# Theoretical Study of the Low-Barrier Hydrogen Bond in the Hydrogen Maleate Anion in the Gas Phase. Comparison with Normal Hydrogen Bonds

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**Abstract:** Relative strengths of normal and low-barrier hydrogen bonds (LBHBs) in the gas phase were analyzed by means of quantum-mechanical and thermodynamic calculations on the mesaconic/citraconic and several maleic/fumaric cis/trans isomerization equilibria. All geometries were fully optimized with correlation effects included via second-order Møller−Plesset perturbation theory. The cis isomer of the maleic monoanion (also known as hydrogen maleate) is greatly stabilized in the gas phase owing to the formation of an intramolecular low-barrier hydrogen bond more than 20 kcal/mol stronger, in free energy terms, than the corresponding normal intramolecular hydrogen bond in maleic diacid. The very short internuclear distance (2.41 Å) obtained at the MP2 level between the hydrogen donor and the hydrogen acceptor in hydrogen maleate, as well as the high value of the NMR chemical shift for the participating proton, are two other characteristics experimentally attributed to the formation of an LBHB. The transition state structure for proton exchange in the maleic monoanion is symmetrical. In this structure, the interactions of the central hydrogen atom with the acceptor and the donor atoms are classified as covalent by Bader's theory of molecular structure. In any case, our calculations indicate that the zero-point energy for maleate monoanion is above the energy barrier for proton transfer. This fact allows free motion of the hydrogen atom lying on the ground vibrational state in accordance with the single symmetrical minimum experimentally predicted in nonpolar solvents.

## Introduction

It has recently been proposed that many catalytic mechanisms can be explained[1−8] through the formation of "short strong" or "low-barrier" hydrogen bonds that stabilize enzyme-bound intermediates and/or transition states. These short strong hydrogen bonds can form when the distance between the hydrogen-acceptor and the hydrogen-donor atoms is less than the sum of the corresponding van der Waals radii[4] (<2.55 Å for O−H−O and <2.65 Å for O−H−N). They are also called low-barrier hydrogen bonds (LBHBs)[9] because there seems to be a single potential energy well with no barrier or a low barrier to proton transfer between the donor and acceptor atoms.[3] On the other hand, one of the most unambiguous physicochemical parameters for characterizing LBHBs is the nuclear magnetic resonance (NMR) chemical shift $\delta_H$ for the participating proton, which ranges from 16 to more than 20 parts per million (ppm).[4]

LBHBs can have energies of formation in the gas phase as high as 31 kcal/mol, whereas ordinary hydrogen bonds of the type between water molecules are relatively weak (5 kcal/mol or even weaker in the gas phase). In an enzyme active site, the formation of an LBHB has been estimated to supply a stabilization energy from 10 to 20 kcal/mol in going from the enzyme−substrate complex to the enzyme−intermediate complex (or the transition state) of the catalytic mechanism.[3]

The requirements for forming an LBHB appear to be similar $pK_a$'s[1−4] (negative logarithm of the acid constant) of the hydrogen-donor and conjugate acid of the hydrogen-acceptor atoms involved in the bond and the absence of a hydrogen-bonding solvent such as water. This last condition is an example of the fact that the features (strength, bond distances, symmetry, ...) of an LBHB can dramatically depend on the environment.[10,11] So, some authors[12,13] have claimed that, owing to the electrostatic interaction with the polar environment, the delocalized charge arising from the electronic configuration of an LBHB destabilizes ionic transition states versus asymmetrical normal hydrogen bonds (non-LBHB) with more concentrated charges in condensed phases. This way, LBHBs could lead to anti-catalysis in enzymatic reactions.

Recently, Schwartz and Drueckhammer[14] have analyzed the effects of changes of solvent medium and hydrogen-bond donor and acceptor functionality on the relative strengths of normal and low-barrier hydrogen bonds in solution. They have experimentally studied the cis/trans isomerization equilibria between the maleic (**1c**)/fumaric (**1d**) diacids and the citraconic (**2c**)/mesaconic (**2d**) diacids, as well as the corresponding equilibria between their associated monoanions (**1a/1b** and **2a/2b**) using tetrabutylammonium as cation (see Scheme 1). It was assumed that neither the methyl substituent introduced in compounds labeled with number **2** nor the ion-pair interactions were relevant. Results of equilibration experiments show that the **1c/1d** and **2c/2d** diacids favor the trans isomers in all solvents studied. Monoanions also favor the trans isomers in protic solvents (water and metanol), though slightly less than

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(1) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1993**, *115*, 11552.
(2) Gerlt, J. A.; Gassman, P. G. *Biochemistry* **1993**, *32*, 11943.
(3) Cleland, W. W; Kreevoy, M. M. *Science* **1994**, *264*, 1887.
(4) Frey, P. A; Whitt, S. A.; Tobin**,** J. B. *Science* **1994**, *264*, 1927.
(5) Kenyon, G. L; Gerlt, J. A.; Petsko, G. A.; Kozarich, J. W. *Acc. Chem. Res.* **1995**, *28*, 178.
(6) Xiang, S.; Short, S. A.; Wolfenden, R.; Carter, C. W. *Biochemistry* **1995**, *34*, 4516.
(7) Cleland, W. W.; Kreevoy, M. M. *Science* **1995**, *269*, 104.
(8) Frey, P. A. *Science* **1995**, *269*, 104.
(9) Cleland, W. W. *Biochemistry* **1992**, *31*, 317.

