Asymmetry of the Hydrogen Bond of Hydrogen Phthalate Anion in Solution. A QM/MM Study

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Abstract: The geometry of hydrogen bonds and, in particular, the proton location in a hydrogen bond is a fundamental question. In the last years, considerable attention has been devoted to the influence of the environment on the hydrogen bond symmetry. Very recently several experimental results, based on the measurement of the ^{18}O-induced ^{13}C isotope shifts at the ipso carbons of labeled dicarboxylic acids in water and several organic solvents, have shown that the intramolecular hydrogen bonds in those monoanions of dicarboxylic acids are asymmetric in water but also, unexpectedly, in all the studied organic solvents. In this paper, the geometrical features of the intramolecular hydrogen bond in hydrogen phthalate anion solvated by water or by chloroform have been studied theoretically. By means of a continuum representation of solvent, a unique stationary point was found, both in water and chloroform, which corresponds, as in the gas phase, to a potential energy minimum with a symmetric intramolecular hydrogen bond in hydrogen phthalate. To introduce specific solute−solvent interactions, a discrete representation of solvent has also been employed performing QM/MM calculations on the whole systems. The stationary points found in water indicate that the intramolecular proton transfer along the hydrogen bond in hydrogen phthalate is already a double well but with a very small energy barrier. When entropic effects are introduced at 300 K by means of Molecular Dynamics simulations, the most probable configurations generated present an asymmetric hydrogen bond in water. In chloroform the calculated proton transfer energy profile along the hydrogen bond has a single well but, again, only a small percent of the configurations obtained from the dynamics simulations at 300 K can be considered symmetric. The existence of a counterion is another factor that preferentially stabilizes the asymmetric structures. The calculations performed with K^+ in chloroform show that the hydrogen bond in hydrogen phthalate anion is clearly asymmetric. The effect of proton delocalization paths, which just involve the motion of the solute keeping the solvent structure frozen, along the hydrogen bond in the structures generated by the classical dynamics simulations has also been taken into account.

Introduction

Hydrogen bonds have a very relevant role in determining the structure and reactivity of a wide range of molecular and supramolecular species in chemistry and biology. Despite the huge amount of experimental and theoretical work that has been successfully devoted to reveal their key features in this century, hydrogen bonds are still nowadays a rich source of new challenging problems. As a typical example, a special class of hydrogen bonds, the so-called low-barrier hydrogen bonds,[1] has recently generated a flurry of activity specially due to the debate on their proposed (but controversial) role in some enzyme-catalyzed reactions.[2]

The geometry of the hydrogen bonds and, particularly, the proton location is a fundamental question. In a hydrogen bond the proton is shared by two electronegative atoms, and the potential energy surface associated with its motion from one to the other is a multidimensional double well or single well. In the first case a classical energy barrier, that is, without including zero-point energy, separates two minimum-energy structures, each one corresponding to the proton attached to one or the other of the electronegative atoms. The second case appears when the classical energy barrier is null and only a minimum-energy structure in the middle of the two electronegative atoms exists. The shape of the potential energy surface can depend on the local environment. However, one has to realize that the former considerations just refer to the electronic aspects of the problem, in the sense that the potential energy surface stems from the electronic Schrödinger equation which does not contain any nuclear kinetic term.

Since nuclei do move always (even at 0 K) their experimental measurements are the result of the average over all the positions they reach during the measurement process. In particular, due to its quantum nature (intrinsically associated with its vibrational wave function which comes from the nuclear Schrödinger

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equation), a proton is not fixed at a frozen geometry, but it is delocalized along the hydrogen bond. For the sake of simplicity, from now on we will focus on hydrogen bonds in which the proton-donor and the proton-acceptor groups are identical. If, as a result of the measurement, the proton appears to be centered between the two heavy atoms (because the corresponding potential energy surface is either a single well or even a double well associated with a low-barrier hydrogen bond), such a hydrogen bond is often called a symmetric one.[3,4] Conversely, if the proton is found closer to one of the proton donors rather than centered between them, the hydrogen bond is asymmetric.[3,4] The corresponding potential energy surface is a double well in which the proton is localized within one of the two wells. Note that the present definition of symmetric and asymmetric hydrogen bond does not refer to the symmetry of the skeletal of the heavy atoms of the molecule, but to the position of the proton in the hydrogen bond.

In the last few years considerable attention has been devoted to the influence of the environment on the hydrogen bond symmetry.[3-9] Hydrogen maleate and hydrogen phthalate anions have been two of the most studied molecules, giving interesting and somewhat surprising results.[3,4,7,8] For many years X-ray and neutron diffraction results have provided well-established evidence that both anions in crystals contain symmetric hydrogen bonds.[3] Recently, Perrin et al.[3,8] have applied the nuclear magnetic resonance (NMR) method of isotopic perturbation of equilibrium[10] to distinguish between symmetric and asymmetric intramolecular hydrogen bonds in monoanions of several dicarboxylic acids in solution. The observed ^{13}C isotope shifts at the carboxyl carbons induced by the monosubstitution of ^{16}O by ^{18}O in one carboxyl group indicated that hydrogen maleate and hydrogen phthalate anions have asymmetric hydrogen bonds in aqueous solution but symmetric hydrogen bonds in organic nonpolar solvents (CD_3CN, DMSO-d_6, and THF-d_8). Perrin et al.[3,8] concluded that the symmetry seen in crystals or nonpolar solvents is broken in aqueous solution because of the water disorder which makes it improbable that both of the carboxyls would be simultaneously solvated in an identical manner, thus leading to an asymmetric hydrogen bond. On the contrary, in organic solvents that do not hydrogen bond to the anion a symmetric hydrogen bond would allow the negative charge to be delocalized over the two carboxyl groups.

Very recently Perrin et al.[4] have considered the ^{18}O-induced ^{13}C isotope shifts at the ipso carbons of the monoanions of a wide variety of mono-^{18}O-labeled dicarboxylic acids, including hydrogen phthalate anion, in water and several organic solvents (DMSO-d_6, THF-d_8, CD_2Cl_2, and $CDCl_3$). Unexpectedly, their results indicate that the hydrogen bonds in the monoanions of dicarboxylic acids are asymmetric in water and all organic solvents. This conclusion for organic solvents is opposite to the original conclusion based on the carboxyl carbons, the asymmetry being now attributed to a counterion effect. Thus, it seems that the carboxyl isotope shifts are inadequate to determine the symmetry of the hydrogen bond.

It has to be realized that symmetry is a key, but very subtle, geometric aspect of a hydrogen bond, whose reliable experi-

Chart 1
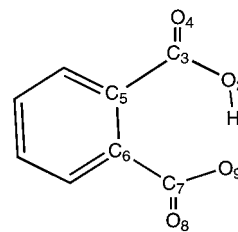
mental characterization is a challenge. Then the purpose of this paper is to discuss theoretically and understand how the solvent and the counterion modify the symmetry of the hydrogen bond in the monoanion of a dicarboxylic acid. To this aim we have specifically studied the intramolecular hydrogen bond of hydrogen phthalate anion in water and in chloroform, as a solvent of low polarity, including the counterion effect.

