Chapter 11

Water-Assisted Reactions in Aqueous Solution

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The results of ab initio computations including MP2 intramolecular electron correlation corrections on two chemical processes, amide hydolysis and ion pair formation in hydrochloric acid, are reported. The influence of water is simulated by considering a supermolecular system with one and two water molecules and the effect of the bulk solvent is modeled by a *continuum* surrounding the solute.

A mechanism involving a water dimer in the amide hydrolysis appears to be energetically favored in the case of both the neutral and the acid-catalyzed reaction. This mechanism can be interpreted as a water-assisted reaction in which the second water molecule is considered as an ancillary molecule (or equivalently as a bifunctional catalytic process).

Using the same model, the ionic dissociation of HCl appears to be impossible when a single water molecule is involved to solvate the proton which is expected to be part of the process. Conversely, solvating the proton, by a water dimer leads to an easy dissociation in a medium having a dielectric permittivity greater than 15.

The particular role of the water dimer in an aqueous solution is discussed in the present contribution, and some general conclusions are proposed.

Aqueous solutions, which are probably the most widely studied chemical systems, constitutes a fascinating subject for chemists. The reason for this special interest is partly due to the fact that liquid water is an essential component of the physical world and that it plays a crucial role in life, but it also comes from the unique properties of the water molecule.

Among the amazing properties of water, one notices that, in the molecule, three atoms have very marked and complementary properties: the two hydrogen atoms are electron deficient to a non-negligible extent, which enables them to form strong hydrogen bonds with atoms bearing electron lone pairs. This is actually the case of the oxygen atom possessing two lone pairs which are very efficient in hydrogen bond formation and cation solvation *(1)*, in particular, the H$^+$ cation coming from the ionic dissociation of another water molecule. Through such interactions, a proton can easily jump from one

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water molecule to another one, which in turn, can give one proton to another neighbor. A water molecule can, therefore, act as a relay in proton transfer phenomena. Finally, the large dipole moment of the molecule, which is even increased by hydrogen bond formation, gives rise to a high dielectric constant modifying to a large extent the structure and energetics of the chemical species present in the solution, in comparison to what can be expected for these species in a gaseous state.

All these remarks lead us to the conclusion that it is not wise to analyze the chemical process in solution by only considering the interaction of the solute with one water molecule. The other molecules of the solution may play a key-role either directly, by acting specifically as an intermediate in the reaction, or indirectly through the modifications of the electrostatic interactions due to the dielectric permittivity of the solvent.

Specific chemical interactions may be observed in chemical processes in which the presence of an extra (or ancillary) water molecule that does not enter the stoichiometry of the process, but modifies the reaction path. Such processes have been analyzed in terms of bifunctional catalysis *(2)*. Typically, these phenomena can be simulated by means of quantum chemical computations on clusters consisting of the solute and a given number of water molecules (usually one or two). The role of the water molecules in the bulk can be investigated by introducing the electrostatic interactions between the cluster and the solvent in the quantum chemical computation.

Methodology

The quantum chemical computations have been carried out using the conventional procedures and the standard basis sets available in the Gaussian92 *(3)* ab initio package. In most cases, the energy values discussed in this paper were obtained employing the 6-31G** basis set ; the second-(MP2) and occasionally third-(MP3), order Møller-Plesset theory was used to assess the influence of intramolecular electron correlation. In the case of small systems, a full geometry optimization was performed with these energy data. However, for larger systems, the optimization was carried out at the Hartree Fock level of approximation using the 3-21G basis set, and the energy was computed on the optimized structure by means of the Self-Consistent Reaction Field (SCRF) approach in which the solvent is represented by a *continuum* characterized by its dielectric permittivity ε (ε=78.5 for water at 25°C) and the solute is embedded in a deformable cavity adapted to its shape. The solute-solvent interactions are evaluated by means of the reaction field factors *(4-6)*, and the charge distribution of the solute is expanded in a multipole series up to order 6. This method allows us to carry out all the usual computations of quantum chemistry on a solvated molecule, including Møller-Plesset perturbation calculations *(7-8)*, with a cavity having a shape adapted to the geometry of the solute. Nevertheless, in order to reduce the computer time, we sometimes used the ellipsoidal approximation *(9)* for the cavity, in particular for geometry optimization.