(10) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 8559.
(11) Perrin, C. L. *Science* **1994**, *266*, 1665.
(12) Warshel, A.; Naray-Szabo, G.; Sussman, F.; Hwang, J. K. *Biochemistry* **1989**, *28*, 3629.
(13) Warshel, A.; Papazyan, A.; Kollman, P. A. *Science* **1995**, *269*, 102.
(14) Schwartz, B.; Drueckhammer, D. G. *J. Am. Chem. Soc.* **1995**, *117*, 11902.

**Scheme 1**



1,R=H
2,R=CH₃
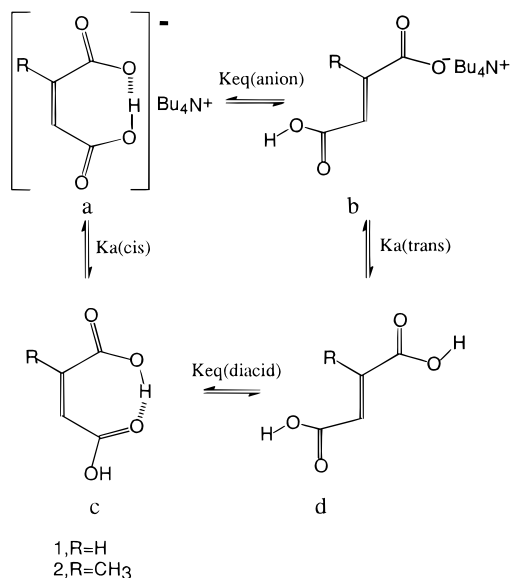
the diacids. Monoanions were found to greatly favor the cis isomer in aprotic solvents (DMSO and CHCl$_3$) under conditions in which the cis isomer forms an intramolecular LBHB. This LBHB of citraconic monoanion in chloroform was estimated to be 5.5 kcal/mol stronger, in terms of Gibbs free energy, than the normal hydrogen bond of the corresponding diacid. This value was considered[14] as a lower limit, since it is likely that larger LBHB energies may be achieved in solvents of lower polarity, although, unfortunately, it was not possible to extend the measurements to this kind of solvents. As an additional comparison, the trans isomer was favored in the isomerization equilibria of the monoanions of the citraconic/mesaconic monoamides in DMSO.

On the other hand, Gilli et al.[15] have classified all classes of short strong O−H···O hydrogen bonds in three fundamental types: negative charge-assisted hydrogen bonding (obtained by adding an electron), positive charge-assisted hydrogen bonding (arising from removing an electron), and resonance-assisted hydrogen bonding (where the two oxygens are interconnected by a system of $\pi$-conjugated double bonds). In these three cases, two energetically equivalent valence bond (VB) resonant forms can exist leading to a short strong hydrogen bond. The corresponding stabilization by resonance is the factor that permits one to overpass the steep increase of the interatomic repulsion term as the O···O distance shortens. Those authors have applied an empirical model to the case of the O−H···O hydrogen bond to postulate that while the O···O distance is shortened from 2.80 to 2.40 Å, the hydrogen bond is transformed from dissymmetrical O−H···O electrostatic interaction to a symmetrical and totally delocalized three-center, four-electron covalent O···H···O bond (the existence of resonant forms in the VB language leads to delocalization in terms of molecular orbitals). Gilli et al.[15] have suggested that such behavior is common to all homonuclear hydrogen bonds, while hetero-nuclear ones (i.e., N−H···O) can only give weaker bonds of mostly electrostatic nature. A more complete justification of the existence of LBHB comes from the EVB formulation due to Warshel's group.[16,17] The hydrogen bond can be described by mixing three resonance forms: two covalent and one ionic VB structures. At short distances, the effective coupling among them can be strong enough, leading to LBHB.

In order to discuss the properties of LBHBs in condensed phases, their features in the gas phase have to be previously analyzed. In this sense, SCF ab initio calculations, including correlation energy via second-order Møller−Plesset perturbation theory (MP2) at the SCF optimized geometries, on three very small systems have been used by Scheiner et al.[18] to argue against any special stability of hydrogen bonds associated with the disappearance of the proton transfer energy barrier by compression or with equalization of the p$K_a$'s.

To shed light into the nature and the electronic and energetic aspects of short strong or low-barrier hydrogen bonds, we have aimed in this paper to theoretically study in the gas phase the same systems experimentally examined by Schwartz and Drueckhammer[14] in different solvents. As stated above, they have suggested that the lower the solvent polarity, the stronger the LBHB. In this sense, the monoanion of the maleic acid (also known as hydrogen maleate anion) in the gas phase provides an excellent opportunity to study an LBHB in comparison with the normal hydrogen bond of the corresponding diacid or the hydrogen bond of the monoanion of the mono-amide.