Methods and Calculation Details

QM Potential Energy Calculations. Quantum mechanical calculations have been done to study the hydrogen phthalate anion system in the gas phase. Full geometry optimization and characterization of the minimum energy structure have been carried out at the B3LYP (hybrid functional of Becke and the Lee, Yang, and Parr's correlation functional)[11] level, within the framework of the density functional theory[12] (DFT), using the 6-31+G(d,p) basis set, and a semiempirical level. Specifically, we have used the AM1 parametrization of the semiempirical neglect of diatomic differential overlap model Hamiltonian,[13] but we have changed the standard AM1 parameters of the oxygen, hydrogen, and carbon atoms for the specific reaction parameters (SRP) adjusted by Kim to study the double proton transfer in formic acid dimer.[14] The adecuacy of these parameters to the system studied in this paper has been tested by comparing the geometrical features of the minimum energy structure of hydrogen phthalate in the gas phase calculated at the B3LYP/6-31+G(d,p) level and at the AM1-SRP level. The distances (O_2-H_1 and O_9-H_1, see Chart 1) and the angle ($O_2-H_1-O_9$) of the two structures encountered, which characterize the intramolecular hydrogen bond, only differ by 0.01 Å and 13.9°, respectively. We have also carried out optimizations at the AM1-SRP level to build the gas-phase energy profile for the intramolecular proton transfer as a function of the difference between the distances O_9-H_1 and O_2-H_1 (see Chart 1).

Another set of quantum calculations have been done to study the effect of immersing the hydrogen phthalate anion in a solvent cavity, using a Self-Consistent Isodensity surface polarized continuum model (SCI-PCM)[15] to represent water or chloroform solvent. We have fully optimized the stationary points at the B3LYP level with the 6-31+G-(d,p) basis set, using an isodensity value of 0.0004 and dielectric constant values of 78.54 or 4.81 for water or chloroform, respectively. At different values of the O_9-H_1 distance the rest of the geometrical parameters have been optimized to build the energy profile for the intramolecular proton transfer as a function of the difference between the O_9-H_1 and O_2-H_1 distances (see Chart 1).

The semiempirical calculations have been done with the Molecular Orbital Package MOPAC 7.0,[16] whereas we used the GAUSSIAN 94[17] package to carry out the DFT calculations.

QM/MM Potential Energy Calculations. To have a discrete representation of the solvent we have used a QM/MM method.

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The QM/MM calculations described in this paper were performed using the ROAR 1.1[18] module of the molecular simulation package AMBER 5.0.[19] ROAR 1.1 is the result of coupling together SANDER,[19] the basic energy minimizer and molecular dynamics program of AMBER, and the semiempirical quantum mechanical program MOPAC 7.0.[16] The theoretical basis of the QM/MM method has already been extensively outlined in numerous publications, so we only comment upon the specific details of our calculations.[20] We have divided the system in two parts: phthalate and solvent. The phthalate molecule is described quantum mechanically allowing it to interact with the solvent, which is defined in a molecular mechanics sense. Wave function polarization effects in the QM motif arise from inclusion of the MM-atom/QM-electron term in the one-electron matrix used in the Fock equations.

Specifically, we have used the AM1-SRP parametrization to represent the QM solute. It has been empirically noted that the optimization of the van der Waals parameters of the QM atoms, by adjusting them such that the interaction energies between QM and MM atoms emulate those determined from ab initio QM calculations and experimental data, can greatly improve the accuracy of the free energies of solvation calculated using the QM/MM methods.[20] However, in this paper we have used standard AMBER force field parameters on the QM atoms for their interactions with the MM atoms, because our aim is to obtain qualitative results rather than highly accurate quantitative results.

We have used the AMBER all-atom force field by Cornell et al.[21] to describe the solvent water molecules and the potassium ion, which is used as counterion. However, the Cornell et al.[21] force field does not include parameters for compounds containing chlorine atoms. For CHCl$_3$, the new flexible all-atom solvent model[22] developed to be consistent with the Cornell et al. force field is used, with the exception of the chloroform charges, which are taken from Eksterowicz et al.[23] These charges are the result of scaling down by 19% the ones determined with RESP[24] and the 6-31G (3df,2p) basis set that lead to better agreement with the experimental dipole moments than the standard RESP charges developed with the 6-31G(d) basis set.[23] Table 1 shows all the nonstandard parameters used in our calculations.

The aqueous solution of hydrogen phthalate anion is modeled as follows. The minimum energy structure obtained with the AM1-SRP method was solvated with 379 TIP3P[25] water molecules contained in a box about $25 \times 25 \times 20$ Å^3. We applied constant volume periodic boundary conditions to the system using the minimum image convention. The nonbond cutoff distance was 9 Å for the MM atoms whereas we used a distance of 100 Å, that is, noncutoff, for the QM atoms. The reason of doing so is based on the high dependence of the energy of the QM portion on the cutoff used.

To solvate hydrogen phthalate anion with chloroform we used a constant volume periodic box about $31 \times 31 \times 30$ Å^3 containing 208

Table 1. Additional Force Field Parameters for Chloroform

bonds	K_b (kcal mol^{-1}Å^{-2})	r_0 (Å)
C−Cl	232.4	1.758
C−H	340.0	1.100

angles	K_θ (kcal mol^{-1} rad^{-2})	θ_0 (deg)
Cl−C−Cl	77.7	111.3
Cl−C−H	38.1	107.7

	nonbonded parameters	
atom	R^* (Å)	ϵ (kcal mol^{-1})
Cl	1.9480	0.265

atoms	atomic charges (in au)
C	−0.386
Cl	0.040
H	0.266

chloroform molecules. This periodic box was built using the GEN[19] option of AMBER from the pure solvent equilibrated box obtained following the molecular dynamics simulation procedure explained in the paper of Fox et al.[22] The nonbond cutoff distance for MM atoms was chosen to be 12 Å, larger than the value used for water because of the larger size of nonaqueous solvent molecules and the lower dielectric constant of chloroform.[22] Some calculations are done with the hydrogen phthalate/chloroform system neutralized with one K$^+$ ion. First the K$^+$ ion was placed 6 Å from both the donor and the acceptor carboxyl oxygen atoms of the intramolecular hydrogen bond of the solute. After 10 ps classical molecular dynamics simulation of the system at constant temperature (300 K) and pressure (1 atm) the K$^+$ had moved to be closer to the acceptor carboxyl group of hydrogen phthalate, that is, about 2.7 Å from each oxygen. We began the following QM/MM calculations from this structure.

The QM/MM minimizations were carried out freezing the nonbonded pair list within a single run. The energy was minimized until a root-mean-square (RMS) gradient below 0.001 kcal/(mol Å) was achieved. The steepest descent method is used because the Powell conjugate gradient method failed in most cases, that is, it got stuck in a place from which the minimization algorithm could not find a way out. We have used the BELLY[18] option of ROAR 1.1 in all the minimizations with a frozen solvent configuration, that is, where only the solute is allowed to move.