Such an approach provides us with the equilibrium structure of the molecule in the solvent. The computed energy corresponds to the sum of the molecular energy and the electrostatic and induction contributions to the solute-solvent free energy of interaction *(10-11)*. In order to evaluate the total free energy of interaction, it is necessary to include two additional terms. The first term, namely the cavitation free energy, represents the energy spent to create the cavity in the solvent. This term can be obtained from several empirical formulae. In this work, we have adapted the formula proposed by Tuñon *et al. (12)*. The second term corresponds to the dispersion energy. It has been shown that when it is incorporated in the SCF computation, this term does not modify the equilibrium properties of the solute substantially *(13)*. In particular, it does not vary much when the geometry of the solute changes. For this reason, we have decided to drop it in this study. This approximation should be kept in mind when one

discusses the energy variations along a reaction path and thinks of the possible variations of the dispersion contribution.

The Water Dimer in Aqueous Solution.

The properties of each individual molecule in liquid water are expected to be different from those of single isolated molecules because of the molecular interactions with the rest of the liquid. As usual, these interactions may be classified into (i) short-range interactions, which are depicted as intermolecular hydrogen bonds and, (ii) long-range interactions, which are, in the present approach, assimilated to the effects of the polarizable *continuum*.

The effects of molecular association can be analyzed by comparing the properties of a water dimer and those of the isolated monomer. This basic problem has been studied thoroughly and, recently, some accurate quantum chemical results have been published (*14-15*). The influence of the liquid surroundings on these species has also been investigated (*16*). This study has been carried out using the 6-311++G(2d,2p) basis set, at both the HF and the MP2 levels of approximation, even for the geometry optimizations within the framework of SCRF computations in the ellipsoidal approximation.

In order to distinguish the two kinds of effects that a given water molecule experience from the other molecules pertaining to the liquid, we shall briefly summarize the results of the study, in which we successively analyze the influence of a single H-bond formation in a water dimer, and that of the surroundings on a single molecule, as well as on its dimer. The modifications of the chemical properties of each molecule are followed by the variations of the Mulliken net atomic charges (*17*). Although the partitioning of the electron density proposed by Mulliken has been criticized (*18-19*), especially for the hydrogen atoms, it is commonly admitted that the variations of these charges is chemically meaningful and may be used to anticipate a variation of a chemical property depending on local charges.

Influence of Hydrogen Bonding. In the isolated state, one linear dimer is found and will be entitled dimer I in this study. However, a second structure (or cis-dimer) has been recognized as an energy minimum in the liquid state. It corresponds to a transition state in the gas phase and will be considered here under the name of dimer II (Figure 1). The geometries of these structures, optimized at the MP2 level, are available in ref. (*16*) and the SCF Mulliken charges are reported in Table I

Table I. Mulliken charges in each water molecule under various association states

	H_1	O_1	H_2	O_2	H_3	H_4	Δq	$\mu(D)$
Monomer	0.2410	-0.4819	0.2410	-0.4819	0.2410		-	2.063
Dimer I	0.2408	-0.5608	0.3177	-0.5230	0.2626		0.0023	2.848
Dimer II	0.2337	-0.5593	0.3248	-0.5275	0.2641		0.0008	4.375

Apart from the variations of the properties of atoms H_2 and O_2 involved in the hydrogen-bond formation, the most noticeable result of this comparison is the strong variations of the charge borne by atom O_1, which becomes more negative, and by those of atoms H_3 and H_4, which become more positive. One is, therefore, led to consider that the result of the dimerization is an increase of the basic properties of molecule 1 and an increase of the acidic properties of molecule 2, regardless of the conformation of the dimer.
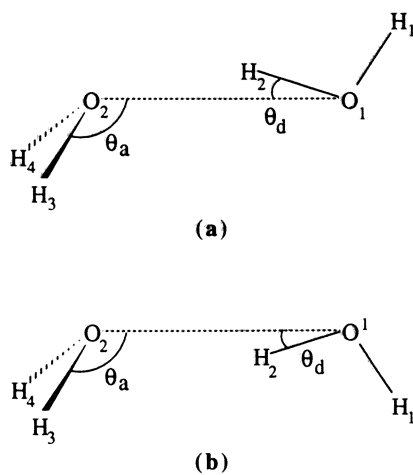
Figure 1: The water dimer
a) dimer I
b) dimer II