## Method of Calculation

Ab initio restricted Hartree−Fock calculations have been carried out using the split valence 6-31+G(d,p) basis set, which includes d and p polarization functions on heavy and hydrogen atoms, respectively, and a diffuse sp shell on heavy atoms.[19] Correlation energy has been included by means of second-order Møller−Plesset perturbation theory.[20,21] Full geometry optimization and direct location of stationary points have been done with the Schlegel gradient optimization algorithm[22] at the two levels of calculation. 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 eigenvalue, respectively. We have to underline that the obtention of MP2 frequencies for these systems requires between 5 and 6 Gbytes of disk usage, which indicates the high computational cost of the calculations.

Analysis of the electronic wave function has been performed by means of the theory of molecular structure proposed by Bader and co-workers.[23−26] 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 $\rho$ 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 because of shared (covalent) interactions. Conversely, for closed-shell (electrostatic) interactions $\nabla^2\rho(\vec{r}_c)$ is positive. This last kind of interactions is dominated by the contraction of charge away

(15) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J.Am. Chem. Soc.* **1994**, *116*, 909.
(16) Warshel, A.; Muller, R. P. *J. Phys. Chem.* **1995,** *99,* 17516.
(17) Warshel, A.; Robert, M. W. *J. Am. Chem. Soc.* **1980,** *102,* 6218.
(18) Scheiner, S.; Kar, T. *J. Am. Chem. Soc.* **1995**, *117*, 6970.
(19) (a) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P.v.R. *J. Comput. Chem.* **1983**, *4,* 294. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80,* 3265.
(20) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46,* 618.
(21) Binkley, J. S; Pople, J. A. *Int. J. Quantum Chem.* **1975**, *9,* 229.
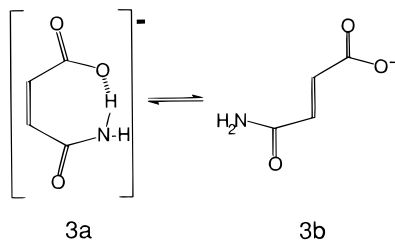(22) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3,* 214.
(23) Bader, R. F. W.; Tal, Y.; Anderson, S. G.; Nguyen-Dang, T. T. *Isr. J. Chem.* **1980**, *19,* 8.
(24) Bader, R. F. W. *Acc. Chem. Res.* **1985**, *18,* 9.
(25) Bader, R. F. W.; Carroll, M. T.; Cheeseman, J. R.; Chang, C. *J. Am. Chem. Soc.* **1987,** *109,* 7968.
(26) Bader, R. F. W. *Atoms in Molecules. A Quantum Theory;* Oxford University Press: New York, 1990.

**Scheme 2**



3a                                    3b

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.[26]

Atomic net charges have been calculated by means of the integration of the electronic charge density over the corresponding atomic basins as done by the PROAIM algorithm.[27]

$\delta_H$ NMR chemical shifts relative to hydrogen atoms in $Si(CH_3)_4$ have been obtained from nuclear magnetic shielding tensors calculated through the IGAIM[28] (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 assumed in the calculations. The analytical second derivatives of the energy with respect to the Cartesian coordinates[29−31] (at both Hartree–Fock and MP2 levels) were used for the determination of vibrational frequencies. The imaginary frequency is neglected in the thermodynamic evaluation for transition-state structures.

Quantum-mechanical calculations have been done with the GAUSSIAN 94 package,[32] and the Bader's analysis has been performed with the AIMPAC code.

## Results and Discussion

It has already been mentioned in the Introduction that some of the properties that seem to characterize LBHBs are the distance between the hydrogen-acceptor and the hydrogen-donor atoms, a low barrier to proton transfer between the donor and acceptor atoms, the hydrogen bond strength, and the NMR chemical shift $\delta_H$. In what follows we will analyze each of these parameters for the species studied in this work.

Firstly, we have performed a geometrical analysis of the minimum energy structures of the eight compounds displayed in Scheme 1 (the tetrabutylammonium cation has not been included in our calculations) and the monoanions of the maleic (**3a**) and fumaric (**3b**) monoamides (see Scheme 2). Their most relevant geometrical parameters at the 6-31+G(d,p)//6-31+G-(d,p) and the MP2/6-31+G(d,p)//MP2/6-31+G(d,p) levels are presented in Tables 1 and 2, respectively. From here on, A and D will stand for the hydrogen-acceptor and the hydrogen-donor atoms, respectively.

(27) Biegler-König, F. W.; Bader, R. F. W.; Tang, T.-H. *J. Comput. Chem.* **1982**, *3*, 317−328.

(28) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1992**, *194*, 1.

(29) Pople, J. A.; Krishnan, A.; Schlegel, H. B.; Binkley, J. S. *Int. J. Quantum Chem., Quantum Chem. Symp.* **1979**, *13*, 225.

(30) Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122.

(31) Trucks, G. W.; Frisch, M. J.; Andres, J. L.; Schlegel, H. B. *J. Chem. Phys.*, submitted for publication.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian 94; Gaussian, Inc.: Pittsburgh, PA, 1995.