Molecular Dynamics Simulation Procedure. Molecular dynamics simulations were carried out in the NVT ensemble for the periodic systems described above. In all cases we started the molecular dynamics simulation from an structure that has been sufficiently minimized.

The system formed by hydrogen phthalate anion solvated with chloroform was heated from 0 to 300 K during 5 ps of simulation, and the temperature was then maintained by coupling to two thermostat chains (one for the MM region and one for the QM region) within the Nosé-Hoover chain temperature scheme,[26] which replaces in the ROAR 1.1[18] program the Berendsen's temperature control method originally used in SANDER.[19] We have used three thermostats for each chain and the program has automatically set the mass values of each of them. We ran a total of 116.45 ps molecular dynamics simulation using a time step of 0.5 fs. The nonbond cutoff distances used for QM and MM atoms were the same used along the minimizations described above, but the nonbond pair list was updated every 25 steps. The SHAKE algorithm[27] was not used. Over the last 100 ps coordinates and energies were saved for analysis every 100 time steps (i.e., every 0.05 ps). We show in Figure 1 the variation of the total energy along these last 100 ps. The fluctuations of the total energy were 6.93% of the average value.

For the case of hydrogen phthalate anion solvated by chloroform and one K$^+$ ion, we followed the same molecular dynamics procedure but the simulations covered 107.85 ps. Coordinates and energies were

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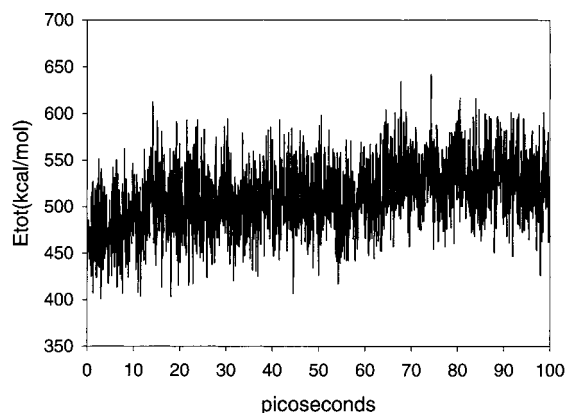(27) van Gunsteren, W. F.; Berendsen, H. J. C. *Mol. Phys.* **1977**, *34*, 1311.

Figure 1. Fluctuations of the total energy over the last 100 ps of the molecular dynamics simulation on the system formed by phthalate anion solvated by discrete chloroform molecules.
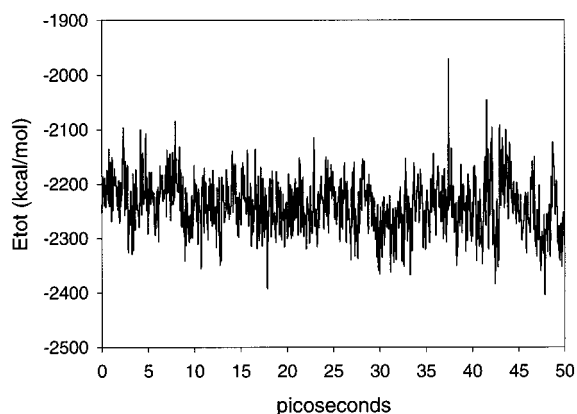

Figure 2. Fluctuations of the total energy over the last 50 ps of the molecular dynamics simulation on the system formed by phthalate anion solvated by discrete water molecules.

also saved for analysis every 100 time steps along the last 100 ps. The value of the energy fluctuations is close to that found for the hydrogen phthalate/chloroform system.

The simulations on the system formed by hydrogen phthalate anion solvated with water molecules covered 57.5 ps, and we followed the procedure explained above. Coordinates and energies were saved for analysis every 50 and 100 steps, respectively, along the last 50 ps. The variation of the total energy along these last 50 ps is shown in Figure 2. The fluctuations of the total energy were 2% of the average value.

Molecular graphics images were produced using the MidasPlus package.[28]

Results and Discussion

As a previous step which will serve as a reference we have studied hydrogen phthalate anion in the gas phase (isolated). Later we have considered the effect of the solvent and the counterion.

In the gas phase only a stationary point exists which corresponds to a potential energy minimum whose main geometrical parameters related to the hydrogen bond are given in the two first rows in Table 2. The proton is in the middle of the hydrogen bond at both the B3LYP/6-31+G(d,p) and the AM1-SRP levels of calculation. The performance of the AM1-SRP level is encouragingly good because it reproduces quite well the B3LYP geometry (it is worthy of note that the standard AM1 method moves the potential energy minimum to an

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asymmetric structure where the distances H_1O_2, O_9H_1, and O_9O_2 are 0.98, 1.87, and 2.77 Å, respectively). This result enables us to use this AM1-SRP for the QM/MM calculations which will be described below. On the other hand, the AM1-SRP energy profile (see Figure 3, where the energy is drawn as a function of the deviation of the proton with respect to its centered position in the hydrogen bond) for the intramolecular proton transfer along the hydrogen bond confirms its single-well character. We have chosen the AM1-SRP level to build up that energy profile for the sake of a better comparison with the QM/MM results. It can be concluded that the hydrogen bond in hydrogen phthalate anion in the gas phase is symmetric. This fact agrees with the symmetric hydrogen bonds seen in crystalline hydrogen phthalate anion in the absence of strong asymmetric crystal forces caused by asymmetrically placed cations.[3,4]

In a first attempt to study the solvent effect, we have used a continuum representation of solvent. To this aim the hydrogen phthalate anion has been introduced in a polarizable solvent cavity with dielectric constant $\epsilon = 4.81$ (chloroform) or 78.54 (water). As in the gas phase, only a stationary point which corresponds again to a potential energy minimum has been located at the B3LYP/6-31+G(d,p) level for each ϵ. The third and fourth rows in Table 2 show that the continuum solvent does not significantly modify the gas-phase geometry of the hydrogen bond, apart from a small shortening of the O_9O_2 distance and a very slight increase of the $O_2H_1O_9$ angle. Indeed solvation stabilizes the charged hydrogen phthalate anion with respect to the isolated molecule, 33.55 and 43.06 kcal/mol for chloroform and water, respectively, at the B3LYP/6-31+G(d,p) level (the greater the dielectric constant, the more intense the energy stabilization). On the other hand, the B3LYP/6-31+G-(d,p) energy profiles as a function of the proton position along the hydrogen bond (Figure 3) keep the single-well shape for the two solvents. Note that each energy profile in Figure 3 takes as its own origin of energies the energy corresponding to its stationary point associated with the proton centered in the hydrogen bond. Thus the absolute stabilization due to solvent is not explicitly shown in Figure 3, all curves being artificially coincident at the origin for the sake of clarity. However, the curvature of each energy profile reflects the relative stabilization of the progressively asymmetric structures with respect to the centered structure within that curve. Taking all this into account, Figure 3 shows that, in comparison to the gas-phase situation, the continuum solvent flattens notoriously the profiles around the centered minimum (other authors have described similar results),[6,7,2c] indicating that the asymmetric structures are more stabilized by the continuum solvent than the symmetric ones, although the inversion of the curve is far to reach. There is no significant difference between the shape of the curves corresponding to the two solvents. The apparent crossing between the gas-phase and the solvent curves beyond ±0.4 Å is a consequence of the resistance of the B3LYP/6-31+G(d,p) hydrogen bond to be compressed at short proton-acceptor oxygen distances.