(Adapted from reference 16)

Influence of the Surroundings. The general effect of a liquid surroundings on a molecule is the polarization that usually increases the molecular electric moments. This effect can be analyzed through the differences in the Mulliken populations, which usually increase under the influence of the solvent. This is visible in the case of a single water molecule as shown on Table II.

Table II: Mulliken charges of oxygen (q_O) and hydrogen (q_H) and dipole moment (μ) of the water monomer in a *vacuum* ($\varepsilon=1$) and in water ($\varepsilon=78$)

	$\varepsilon=1$	$\varepsilon=78$	variation
q_O	-0.4819	-0.5860	-0.1041
q_H	0.2410	0.2930	+0.0520
μ(D)	2.063	2.382	0.319

The modifications of the electronic properties of the molecules are quite substantial. Qualitatively, the effects have many analogies with those intervening in H-bond formation, and one notices that the predicted variations of both the basic properties of oxygen and the acidic properties of hydrogen are even more pronounced than the largest variations anticipated from the analysis of the dimers.

Joined Effects of Hydrogen Bonding and Solvation. In order to have a global view of the possible modifications of the chemical properties of a water molecule under the joined influence of short- and long-range interactions, we now analyze the variations of the Mulliken charges between a single isolated water molecule and a solvated dimer. The results relative to the dimers I and II are given in Table III.

Table III: Variation of the Mulliken electron population due to the joined effects of hydrogen bonding and solvation

Atoms	H_1	O_1	H_2	O_2	H_3	H_4
Dimer I	+0.0701	-0.1832	+0.1145	-0.1449	+0.0776	
Dimer II	+0.0714	-0.1955	+0.1136	-0.1472	+0.0787	

This table shows that the combined effects increase further the contrast between the charges borne by the oxygen and the hydrogen atoms. If one discards the hydrogen bonded atoms O_2 and H_2 which are less available for reacting (although O_2 has a second lone pair), we notice that the basic or nucleophilic properties of the oxygen O_1 increases noticeably, as well as the acidic or electrophilic properties of the hydrogen atoms (especially H_3 and H_4, but also H_1 which is almost not modified in the isolated dimer).

The differences between dimer I and dimer II are negligible. Dimer II undergoes a stronger solvent effect due to its larger dipole moment which is also responsible for the fact that its conformation, in the liquid state, corresponds to an energy minimum which is only 0.02 kcal.mol^{-1} above dimer I, both at the HF or MP2 level.

The conclusion of this analysis is that the chemical properties of water may be very different in the liquid state and in the isolated unassociated state, which is often the only structure considered in quantum chemical computations.

These modifications are multiple. In addition to the enhancement of the nucleophilic and electrophilic properties of oxygen and hydrogen atoms, especially those which are not part of hydrogen bonds, one notices that the dimer appears to be

quite deformable. In other words, the pair O_1-H_3 or H_4, is able to react with a pair of electrophilic and nucleophilic sites in a partner molecule, even if the relative position of these sites is not favorable for a reaction with a single water molecule. After the reaction, a water molecule may be regenerated from the dimer. This is the reason why one sometimes talks about ancillary molecules, or of bifunctional catalysis (2).

Hydrolysis of Amides (20)

This reaction is a model of the chemical hydrolysis of peptides. In this case, it is known to be catalyzed by several proteolytic enzymes, but the reaction may also occur in aqueous solutions, especially in acidic media.
The overall stoichiometry of the reaction may be written as shown in Scheme 1.