**Table 1.** Most Relevant Geometrical Parameters of the Minimum Energy Structures at the 6-31+G(d,p)//6-31+G(d,p) Level[a]

|  | D−A | D−H | A−H | D−H−A |
|---|---|---|---|---|
| **1a** | 2.49 | 1.00 | 1.49 | 172.15 |
| **1b** |  | 0.95 |  |  |
| **1c** | 2.69 | 0.96 | 1.73 | 164.20 |
| **1d** |  | 0.95 |  |  |
| **2a** | 2.47 | 1.00 | 1.47 | 171.34 |
| **2b** |  | 0.95 |  |  |
| **2c** | 2.62 | 0.96 | 1.67 | 166.67 |
| **2d** |  | 0.95 |  |  |
| **3a** | 2.68 | 1.01 | 1.71 | 158.09 |
| **3b** |  | 0.99 |  |  |
| **1a** + $H_2O$ (D) | 2.47 | 1.01 | 1.45 | 172.31 |
| **1a** + $H_2O$ (A) | 2.50 | 0.99 | 1.52 | 171.36 |

[a] The labels are defined in Schemes 1 and 2. A and D stand for the hydrogen-acceptor and the hydrogen-donor atoms, respectively. H denotes the atom forming the hydrogen bond. Distances and angles are given in Å and degrees, respectively.

**Table 2.** Most Relevant Geometrical Parameters of the Minimum Energy Structures at the MP2/6-31+G(d,p)//MP2/6-31+G(d,p) Level[a]

|  | D−A | D−H | A−H | D−H−A |
|---|---|---|---|---|
| **1a** | 2.41 | 1.12 | 1.30 | 178.09 |
| **1b** |  | 0.97 |  |  |
| **1c** | 2.65 | 0.99 | 1.67 | 169.61 |
| **1d** |  | 0.95 |  |  |
| **3a** | 2.64 | 1.04 | 1.63 | 163.19 |
| **3b** |  | 1.01 |  |  |
| **1a** + $H_2O$ (A) | 2.45 | 1.06 | 1.39 | 176.95 |

[a] The labels are defined in Schemes 1 and 2. A and D stand for the hydrogen-acceptor and the hydrogen-donor atoms, respectively. *H* denotes the atom forming the hydrogen bond. Distances and angles are given in Å and degrees, respectively.

Let us begin with Hartree–Fock results. The short D−A distance in the maleic monoanion (**1a**) seems to indicate the existence of a LBHB, and it is clearly shorter than the D−A distance in the maleic diacid (**1c**). The introduction of a methyl substituent to give **2a** and **2c** slightly reduces the A−H distance (and therefore the **D−A** one), but it does not significantly change the features of the hydrogen bonds, so confirming the experimental assumption.[14] The D − A distance in the monoanion of the maleic monoamide (**3a**) is in between the corresponding values in **1a** and **1c**, specially taking into account that the donor atom in **3a** (a nitrogen atom) has longer van der Waals radii than the donor atom (an oxygen atom) in **1a** and **1c**. The D − H distance is always longer in the cis forms, where the hydrogen bond exists, than in the trans forms, the difference being greater for the **1a**/**1b** and **2a**/**2b** pairs. Indeed this is due to a short A−H interaction that weakens the D−H bond in these cases. On the other hand, all atoms in structures **1a**, **1c**, and **3a** are almost coplanar. The effect of one water molecule can be seen in the last two rows of Table 1. The minimum energy structure corresponding to the maleic monoanion with a water molecule solvating the donor oxygen (**1a** + $H_2O$ (D)) has a slightly shorter D - A distance than in **1a**. This is due to the fact that the water molecule increases the acidity of the donor oxygen, so reinforcing the hydrogen bond. That is, because the nonsolvated maleic monoanion turns out to be clearly asymmetrical at the Hartree–Fock level, the introduction of a water molecule solvating the donor oxygen moves the hydrogen bond toward a slightly more symmetrical structure. On the contrary, a water molecule near the acceptor oxygen diminishes its basicity, so weakening the hydrogen bond and increasing the D - A distance in **1a** + $H_2O$ (A).

MP2 geometries (see Table 2) confirm the trends above described arising from Hartree-Fock structures. In this case, however, in the structure **3a** the carboxylate group is somewhat

**Table 3.** Most Relevant Geometrical Parameters of the Transition State for the Intramolecular Proton Transfer in the Maleic Monoanion[a]

|  | D–A | D–H | A–H | D–H–A |
|---|---|---|---|---|
| 6-31+G(d,p)//6-31+G(d,p) | 2.36 | 1.18 | 1.18 | 175.46 |
| MP2/6-31+G(d,p)//MP2/6-31+G(d,p) | 2.40 | 1.20 | 1.20 | 178.47 |

[a] A and D stand for the hydrogen-acceptor and the hydrogen-donor atoms, respectively. H denotes the atom forming the hydrogen bond. Distances and angles are given in Å and degrees, respectively.