From the results just described in the previous paragraph it can be seen that the intramolecular hydrogen bond in hydrogen phthalate anion seems to be symmetric in chloroform and even in water, at least while a continuum model of solvent is used. This theoretical statement would clearly contradict the experimental findings by Perrin et al.[3,4,8] However, it has to be realized that the solvent cavity models do not take into account specific, local interactions with the solute, like the formation of intermolecular hydrogen bonds between the solvent and the solute. Then, to introduce those effects by means of a discrete

Table 2. Main Geometrical Parameters of the Stationary Points Related with the Intramolecular Hydrogen Bond in Hydrogen Phthalate Anion in the Gas Phase or in Solution (Water or Chloroform), at the Different Levels of Theory Studied in This Work[a]

	$d(H_1-O_2)$	$d(O_9-H_1)$	$d(O_9-O_2)$	$\alpha(O_2-H_1-O_9)$
B3LYP/6-31+G(d,p) gas phase	1.19	1.19	2.38	178.3
AM1-SRP gas phase	1.20	1.20	2.38	164.4
B3LYP/6-31+G(d,p)/solvent cavity $\epsilon = 4.81$	1.19	1.19	2.37	178.6
B3LYP/6-31+G(d,p)/solvent cavity $\epsilon = 78.54$	1.19	1.19	2.37	178.7
QM/MM water/asymmetric structure	1.02	1.73	2.46	124.3
QM/MM water/symmetric structure	1.20	1.22	2.33	149.0
QM/MM chloroform/symmetric structure	1.19	1.22	2.38	159.8
QM/MM chloroform/counterion/asymmetric structure	1.03	1.66	2.56	143.1
QM/MM chloroform/counterion/symmetric structure	1.20	1.19	2.32	150.8

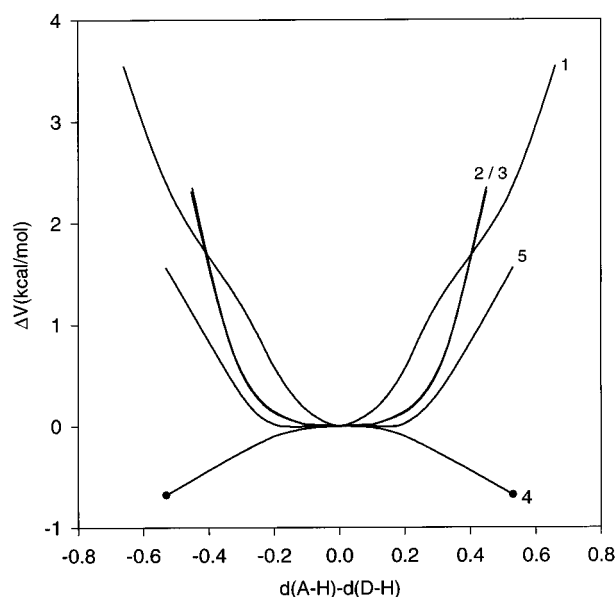[a] Distances and angles are given in Å and deg, respectively.

Figure 3. Monodimensional energy profiles for the intramolecular proton transfer as a function of the deviation of the proton with respect to its centered position in the hydrogen bond at different levels of theory: (1) AM1-SRP gas phase, (2) B3LYP/6-31+G(d,p)/solvent cavity $\epsilon = 4.81$, (3) B3LYP/6-31+G(d,p)/solvent cavity $\epsilon = 78.54$, (4) QM/MM/water, and (5) QM/MM/chloroform. Solid circles indicate the locations corresponding to the minimum-energy structures at the QM/MM/water level. Note that each energy profile takes as its own origin of energies the energy corresponding to its stationary point associated with the proton centered in the hydrogen bond. Distances are given in Å.

representation of solvent, we have performed QM/MM calculations, using the AM1-SRP level to describe the quantum mechanical part (hydrogen phthalate anion), in the manner described in the Methods and Calculation details section.

Let us first report the results obtained for water as solvent (379 TIP3P water molecules). Full optimization of the whole system (solute + solvent), except for the fact that a TIP3P water molecule is rigid, leads to two equivalent asymmetric potential energy minima, each one corresponding to the proton H_1 attached to either O_2 or O_9. Likewise, the minimization of the root-mean-square gradient starting at the configuration region that lies around the symmetric structure provides a transition state that corresponds to the intramolecular proton transfer along the hydrogen bond between the two minima. We have to point out that, in this paper, when the discrete solvent is included, we have used the term transition state to denote the stationary point corresponding to the maximum energy point along the intramolecular proton transfer. The main geometrical parameters of one of the minima and of the transition state related to the hydrogen bond are given in the fifth and sixth rows, respectively,

in Table 2. To visualize the network of intermolecular hydrogen bonds between solute and solvent, plots of both structures including hydrogen phthalate anion and only the water molecules with some atoms closer than 3 Å from another atom of the solute are exhibited in Figure 4, parts a and b. The transition state is an almost symmetric structure with the proton forming the intramolecular hydrogen bond practically in the middle of both oxygen atoms. The deviation of 0.01 Å from the exact midpoint is due to the difficulty of converging the RMS gradient below 0.001 kcal/(mol Å) in a flat region corresponding to such a large system, but it is not significant to our purposes. Note that the formation of the intermolecular hydrogen bonds force the $O_2H_1O_9$ angle to close. From the minimum (Figure 4a) to the transition state (Figure 4b) the positive proton moves away from the donor oxygen (O_2) toward the center of the hydrogen bond, thus approaching to the acceptor oxygen (O_9). Conversely, along this process, part of the negative net charge that lies on the two oxygen atoms of the carboxyl acceptor group (O_8 and O_9) at the minimum is transferred to the two oxygen atoms of the carboxyl donor group (O_2 and O_4) at the transition state. As a consequence, in going from the minimum to the transition state, the solvation shell around the carboxyl acceptor and carboxyl donor groups clearly expands and contracts, respectively, due to the charge migration in the solute. At the minimum, there are 5 water molecules hydrogen bonded to the carboxyl acceptor group versus only 3 water molecules that are attached to the carboxyl donor group; however, at the transition state there are 4 water molecules for each carboxyl.