Scheme 1
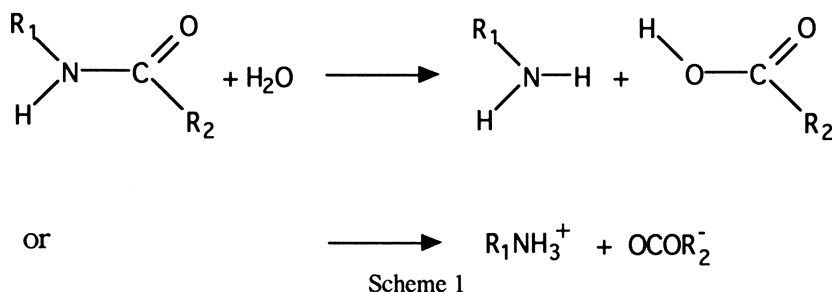
Where only one water molecule enters the reaction stoichiometry.
In this study, we carefully analyze the simplest case in which R_1=R_2=H (formamide), using the theoretical methodology summarized above.
The dissociative addition of a single water molecule to formamide (FA) has been studied previously in the isolated state by Bader *et al.* (21). These authors found a transition state 42.0 kcal.mol^{-1} above the reactants.
In the present study, we consider an alternative process in which a water dimer is added to the amide molecule. These two processes are then investigated in the case of a reaction catalyzed by an acidic medium. Following the results of the earlier study by Bader *et al.* (21), the presence of an excess of protons in the solution is simulated considering the complex formed by a hydronium H_3O^+ ion interacting with the oxygen atom of the amide. These reactions are first considered in the isolated state. The influence of the bulk water represented by a *continuum* will be examined afterwards.
The computations have been carried out at the MP2 or MP3/6-31G**//3-21G level of approximation. In addition to the usual energy calculations, the free energies have been estimated by computing the vibrational contribution to the partition function.

Are There One or Two Water Molecules Directly Involved in the Process?

We report in Table IV the energy variations $\Delta E^{\neq}$ and the free energy variations $\Delta F^{\neq}$ between the transition state and the reactants for these two processes, in the case in which the molecular species are assumed to react *in vacuo*. We consider the neutral (uncatalyzed) reaction and the hydronium-catalyzed one. These results correspond to the effects due to intermolecular MP3 computation of electron correlation. They, therefore, slightly depart from the MP2 data reported earlier (21).

Table IV: Energy barrier ($\Delta E^{\neq}$) and free energy barrier ($\Delta F^{\neq}$) (in kcal.mol^{-1}) of different processes of the hydration of formamide (FA). (Energies computed at the MP3/6-31G**//3-21G level)

reactants	$\Delta E^{\neq}$		$\Delta F^{\neq}$	
	H_2O + FA	$(H_2O)_2$ + FA	H_2O + FA	$(H_2O)_2$ + FA
neutral reaction	48.3	33.0	59.3	55.5
H_3O^+-catalyzed reaction	26.4	-3.8	37.2	20.1

This table shows that the assistance of a second water molecule lowers the energy barrier. The difference is less marked if one considers the free energy variations. This is due to the fact that the decrease of the entropy when passing from the reactants to the transition state is greater in the case of the water-assisted process.

If one considers the H_3O^+-catalyzed reaction, which is the most realistic one, it is clear that the assistance of a second water molecule is very favorable. One may then easily imagine that, in an aqueous solution, the probability for a pair of water molecule to react is quite large, and that the process is very likely to involve such a dimer. The structure of the transition state and of the reaction intermediates I_1 on the reactant side, and I_2 on the product side, are schematized on Figure 2.

Role of the Surroundings. The presence of a *continuum* does not greatly modify the conclusions emerging from the study carried out for the isolated species. For the water-assisted neutral reaction, the energy barrier is increased by an amount of 1.8 kcal.mol^{-1}. The most noticeable effect of the solvent appears on the reaction coordinate. This effect is visible on Table V, which indicates the main changes for the transition state of the neutral, water-assisted reaction in a gaseous state ($\varepsilon=1$), and in the solution ($\varepsilon=78.4$). The atoms are numbered according to Figure 2.