**Table 4.** 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 Maleic Monoanion

|  | $\Delta V^{\ddagger}$ | $\Delta E_0$ | $\Delta S^{\circ\ddagger}$ | $\Delta G^{\circ\ddagger}$ |
|---|---|---|---|---|
| 6-31+G(d,p)//6-31+G(d,p) | 1.88 | −0.85 | −1.87 | −0.51 |
| MP2/6-31+G(d,p)//MP2/6-31+G (d,p) | 0.03 | −0.99 | −1.35 | −0.79 |

[a] In kcal/mol. [b] In cal mol$^{-1}$ K$^{-1}$.

twisted (25°) about the C-C bonds. Anyway, it is noteworthy that MP2 D-A distances are shorter than the corresponding Hartree-Fock ones, especially in the maleic monoanion (**1a**). The O−O distance calculated for this molecule (2.41 Å) is in very good agreement with the corresponding experimental measurements for different salts of hydrogen maleate (2.40−2.44 Å).[33]

One of the fundamental questions regarding hydrogen bonds is whether the potential energy surface for motion of the hydrogen has a single minimum or two. If single, the hydrogen is centered between the two electronegative atoms. If there are two minima, the hydrogen is closer to one electronegative atom (the donor) than to the other (the acceptor). There are then two distinct tautomeric forms, which interconvert each other through the centered structure which plays the role of transition state for the intramolecular proton transfer. X-ray[34] and neutron diffraction[35] studies indicate that the hydrogen bond in the maleic monoanion involves a single symmetrical minimum in crystals. As a matter of fact, recent studies reveal a slight asymmetry in several salts, the greatest difference (0.288 Å) between the two O − H distances appearing in the sodium salt.[36] In turn, NMR experiments[10,11] show that this monoanion exists as a single symmetrical structure in a nonpolar solvent but as two equilibrating tautomers in aqueous solution. These changes demonstrate the effect of the environment. Until now, theoretical calculations have shown that the hydrogen bond in the maleic monoanion is asymmetrical with a double well at the Hartree−Fock level using different basis sets,[33,37,38] although the introduction of electron correlation at MP2 level, keeping the Hartree-Fock optimized geometries frozen, seems to predict a single well.[33,38] However our MP2 results still yield two minima, although geometrically much closer than our two Hartree-Fock minima. That is, the interconversion between the two minima involves a hydrogen jump of about 0.49 Å at Hartree-Fock level, but of only 0.18 Å at MP2 level.

Let us turn our attention to the intramolecular proton transfer in the maleic monoanion (**1a**). Geometric and energetic features of the corresponding transition state are given in Tables 3 and 4, respectively. Indeed the transition state is symmetrical at the two levels of calculation. The Hartree-Fock classical energy

(33) Ríos, M. A.; Rodríguez, J. *Can. J. Chem.* **1993**, *71*, 303 and references therein.
(34) Darlow, S. F.; Cochram, W. *Acta Crystallogr.* **1961**, *14*, 1250.
(35) Peterson, S. W.; Levy, H. A. *J. Chem. Phys.* **1958**, *29*, 948.
(36) Olovsson, G.; Olovsson, I.; Lehmann, M. S. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1984**, *C40*, 1521.
(37) George, P. *J. Phys. Chem.* **1983**, *87*, 1839.
(38) Hodošček, M.; Hadži, D. *J. Mol. Struct. (THEOCHEM)* **1990**, *209*, 411.

**Table 5.** Classical Energy of Reaction,[a] Entropy of Reaction,[b] and Gibbs Free Energy of Reaction[a] for the Cis/Trans Isomerization

|  | $\Delta V$ | $\Delta S^{\circ}$ | $\Delta G^{\circ}$ |
|---|---|---|---|
| | 6-31+G(d,p)//6-31+G(d,p) | | |
| **1a → 1b** | 10.07 | 3.93 | 9.09 |
| **1c → 1d** | −5.98 | 1.41 | −6.61 |
| **2a → 2b** | 12.72 | 5.02 | 11.53 |
| **2c → 2d** | −3.09 | 2.10 | −3.70 |
| **3a → 3b** | 5.88 | −0.41 | 5.69 |
| | MP2/6-31+G(d,p)//MP2/6-31+G(d,p) | | |
| **1a → 1b** | 14.14 | 4.14 | 14.62 |
| **1c → 1d** | −4.21 | 4.85 | −5.81 |
| **3a → 3b** | 7.89 | 2.84 | 7.19 |

[a] In kcal/mol. [b] In cal mol$^{-1}$ K$^{-1}$.

barrier is modest, but the MP2 one turns out to be vanishingly small so that it has no practical physical meaning. Anyway, the adiabatic potential energy barrier (that is, including zero-point energy) is negative at both levels. Despite the negative value of the entropy barrier (due to the higher order associated with the symmetrical transition state), the Gibbs free energy barrier is also negative. However, the values of these thermodynamic magnitudes should be taken with caution in the present case because they come from a harmonic model. Although the harmonic analysis is useful, its application for the vibrational normal modes in which the proton transfer reaction coordinate has an important contribution could be rather unrealistic because of the small classical proton transfer energy barrier. Another point of view that describes probably better the physical situation is that the ground vibrational level corresponding to the motion along the reaction coordinate lies above the adiabatic barrier, this way allowing the free shift of the proton between the two oxygen atoms. That is to say, the bridging hydrogen atom is delocalized. In this sense, the hydrogen bond in the maleic monoanion can be indeed called a low-barrier hydrogen bond. Keeping this in mind, the existence of two minima in terms of classical energy is not relevant, since the proton will not be trapped in either of them. On the contrary, an analysis of the nuclear wave function of that ground vibrational state would probably show that the most likely region to find the proton is the one close to the symmetrical structure, in good agreement with the above-mentioned experimental results.