From the energetic point of view, the two asymmetric structures (minima) are 0.68 kcal/mol below the symmetric one (transition state), in such a way that the energy profile for the intramolecular proton transfer along the hydrogen bond in discrete water already becomes a double well (see Figure 3). It has to be stressed that polarity is not sufficient for inverting the curve, the formation of the intermolecular hydrogen bonds with solvent being required to get that inversion, as previously noted by other authors.[4]

Note that the term structure refers in this paper to a particular point of the potential energy surface (that is, a fixed geometry without any nuclear kinetic energy), while the hydrogen bond involves a delocalization of the proton over a wide set of structures. Now the point is whether the hydrogen bond of hydrogen phthalate anion in aqueous solution is symmetric or asymmetric. At first glance, the double-well seems to indicate an asymmetric hydrogen bond, but one has to be aware of the quantum character of the proton. Given the very small energy barrier of the intramolecular proton-transfer transition state it would be thought that a low-barrier hydrogen bond could exist, in such a way that the maximum value of the probability density function to find the proton would appear precisely over the transition-state region, thus leading to a symmetric hydrogen
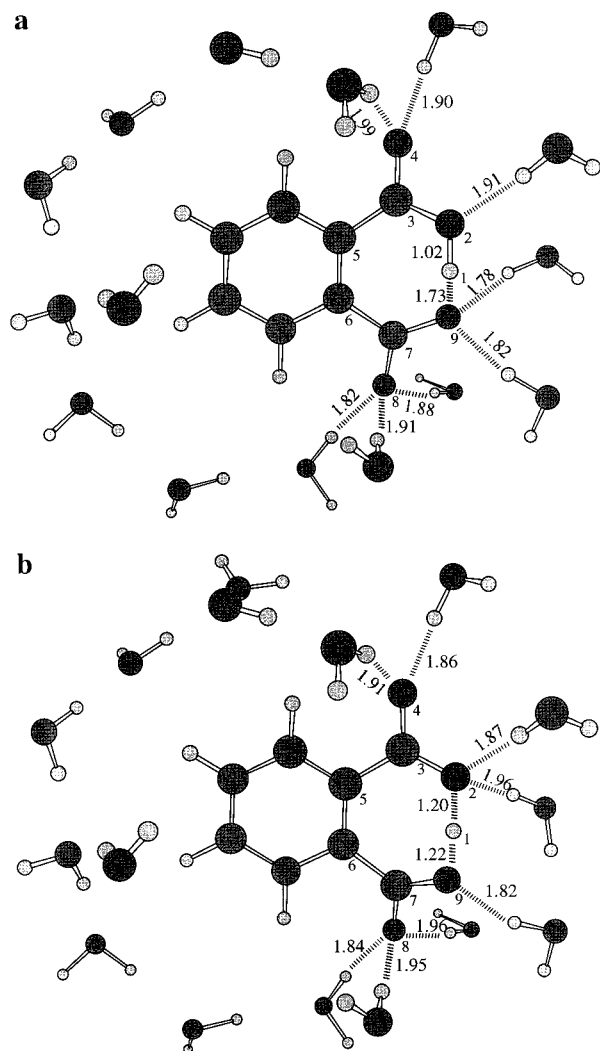
Figure 4. (a) Plot of one of the asymmetric potential minimum-energy structures found at the QM/MM level in water, including hydrogen phthalate anion and only the water molecules with some atoms closer than 3 Å from one atom of the solute. Distances are given in Å. (b) The same as in part a for the transition state structure of the intramolecular proton transfer along the hydrogen bond.

Figure 5. (a) Histogram bars whose height denotes the percentage of the configurations (corresponding to the last 50 ps of the QM/MM Molecular Dynamics simulation of the system formed by hydrogen phthalate anion and 379 water molecules) for which the difference of distances of the proton to the acceptor and donor oxygen atoms is a given value (within intervals of 0.05 Å; numbers below the *x*-axis indicate the midpoint of each interval). (b) Energy profiles for the motion of the proton along the intramolecular hydrogen bond in the hydrogen phthalate anion keeping frozen the water molecules at the positions corresponding to a chosen symmetric structure that belongs to the first bar on the left in part a (solid line), and at their positions in a chosen asymmetric structure that pertains to the highest bar in part a (dashed line). $d(A-H) - d(D-H)$ denotes the difference between the distance of the proton to the acceptor atom and the distance of the proton to the donor atom. Distances are given in Å.

bond. However, a careful analysis of the problem shows that this assumption would be wrong. Along the aqueous energy profile of Figure 3 connecting both minima through the transition state, the solute atoms (specially the proton and the oxygen atoms of both carboxyl groups) move together with many water molecules (compare structures corresponding to Figure 4, parts a and b). As a consequence, the path length of the proton transfer in mass-weighted Cartesian coordinates is extremely long, leading to a ground vibrational level very close to the bottom of the wells and clearly below the small classical energy barrier (it is a particular case of the well-known effect consisting of the wider the quantum box or the well, the lower the quantum energy levels). It is then a conventional hydrogen bond whose vibrational wave function has its greater amplitude just over both minima, the proton being localized in the neighborhood of either of both oxygen atoms forming the hydrogen bond.

The former considerations have been done on the basis of a collective quantum motion of solute + solvent along the delocalization path. Bearing in mind that the proton is much lighter that the ensemble of water molecules, many other proton delocalization paths exist along the hydrogen bond, which just involve the motion of the solute keeping the solvent structure
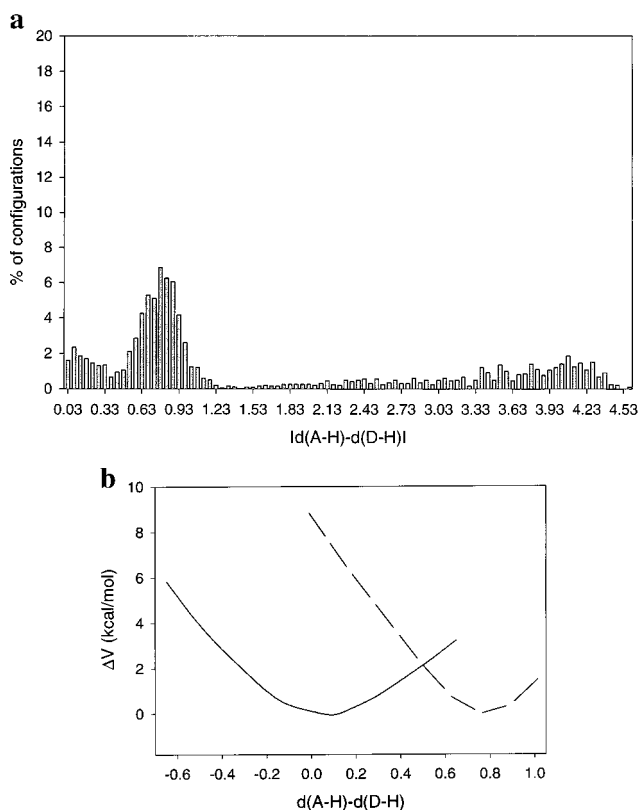
frozen. Each solvent structure is reached as a result of the classical thermal reorganization and allows for the delocalization of the proton along its energy profile corresponding to that fixed solvent configuration. Then we have performed a QM/MM Molecular Dynamics simulation in the system formed by hydrogen phthalate anion and the 379 water molecules at 300 K, moving classically both the solute atoms and the solvent molecules.[29] To analyze the results, the configurations corresponding to the last 50 ps of the simulation have been scanned as a function of the deviation of the proton with respect to its centered position in the hydrogen bond. The corresponding histogram bars are displayed in Figure 5a. Each bar corresponds to the set of configurations for which the difference of distances of the proton to the acceptor and donor oxygen atoms is a given value (within intervals of 0.05 Å; numbers below the *x*-axis in Figure 5a indicate the midpoint of each interval). The height of each bar denotes the percentage of configurations that belongs