Table V: Main interatomic distances in the transition state for the water-assisted neutral molecule in a *vacuum* ($\varepsilon=1$) and in water ($\varepsilon=78.4$)

bondlengths	CN	CO_1	CO_2	O_2H_1	O_3H_1	O_3H_2	NH_2
$\varepsilon=1$	1.572	1.239	1.674	1.205	1.190	1.190	1.298
$\varepsilon=78.4$	1.530	1.273	1.595	1.293	1.120	1.098	1.460

The CN and CO_2 bondlengths are substantially shorter in solution, *i.e.*, the cleavage of the bond is retarded, although the nucleophilic attack on the carbon atom is favored. Conversely, the NH_2 bond is longer in solution. The same tendency has been pointed out in the case of the catalyzed reaction.

These modifications indicate a strong coupling between the reacting molecule and the surroundings which may influence the reaction kinetics to a larger extent that one would anticipate from the above energetics considerations.

One, therefore, concludes that the water-assisted process has to be considered as a good candidate to explain the hydrolysis of amides. In this process, the OH group that is bonded to the carbon atom to generate a carboxylic acid comes from one water molecule, and the hydrogen that is fixed to the nitrogen atom comes from another one. The two remaining moieties recombine to produce a water molecule, so that the reaction balance does not depend on the presence of the second water molecule. The reaction appears to proceed through an intermediate product which can be described as a cluster
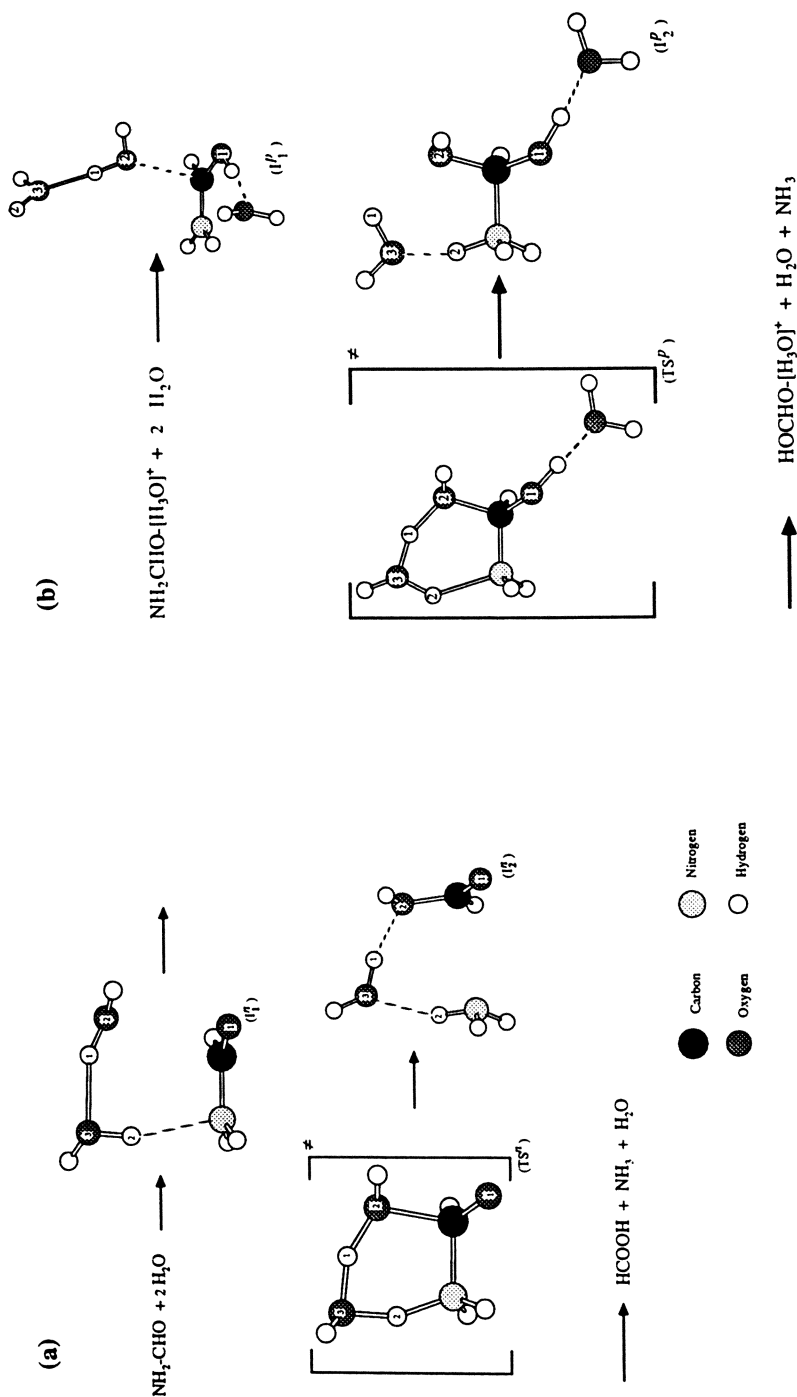
Figure 2: Reaction path of the water-assisted formamide hydrolysis reaction *in vacuo*
a) neutral reaction
b) H$_3$O$^+$ catalyzed reaction