On the other hand, only an asymmetrical minimum exists for the maleic diacid (**1c**) or the monoanion of the maleic monoamide (**3a**) (corresponding to the structures displayed in Schemes 1 and 2, respectively). This fact can be easily understood considering the quite lower basicity of the hydrogen acceptor atom in **1c** and the quite lower acidity of the hydrogen donor atom in **3a** relative to the maleic monoanion (**1a**).

Relative strengths of the hydrogen bonds can be evaluated from the study of the cis/trans isomerization equilibria displayed in Schemes 1 and 2. Table 5 collects the results. For the sake of brevity, we will only comment on the MP2 ones here. The cis maleic monoanion (**1a**) is 14.14 kcal/mol more stable than the trans fumaric monoanion (**1b**) in terms of classical energy (an old CNDO2 calculation[39] provided an exaggerated value of 29.8 kcal/mol) and 14.62 kcal/mol in terms of Gibbs free energy. On the contrary, the trans fumaric diacid (**1d**) is more stable than the cis maleic diacid (**1c**). Thus, the difference in hydrogen bond strengths between the strong hydrogen bond in **1a** and the normal hydrogen bond in **1c** is 18.35 kcal/mol and 20.43 kcal/mol in classical energy and Gibbs free energy, respectively. These theoretical results turn out to be in very good qualitative agreement with the experiments of Schwartz and Drueckhammer.[14] From a quantitative point of view, it has

(39) Murthy, A. S. N; Bhat, S. N; Rao, C. N. R. *J. Chem. Soc. A* **1970**, *1970*, 1251.

**Table 6.** Analysis of the 6-31+G(d,p)//6-31+G(d,p) Electronic Wave Function of the Stationary Points[a]

| | $\rho(\text{D-H})^b$ | $\rho(\text{A-H})^b$ | $\nabla^2\rho(\text{D-H})^c$ | $\nabla^2\rho(\text{A-H})^c$ | $q_D{}^d$ | $q_A{}^d$ | $q_H{}^d$ | $\delta_H{}^e$ |
|---|---|---|---|---|---|---|---|---|
| **1a** | 0.31 | 0.07 | −2.13 | 0.19 | −1.44 | −1.90 | 0.75 | 12.44 |
| **1b** | 0.39 | | −2.54 | | −1.34 | | 0.65 | 2.02 |
| **1c** | 0.37 | 0.04 | −2.68 | 0.14 | −1.39 | −1.41 | 0.72 | 7.02 |
| **1d** | 0.38 | | −2.57 | | −1.34 | | 0.67 | 3.31 |
| **3a** | 0.33 | 0.04 | −1.93 | 0.15 | −1.59 | −1.48 | 0.62 | 8.19 |
| **3b** | 0.36 | | −2.00 | | −1.63 | | 0.45 | 2.03 |
| ts/**1a** | 0.18 | 0.18 | −0.44 | 0.44 | −1.45 | −1.45 | 0.74 | 18.79 |

[a] A, D and H stand for the hydrogen-acceptor atom, the hydrogen-donor atom, and the atom forming the hydrogen bond, respectively. The label ts/**1a** denotes the transition state for the intramolecular proton transfer in **1a**. [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] Atomic net charges (in au). [e] NMR chemical shift (in ppm).

to be recalled that these authors estimate that the hydrogen bond in **2a** is only 5.5 kcal/mol (in Gibbs free energy) stronger than in **2c** with chloroform as a solvent, although they think that larger values could be obtained in lower dielectric constant media. In this sense, our gas-phase theoretical calculations represent a scenario of lowest polarity. Another point to be considered is that the presence of a cation in the experiments could weaken the hydrogen bond in the charged monoanions, this way leading to a lesser stabilization of the corresponding cis structures.

MP2 results show that, paralleling geometrical features, the strength of the hydrogen bond in the monoanion of the maleic monoamide (**3a**) is in between the hydrogen bonds in **1a** and **1c**. Unexpectedly, the cis form (**3a**) is still clearly more stable than the trans isomer (**3b**) in the gas phase. The discrepancy with the experiments in DMSO could be explained by the action of the solvent and the cation.

On the other hand, the systems of Scheme 1 provide an excellent example to understand the role of an LBHB in facilitating some chemical reactions, at least in the gas phase. The loss of one carboxylic hydrogen of the trans fumaric diacid (**1d** → **1b**) is quite difficult. However, the deprotonation of the cis maleic diacid (**1c** → **1a**) is much easier. The $pK_a$ of **1c** turns out to be 61.1 and 79.4 units less than the $pK_a$ of **1d** at Hartree-Fock and MP2 levels, respectively. The reason is that, along the deprotonation of **1c**, a normal hydrogen bond is substituted by a very strong hydrogen bond, which stabilizes the final product **1a**. Note that the values of $pK_a$ are unusually high because there is not any base to capture the lost proton in our gas-phase calculations.

In order to discuss the properties of the Hartree-Fock electronic wave function, the values of the charge density and the Laplacian at the bond critical points of the hydrogen bond of the stationary points are collected in Table 6, along with the net charge of the three atoms involved in the hydrogen bond and the NMR chemical shift. The corresponding values for MP2 structures are presented in Table 7 and in Figure 1.