(29) To carry out all the MD simulations described in this paper we have considered as equivalent the oxygen atoms that share the proton in the hydrogen bond, as we have applied on both of them the arithmetic mean between the van der Waals parameters corresponding to the sp^3 oxygen in a protonated carboxyl acid and the ones that correspond to a sp^2 oxygen in an anionic acid.

to each interval. We will consider symmetric structures those belonging to the bar associated with 0.03 Å (first on the left). This convention implies a wide criterion because structures for which the difference of distances is as great as 0.05 Å are still considered symmetric. Even in this way, only 1.6% of configurations could be assumed to be symmetric. Most of the configurations appear within the range below the bars forming a triangle-like contour, which is a highly asymmetric region. In addition there is a long queue of bars on the right of the triangle-like contour that correspond to configurations where the O−H bond has turned around the C−O bond of the carboxyl donor group in such a way that the proton tends to form an intermolecular hydrogen bond with a water molecule (simultaneously, the carboxyl acceptor group also can turn, exchanging its two oxygen atoms). Indeed these are extremely asymmetric structures in which the intramolecular hydrogen bond has been broken. It has to be remarked that, since the energy barrier is so low, during the simulation the proton does jump between O_2 and O_9, although the residence time of the proton in the middle region of the hydrogen bond is very small.

Now we have to check which is the effect of proton delocalization on the structures of Figure 5a. To this aim, for example, we have chosen one symmetric structure (with $O_2H_1 = O_9H_1 = 1.17$ Å), which belongs to the first bar on the left in Figure 5a, and one asymmetric structure (with $O_2H_1 = 1.00$ Å and $O_9H_1 = 1.78$ Å), which pertains to the highest bar in Figure 5a. The corresponding energy profiles for proton motion along the intramolecular hydrogen bond[30] in the hydrogen phthalate anion keeping the water molecules frozen are displayed in Figure 5b. It can be seen that if the solvent readjustment as the proton moves is not allowed, the energy profile for proton motion is a single well around each position reached as a result of the unconstrained Molecular Dynamics simulation (this result could be expected due to the high polarity of water and its ability to form hydrogen bonds). Then, the ground wave function of the proton will be confined in the neighborhood of its classical position in each solvent configuration. As a consequence, even taken into account the quantum character of the proton, each classical symmetric or asymmetric structure will give rise to a proton symmetrically or asymmetrically positioned, respectively, in the intramolecular hydrogen bond. According to the scanning in Figure 5a, we can conclude that, in agreement with Perrin et al., the hydrogen bond in hydrogen phthalate anion in water turns out to be clearly asymmetric, as a consequence of the low probability that the solvent produces configurations involving equivalent environments around each carboxyl group thus centering the proton. This would be in this case an entropic problem rather than a mere enthalpic one.[3,4,8]

Let us turn our attention to the case of chloroform as discrete solvent (208 flexible chloroform molecules). QM/MM full optimization of the whole system, starting at the region of the asymmetric configurations, leads to an almost symmetric minimum (the proton only deviates 0.15 Å from the exact midpoint of the hydrogen bond; see row seven in Table 2 and Figure 6), but no asymmetric minimum has been found. As seen in Figure 6, there are a lot of intermolecular hydrogen bonds
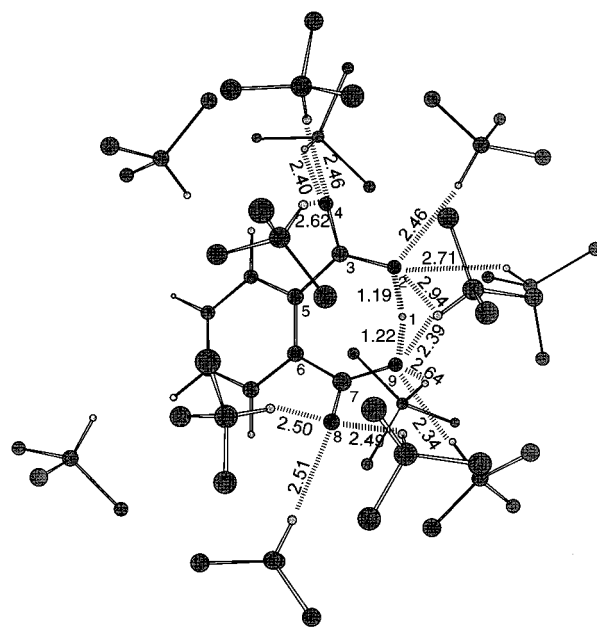
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(30) The reaction path was followed by holding the distance of the proton to the acceptor atom very close to a desired value, through the application of a harmonic restraint ($k = 10000$ kcal/(mol Å²)). To obtain more accurate energies and geometries for each step of the reaction profile, we have done a linear interpolation between the van der Waals parameters of the donor and acceptor atoms when they are considered as equivalent (like in ref 29) and when they are really different treated as donor (sp³ oxygen) and acceptor (sp² oxygen) atoms. That is, we have generated a series of van der Waals parameters intermediate between these two states that have been used to calculate the different points along the intramolecular proton transfer.
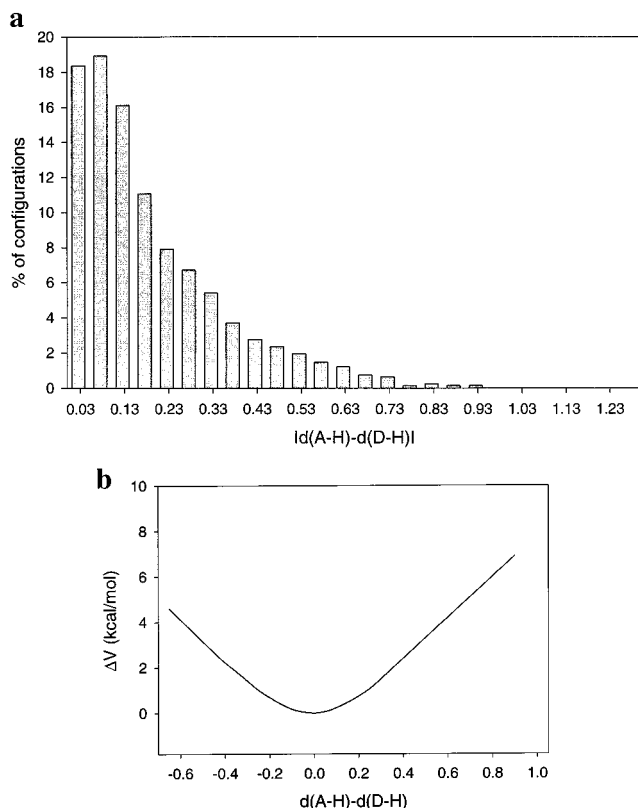

Figure 6. Plot of the almost symmetric potential minimum-energy structure found at the QM/MM level in chloroform, including hydrogen phthalate anion and only the chloroform molecules with some atoms closer than 3 Å from one atom of the solute. Distances are given in Å.

between the four carboxyl oxygen atoms and the hydrogen atoms of chloroform molecules. Within a radius of 3 Å from any atom of the solute there are 10 solvent molecules hydrogen bonded to the carboxyl groups. Note that the large number of degrees of freedom makes it very difficult to obtain a perfectly symmetric structure. On the other hand, the intermolecular hydrogen bonds with chloroform are clearly quite a bit longer and, therefore, weaker than the intermolecular hydrogen bonds with water (Figure 4).