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formed by an ammonia molecule and a formic acid bridged to the extra water molecule, in the case of the neutral reaction. In the case of the acid-catalysed reaction, the greater electrophilicity of the carbon atom, induced by the protonation of the carbonyl group, favors a structure which is closer to the tetrahedral intermediate, as shown on Figure 2.

This multicenter mechanism is not too surprising. Enzymatic hydrolysis of peptides, especially in serine proteases is also analyzed as a multicenter process in which the functionnal chains present in the active site play a role similar to the second water molecule (22).

Ionic Dissociation of Hydrogen Chloride in Water (23)

Most of the common textbooks explain the ionic dissociation of hydracids in water by the high dielectric permittivity of the solvent. Specific solvation processes are considered too, and among them the solvation of the proton is usually assumed to produce the H_3O^+ hydronium ion. Nevertheless, on the basis of vibrational spectroscopy data, some authors have postulated that a second water molecule is directly involved in the process leading to the $(H_5O_2)^+$ protonic species (24-26). In order to study the influence of various factors on the formation of the ion pair $H_3O^+Cl^-$ we report the results of computations performed at the MP2/6-31+G** level. This study analyzes the influence of one and two water molecules on the formation of the ion pair, in the isolated state and in a solvent. The structure of the species on which the computations have been performed is shown schematically on Figure 3.

HCl Interacting With One Water Molecule. In the gaseous state, the two molecules form a complex which can be depicted by considering a hydrogen bond between the hydrogen atom of HCl and a lone pair from H_2O.

The presence of a water-like *continuum* around this complex does not modify our conclusions substantially. The potential energy surface exhibits only one minimum (Figure 4) and the complex is closely related to the gas phase ($\varepsilon=1$) structure (Table VI).

Table VI: Geometric and energetic characteristics of the H_2O-HCl complex (atom numbers as on Figure 3)

	d_{Cl-H4} (Å)	d_{H4-O2} (Å)	< H4-O2-H1 (degree)	energy (a.u.)
$\varepsilon=1$	1.282	1.903	145.7	-536.46532
$\varepsilon=78.4$	1.289	1.847	134.5	-536.48072

Note: the ion pair $H_3O^+Cl^-$ has not been observed.

The System $(H_2O)_2$HCl. In the gaseous state, HCl again forms a hydrogen-bonded complex with the water dimer, but now, in a medium with a high dielectric constant ($\varepsilon>15$), our computations indicate a dissociation of the $H_5O_2^+Cl^-$ ion pair which is manifested by the fact that the Cl-H bondlength increases continuously, hence preventing a geometry optimization process to converge.

At the other end of the solvent polarity scale ($\varepsilon=2$), the hydrogen-bonded complex is again the only stable structure.