At both levels of calculation, the values of the charge density at the bond critical points exhibit a quite good correlation with the bond distances: the shorter the bond, the larger the $\rho$ value. So, the D-H and the A-H bonds in a given structure are somewhat more similar at the MP2 level than at the Hartree-Fock level. Very interestingly, the analysis of the Laplacian shows that each hydrogen bond involves a covalent interaction with the donor atom and an electrostatic interaction with the acceptor atom, except for the intramolecular proton transfer transition state in the maleic monoanion, where both interactions are covalent (both bond critical points appear inside the negative zone of the Laplacian). This result is in agreement with the assumption of Gilli et al.[15] that the degree of covalency increases with the shortening of the D - A distance and that in very short hydrogen bonds both O - H become essentially covalent (the O-O distances are as short as 2.36 Å and 2.40 Å for Hartree - Fock and MP2 transition states, respectively). Recall that, as

above stated, it is expected that the proton be preferably located close to a symmetrical position (the one corresponding to the transition state) in the maleic monoanion; this way two covalent interactions should be predicted.

On the other hand, a ring point appears in the center of each cis structure. This ring point is a minimum of the charge density on the plane considered, but a maximum in the orthogonal direction, and indicates the existence of a closed chain of bond paths linking the seven nuclei around it.

The appearance of a low-field proton signal (i.e., at high $\delta_H$ values) in the NMR spectrum is a well-known effect of forming a hydrogen bond. Unusually high values of the chemical shift characterize LBHBs in simple compounds. So, the acidic proton in the tetrabutylammonium salt of the maleic monoanion exhibits a NMR chemical shift of more than 20 ppm in several organic solvents.[4,40,41] An analysis of calculated $\delta_H$ values for MP2 structures allows us to distinguish between the trans isomers (no hydrogen bond, hence small chemical shift) and the cis isomers (hydrogen bond, then high chemical shift), and to classify hydrogen bonds in three groups following an increasing order of $\delta_H$ values: (a) normal neutral hydrogen bond (in **1c**); (b) normal charged hydrogen bond (in **3a**); and (c) LBHB (in **1a**), with $\delta_H = 17.78$ (18.85 in the symmetrical transition state that describes better the features of the hydrogen bond in the maleic monoanion). It can be observed that the chemical shift values for Hartree-Fock structures are smaller (especially in the case of **1a**), although the qualitative description is similar. On the other hand, it has to be noted that net charges on hydrogen atoms do not correlate with chemical shifts. This is due to the fact that $q_H$ values are only directly related to the local diamagnetic term of the shielding constant, but there exist additional contributions like the local paramagnetic term (which depends on excited electronic states) and the magnetic anisotropy of neighboring bonds.

## Conclusions

In this paper we have theoretically studied the intramolecular hydrogen bond in the maleic monoanion in the gas phase. This hydrogen bond presents all the properties that have been attributed to a low-barrier hydrogen bond: (a) a very short distance between the hydrogen-donor and the hydrogen-acceptor atoms; (b) delocalization of the bridging hydrogen atom lying on the ground vibrational state, whose energy is above the adiabatic energy barrier for intramolecular proton exchange; (c) an enhanced strength relative to a normal hydrogen bond (more than 20 kcal/mol stronger than the corresponding normal hydrogen bond in the maleic diacid); and (d) an unusually very high value of $\delta_H$ NMR chemical shift.

(40) Gunnarsson, G.; Wennerström, H.; Egan, W.; Forsén, S. *Chem. Phys. Lett.* **1976**, *38*, 96.