From the energetic point of view, the energy profile for the intramolecular proton transfer along the hydrogen bond (see Figure 3) in discrete chloroform is still a single well, although quite flat around its minimum symmetric structure compared to the curves corresponding to the continuum solvents. Then it is clear that the polarity of the solvent stabilizes more the asymmetric structures than the symmetric ones, but the inversion of the curves only is reached if the solvent is able to form sufficiently strong intermolecular hydrogen bonds with the solute. This is not the case for chloroform, but for water.

The scanning of the configurations corresponding to the last 100 ps of the QM/MM Molecular Dynamics simulation in the hydrogen phthalate anion surrounded by 208 chloroform molecules at 300 K is shown in Figure 7a. The distribution of the histogram bars dramatically differs from the case of water. For chloroform most of the configurations deviate from the symmetry much less than the configurations included in the triangle-like contour in the case of water (see Figure 5a) and no configurations implying the rotation of the carboxyl donor group have been detected (that is, the intramolecular hydrogen bond does not break along the simulation, probably due to the fact that chloroform is unable to form intermolecular hydrogen bonds with the O−H proton strong enough to compensate the breakage of the intramolecular bridge). However, and despite the single-well potential energy profile, only around 18% of configurations (those belonging to the bar associated with 0.03 Å) can be considered to be symmetric. As expected, the energy profile for the motion of the proton along the intramolecular hydrogen bond in the hydrogen phthalate anion keeping the chloroform molecules surrounding it frozen (see Figure 7b) is

a

b

Figure 7. (a) Histogram bars whose height denotes the percentage of the configurations (corresponding to the last 100 ps of the QM/MM Molecular Dynamics simulation of the system formed by hydrogen phthalate anion and 208 chloroform molecules) for which the difference of distances of the proton to the acceptor and donor oxygen atoms is a given value (within intervals of 0.05 Å; numbers below the *x*-axis indicate the midpoint of each interval). (b) Energy profile for the motion of the proton along the intramolecular hydrogen bond in the hydrogen phthalate anion keeping frozen the chloroform molecules at the positions corresponding to a chosen symmetric structure that belongs to the first bar on the left in part a. $d(A-H) - d(D-H)$ denotes the difference between the distances of the proton to the acceptor and the donor atoms. Distances are given in Å.

also a single well for a typical configuration of that interval (specifically, Figure 7b corresponds to a configuration with $O_2H_1 = O_9H_1 = 1.19$ Å). That is, again the proton appears to be confined near its classical position in each solvent configuration. On the other hand, it has to be noted that the configurations corresponding to the second bar (the one centered at 0.08 Å) and beyond are already rather asymmetric. For instance, a typical configuration of that interval has $O_2H_1 = 1.16$ Å and $O_9H_1 = 1.24$ Å. Then we can conclude that, although symmetric structures have strictly less energy than asymmetric ones (as a matter of fact they are almost degenerated in a wide range of proton location), the entropic term (directly related to the disorder of the solvent) dominates, in such a way that the residence time of the proton within the symmetric region is rather small. Therefore, we think that the hydrogen bond in hydrogen phthalate anion in chloroform could be considered rather asymmetric by itself (that is, even before including the influence of the counterion), although the precise frontier between what will be experimentally measured as a symmetric or an asymmetric hydrogen bond is somewhat diffuse.

At this point it is interesting to explore the effect of the introduction of a counterion. To this aim we have repeated the QM/MM calculations in the hydrogen phthalate/chloroform system but including one K^+ cation. Proceeding as in the two
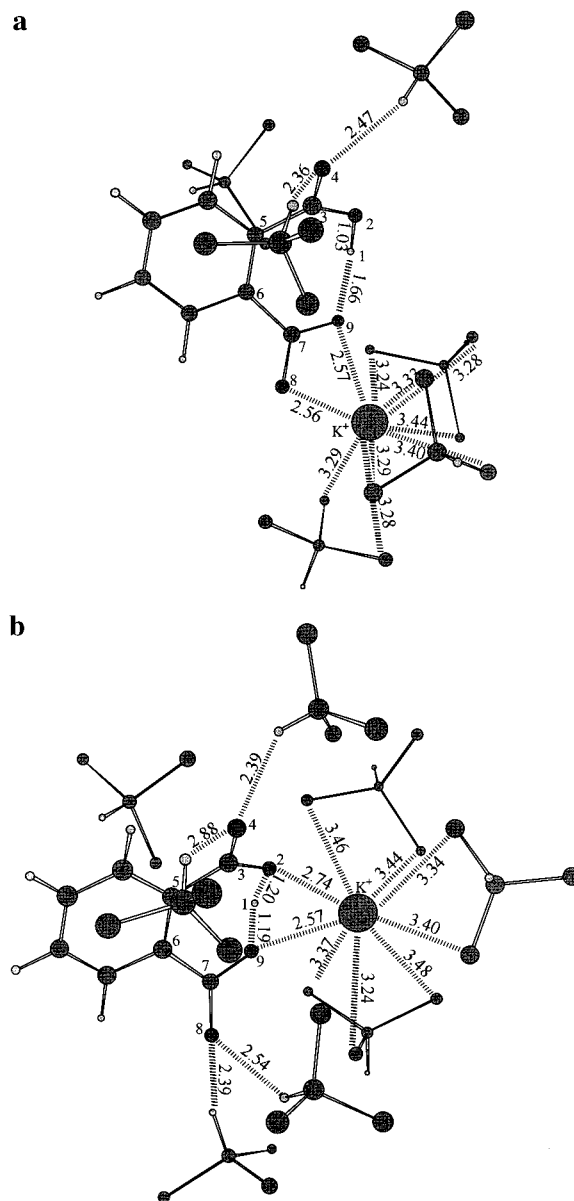
a

b

Figure 8. (a) Plot of one of the asymmetric potential minimum-energy structures found at the QM/MM level in chloroform with a counterion, including hydrogen phthalate anion and only the molecules with some atoms closer than 3 Å from one atom of the solute or closer than 4 Å from K^+. Distances are given in Å. (b) The same as in part a for the transition state structure of the intramolecular proton transfer along the hydrogen bond.

