
$\mathbf{3}_n$	0.28	0.06	−1.35	0.17	4.86
$\mathbf{4}_n$	0.30	0.05	−1.51	0.16	3.72

[a] O, N, and H stand, respectively, for the oxygen, the nitrogen and the hydrogen atoms that form the hydrogen bond. Subscripts i or n indicate the ionic or neutral complex with 1-methylimidazole of the corresponding carboxylic acid. The label $\mathbf{3}_{TS}$ denotes the transition state for the intramolecular proton transfer in the complexes formed by the carboxylic acid **3**. [b] Charge density (in au) at the bond critical point of the corresponding bond. [c] Laplacian (in au) at the bond critical point of the corresponding bond. [d] NMR chemical shift (in ppm).

the case for the systems studied in this work. Since $\Delta V_n \gg \Delta V_i'$ (see Table 2), eq 1 requires that $\Delta V_A \gg \Delta V_B$ (a very clear mismatching of pK_as in terms of Gibbs free energy) to achieve degeneration ($\Delta V_n = \Delta V_i$) of both wells. This condition is fulfilled by the carboxylic acid **3**, but the pK_as of the carboxylic acids **1** and **2** are too close to the pK_a of 1-MeImH$^+$, and the pK_a of the carboxylic acid **4** becomes somewhat too far from it.

The same kind of thermodynamic cycle (see Scheme 2) should be also valid for systems in solution, although the numerical values associated with each step will vary when the environment changes. So, all these carboxylic acids are more acidic than 1-MeImH$^+$ in aqueous solution, where it is likely that ΔV_n and $\Delta V_i'$ become much more similar than in the gas phase,[22] in such a way that $\Delta pK_a = 0$ practically implies energy degeneration in this case. Note, however, that this matching of pK_as does not necessarily mean LBHB. Interestingly, on the basis of proton NMR chemical shifts measurements, Frey and co-workers[17] have found that the carboxylic acid **3** is also the best candidate for an LBHB with 1-MeIm in several organic aprotic solvents. They have assumed that this fact comes from matching of pK_as, although their actual values in these solvents are unknown (as a matter of fact they differ by 4.9 units in water). More probably, both pK_as mismatch just the adequate amount to compensate the possible difference in the above mentioned interaction energies.

Another important point is whether an LBHB is always a strong hydrogen bond. Our preliminary results in the gas phase seem to indicate that this is not true. A short strong hydrogen bond can be an LBHB if the corresponding double well involves two degenerated minima (for instance, in the hydrogen maleate anion in the gas phase).[37] However, a delocalized LBHB is not necessarily stronger than a localized hydrogen bond (recall that in this work the carboxylic acid **1** forms a localized hydrogen bond clearly stronger than the LBHB corresponding to the carboxylic acid **3**).

On the other hand, the other physicochemical parameter that has been used for characterizing LBHBs is the NMR chemical shift δ_H for the participating proton, which ranges from 16 to more than 20 ppm. As mentioned above, this is in fact the criterion used by Frey and co-workers[17] to identify LBHBs in molecular complexes composed of carboxylic acids and 1-MeIm. In order to relate those unusually low-field signals with the existence of an LBHB, we have analyzed the electronic wave function at several stationary points corresponding to the complexes studied in this work. As a result of this analysis, values of the electronic charge density and its Laplacian at the bond critical points of the hydrogen bond along with NMR proton chemical shift values are collected in Table 4. We have just considered the stationary points that better describe the actual location of the bridging proton in each case. For the carboxylic acid **1** we have said that the proton is trapped in the well corresponding to the ionic complex ($\mathbf{1}_i$). At this structure it can be seen that the proton is rather attached to the nitrogen atom of 1-MeIm (ρ(H−N) is larger than ρ(O−H) at the corresponding critical points) through a covalent bond, whereas the O−H interaction is electrostatic. An analogous description is suitable for the carboxylic acid **2**. The carboxylic acid **4** shows the opposite situation (neutral complex): the proton keeps covalently attached to the oxygen atom of the carboxylic acid and presents an electrostatic interaction with the nitrogen atom. Indeed a different behavior is predicted for the delocalized LBHB corresponding to the carboxylic acid **3**. Neither the ionic nor the neutral complexes adequately represent the proton location in this case. The most likely region of finding the proton in the vibrational ground state will be rather close to that occupied at the transition state. So, the shifting proton in this LBHB is viewed as being covalently bonded to both the carboxylic oxygen atom and the nitrogen atom of 1-MeIm. This double covalent interaction of the proton in the central region of the hydrogen bond is the fact that causes the unusually high value of the chemical shift, which is lower when one interaction is covalent and the other is electrostatic (i.e., with the proton attached to either the oxygen or the nitrogen atoms), as seen in Table 4. Anyway, the chemical shifts calculated at the 6-31+G level turn out to be smaller than the experimental values.[17] However, single-point 6-31+G(d,p) calculations at the 6-31+G structures show the same qualitative trends, although they reproduce quite well the experimental chemical shifts (values of $\delta_H = 20.78$, 17.17, and 13.22 ppm are obtained for the transition state, the ionic complex and the neutral complexes, respectively, formed by the carboxylic acid **3**). At this point, it should be remarked that although the maximum chemical shift appears to be associated with an LBHB situation our results lead to a large δ_H value even for a localized HB in an ionic complex.

Finally, we have to mention again that many other ways to form complexes exist in these chemical systems. So, the structures presented in Figures 1−3 lead to a new family of structures (practically degenerated with the former ones) by 1-MeIm rotation of 180° around the single hydrogen bond, in such a way that the methyl group in 1-MeIm and the R group in the carboxylic acid to the same side with respect to the hydrogen bond. A set of complexes involving two hydrogen bonds (by means of the two oxygen atoms of the carboxylic group) exists as well. For the sake of brevity, we have just focused on the structures shown in Figures 1, 2, and 3, which have enabled us to discuss the requirements for forming an LBHB.

Conclusions

In this paper we have theoretically studied in the gas phase the hydrogen bonds formed between four carboxylic acids and 1-methylimidazole (1-MeIm), which had been already experimentally studied in aprotic organic solvents by Frey and co-workers.[17] Our results indicate that only one of the carboxylic acids is able to form a low-barrier hydrogen bond (LBHB) with 1-MeIm. However, this LBHB corresponds to a carboxylic acid whose pK_a in the gas phase is very far from matching the pK_a of 1-MeImH$^+$. We suggest that, for short hydrogen bonds, energy degeneration (or nearly degeneration) of the two minima in a double-well hydrogen bond is a requirement for forming an LBHB.

Energy degeneration in the double well is the result of several contributions: pK_as of the two groups involved in the hydrogen

bond and interaction energies between the two fragments obtained by direct dissociation of each minimum. In a globally neutral hydrogen bond (in this case the two minima correspond to A−H···B and A^-···H−B^+, respectively), an LBHB requires that both pK_as mismatch just the suitable amount to compensate the difference between the A−H/B interaction energy and the A^-/H−B^+ interaction energy. This difference will be greater in the gas phase than in a polar environment.

In a globally ionic hydrogen bond (with two minima like A−H···B^- and A^-···H−B) both interaction energies (A−H/B^- and A^-/H−B) will tend to be more similar than in a globally neutral hydrogen bond. Then, in the ionic case more similar pK_as will be required for forming an LBHB, although the energy degeneration will be still determinated by the overall thermodynamic cycle.

Finally, we suggest that a delocalized LBHB is not necessarily stronger than a localized hydrogen bond, although a short strong hydrogen bond can be an LBHB if the corresponding double well involves two degenerate minima.

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