(41) Brezinski, B.; Szafran, M. *Org. Magn. Reson.* **1981**, *15*, 78.
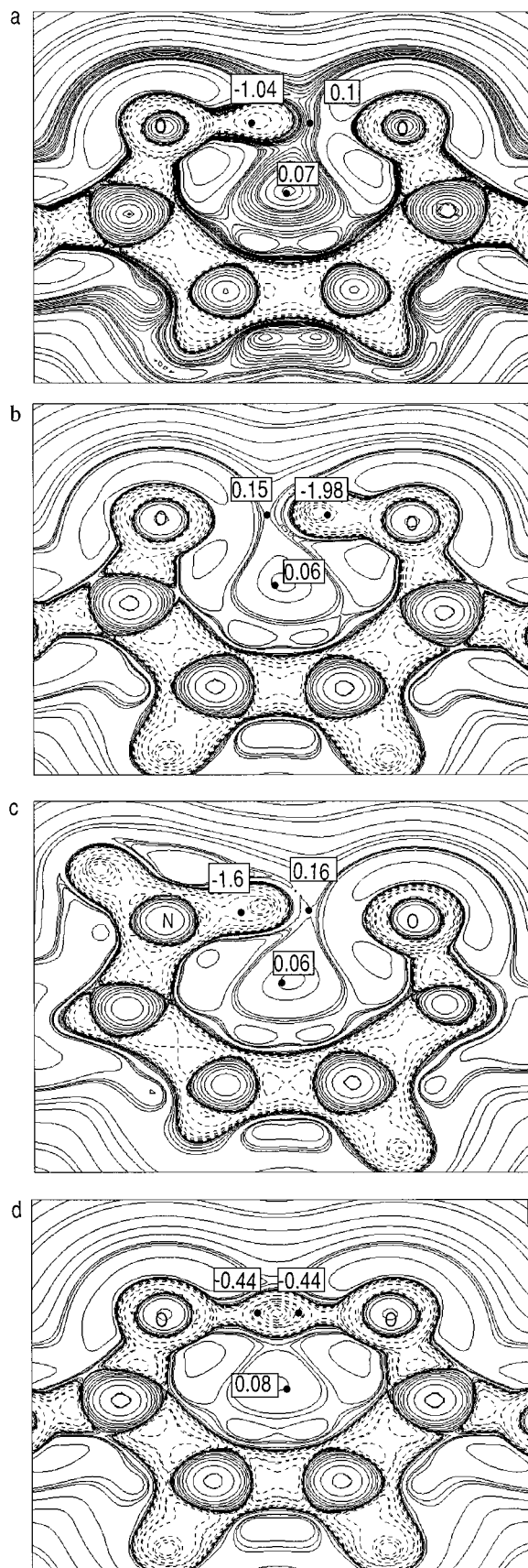
**Figure 1.** Isodensity contour plots of the MP2/6-31+G(d,p)//MP2/6-31+G(d,p) Laplacian $\nabla^2\rho(\vec{r})$ in the plane containing the three atoms that intervene in the hydrogen bond at the stationary points corresponding to (a) **1a**; (b) **1c**; (c) **3a**; (d) transition state of the intramolecular proton transfer in **1a**. Dashed lines correspond to regions in which $\nabla^2\rho(\vec{r}) < 0$, and solid lines correspond to regions in which $\nabla^2\rho(\vec{r}) > 0$. Numbers indicate the $\nabla^2\rho(\vec{r})$ values (in atomic units) at the bond critical points of the hydrogen bond and the ring point.

**Table 7.** MP2/6-31+G(d,p)//MP2/6-31+G(d,p) Charge Densities[a] at the Bond Critical Points, Atomic Net Charges,[a] and NMR Chemical Shift[b] of the Stationary Points[c]

|       | $\rho$(D-H) | $\rho$(A-H) | $q_D$  | $q_A$  | $q_H$ | $\delta_H$ |
|-------|-------------|-------------|--------|--------|-------|------------|
| **1a** | 0.24       | 0.09        | −1.26  | −1.26  | 0.66  | 17.78      |
| **1b** | 0.36       |             | −1.17  |        | 0.60  | 2.96       |
| **1c** | 0.34       | 0.05        | −1.21  | −1.19  | 0.66  | 8.89       |
| **1d** | 0.35       |             | −1.18  |        | 0.63  | 4.36       |
| **3a** | 0.30       | 0.06        | −1.37  | −1.28  | 0.57  | 10.55      |
| **3b** | 0.34       |             | −1.27  |        | 0.42  | 2.60       |
| ts/**1a** | 0.18    | 0.18        | −1.25  | −1.25  | 0.65  | 18.85      |

[a] In au. [b] $\delta_H$ (in ppm) has been obtained within the coupled perturbed Hartree−Fock formalism at the MP2 stationary points. [c] A, D and H stand for the hydrogen-acceptor atom, the hydrogen-donor atom and the atom forming the hydrogen bond, respectively. The label ts/**1a** denotes the transition state for the intramolecular proton transfer in **1a**.

Then there is no doubt that this kind of hidrogen bond exists, at least in the gas phase. It does not appear as a result of compressing a normal hydrogen bond to be shorter than its equilibrium distance. On the contrary, an LBHB is the spontaneous result of a set of interactions that give rise to a hydrogen bond with a very short equilibrium length, in such a way that the remaining properties appear. The distances between the hydrogen and the donor atom and between the hydrogen and the acceptor atom are small enough for both bonds to be covalent.

The role of the p$K_a$ of the two heteroatoms involved in the hydrogen bonds for the systems studied in this work merits special mention. In the maleic monoanion, which contains an LBHB, both heteroatoms (oxygen atoms) have indeed the same acidity (and basicity). If the basicity of one of them is lowered, the corresponding atom becoming the hydrogen acceptor atom (this is the case of the maleic diacid), or the acidity of one of them is decreased, the corresponding atom becoming the hydrogen donor atom (this is the case of the monoanion of the maleic monoamide), the hydrogen bond becomes normal. However, the hydrogen bond in the monoamide is clearly stronger than in the diacid because the first one involves a charged fragment, although both are normal.

It is noteworthy that, in spite of the existence of a double well potential, the delocalization of the bridging hydrogen atom leads to a symmetrical structure for the maleic monoanion in gas phase, in good agreement with the experimental results.

The unusually low p$K_a$ for the first deprotonation of maleic acid illustrates the way in which an LBHB acts in a chemical reaction. When along the process the features of the hydrogen bond change in such a way that a normal hydrogen bond is substituted by a strong LBHB, the extra stabilization facilitates the reaction.

More experimental and theoretical work is required in order to discuss the extension of the present conclusions to other systems in the gas phase and, especially, to understand the features and the role of LBHBs in solution and in enzymic catalysis. Additional theoretical work in this scope is now in progress in our laboratory.