cases described above, we have found that the energy profile for the intramolecular proton transfer along the hydrogen bond is a double well with two equivalent asymmetric minima (eighth row in Table 2 and Figure 8a) separated by a symmetric transition state (last row in Table 2 and Figure 8b). The localization of the transition state structure has been done until a root-mean-square gradient of less than 0.005 kcal/(molÅ) and a change in energy over the last 200 steps of less than 0.02 kcal/mol have been achieved. At the minima, the K^+ cation associates closely to the two oxygen atoms of the carboxyl acceptor group. The presence of the counterion modifies the network of intermolecular hydrogen bonds in such a way that now within a radius of 3 Å from any atom of the solute there are only 2 or 4 chloroform molecules hydrogen bonded to the carboxyl groups, at the minima or at the transition state, respectively. The chloroform molecules closer than 4 Å from
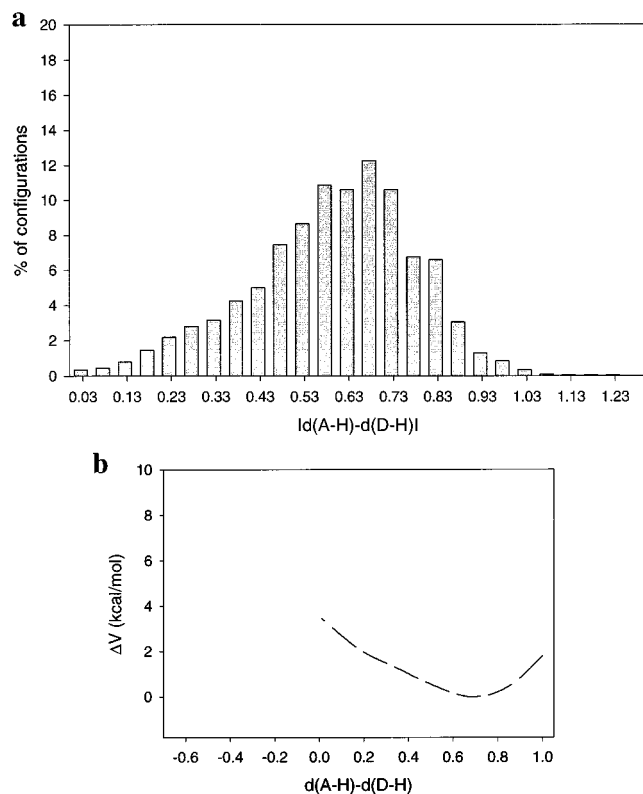
a

b

Figure 9. (a) Histogram bars whose height denotes the percentage of the configurations (corresponding to the last 100 ps of the QM/MM Molecular Dynamics simulation of the system formed by hydrogen phthalate anion, 208 chloroform molecules, and one K^+ cation) for which the difference of distances of the proton to the acceptor and donor oxygen atoms is a given value (within intervals of 0.05 Å; numbers below the *x*-axis indicate the midpoint of each interval). (b) Energy profile for the motion of the proton along the intramolecular hydrogen bond in the hydrogen phthalate anion keeping frozen the chloroform molecules and the K^+ cation at the positions corresponding to a chosen asymmetric structure that belongs to the highest bar in part a. $d(A-H) - d(D-H)$ denotes the difference between the distance of the proton to the acceptor atom and the distance of the proton to the donor atom. Distances are given in Å.

the K^+ cation have also been pictured in Figure 8. To reach the transition state, the K^+ has to migrate toward a rather symmetrical position with respect to the hydrogen bond, implying an energy barrier of roughly 23 kcal/mol, clearly much greater than in the case of water without counterion. In other words, the counterion stabilizes much more the asymmetric structures than the symmetric ones.

The scanning of the configurations corresponding to the last 100 ps of the QM/MM Molecular Dynamics simulation in the hydrogen phthalate anion surrounded by 208 chloroform molecules and one K^+ cation at 300 K is shown in Figure 9a. The distribution of the histogram bars for the system including the K^+ cation has nothing to do with the case of chloroform without counterion. With K^+ only 0.35% of configurations (those belonging to the bar associated with 0.03 Å) can be considered to be symmetric. Most of the configurations appear grouped around the highest bar at 0.68 Å, a region involving very asymmetric structures, forming a triangle-like contour that is similar to that of water (Figure 5a). The high transition state energy barrier imposed by the presence of K^+ prevents the proton shifting between O_2 and O_9, thus reducing the number of symmetric structures to a negligible amount. Finally, we have confirmed that the energy profile for the proton motion along the intramolecular hydrogen bond of hydrogen phthalate anion,

keeping frozen the chloroform molecules surrounding it and the K^+ (see Figure 9b), is again a single well (specifically, Figure 9b corresponds to a configuration with $O_2H_1 = 1.03$ Å and $O_9H_1 = 1.69$ Å which belongs to the highest bar). That is, again the proton appears to be confined near its classical position in each solvent configuration. So it is clear that, in agreement with Perrin et al.,[4] the hydrogen bond of hydrogen phthalate anion in chloroform including a counterion turns out to be asymmetric.

Conclusions

We have studied theoretically the symmetry of the intramolecular hydrogen bond of hydrogen phthalate anion in the gas phase, in water, and in chloroform (a solvent of low polarity), confirming essentially the experimental results obtained previously by Perrin et al.[4] In the gas phase the hydrogen bond is symmetric. By means of a continuum solvent model we have shown that polarity of solvent tends to stabilize more the asymmetric structures, although the symmetric structure still has less energy for both chloroform and water. Then, if specific interactions with the solute (like formation of solute−solvent intermolecular hydrogen bonds) are not taken into account, the solvent is unable to produce an asymmetric hydrogen bond. QM-(AM1-SRP)/MM calculations, which permit the use of a discrete representation of solvent, show that hydrogen bonds with solvent introduce an additional stabilization of the asymmetric structures with respect to the symmetric one. Hydrogen bonds with water are strong enough to decrease the energy of the asymmetric structures slightly below the symmetric one, in such a way that the energy profile for the intramolecular proton transfer along the hydrogen bond of the hydrogen phthalate anion in water is already a double well. Although the energy barrier is very small, the entropic effects at 300 K (solvent molecules are disordered which makes it very difficult to reach equivalent environments around each carboxyl group) lead to an asymmetric hydrogen bond in water.

Conversely, hydrogen bonds with chloroform are weaker than with water, not leading to a double-well energy profile for the intramolecular proton transfer, but to a very flat single well. Although symmetric and asymmetric structures coexist (no significant preference for any of them from the energetic point of view), it seems that again the entropic effects at 300 K would lead to a fundamentally asymmetric hydrogen bond in chloroform even in the absence of a counterion.

The existence of a counterion is the third factor that preferentially stabilizes the asymmetric structures. In this case, the energy term is quite significant and along with the entropic term causes the hydrogen bond in the hydrogen phthalate anion in chloroform (and indeed in water) with a counterion to be asymmetric.

To summarize, our theoretical calculations, in agreement with Perrin et al.,[4] predict that hydrogen phthalate anion (and, in general, monoanions of dicarboxylic acids) has an asymmetric intramolecular hydrogen bond not only in aqueous solution but also in organic solvents, as a combined result of factors that modify the energy term (solvent polarity, capability to form solute−solvent hydrogen bonds, and the presence of a counterion) and as a result of the entropic term (disorder of solvent molecules).

QM/MM Study of the H Bond of Hydrogen Phthalate Anion

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