In order to study the influence of the surroundings, we have varied the dielectric permittivity of the *continuum*. For $\varepsilon=10$, two local minima appear on the potential
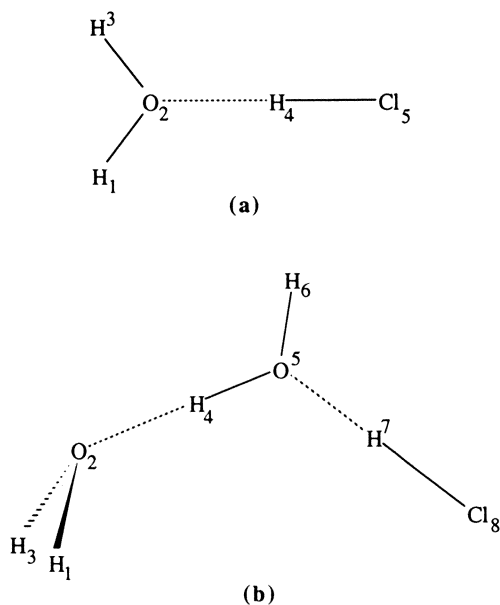
Figure 3: mono- (a) and dihydrated (b) complexes of hydrogen chloride.

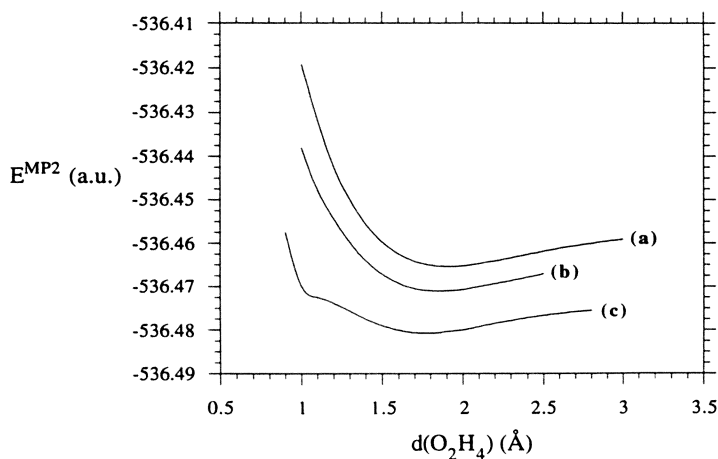(Reproduced from reference 23. Copyright 1994 American Chemical Society)

Figure 4: Potential energy curve of the H_2O-HCl complex.
    a) *in vacuo*
    b) in a non polar medium ($\varepsilon=2$)
    c) in water ($\varepsilon=78.3$)

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energy surface: one corresponding to the hydrogen-bonded complex, and the other one to the expected ion pair, 1.2 kcal.mol^{-1} lower than the first one (see Table VII).

Table VII: Geometric and energetic features of the $(H_2O)_2HCl$ complex

	d_{Cl-H7} (Å)	d_{H7-O5} (Å)	d_{O2-H4} (Å)	energy (a.u.)
$\varepsilon=1$	1.291	1.809	1.860	-612.71491
$\varepsilon=10$	1.305	1.758	1.950	-612.74499
	2.085	0.994	1.408	-612.74685

These results clearly indicate that the modification of the basicity of the oxygen atom of the first water molecule, under the influence of dimerization, obviously plays an important role. This is visible on the results obtained in the gas phase, where HCl is bonded to a single water molecule; the Cl-H bondlength is shorter than when HCl interacts with the dimer (1.282 Å vs 1.291 Å). In addition, the length of the hydrogen bond decreases accordingly (1.903 Å vs 1.809 Å). These results are in agreement with a stronger interaction with the dimer than with the monomer. Nevertheless, this interaction per se is not strong enough to dissociate the HCl molecule. The influence of the dielectric constant then becomes crucial to allow this chemical modification.

When the dielectric constant of the solvent is increased, this ion pair is stabilized. From $\varepsilon=10$ to $\varepsilon=15$, the ionic complex is, as expected, further stabilized, leading to a very flat minimum which preludes the ionic dissociation. For this modification of the permittivity, the main structural change is an increase of the Cl-H bondlength from 2.085 Å to 2.178 Å. The H_7-O_5 bond is slightly shorter (0.991 Å) and the H_4-O_2 bond is almost unchanged (1.409 Å). The Mulliken net charge of the chlorine atom reaches -0.954, hence confirming the ionic nature of the system. This ion pair can be interpreted as a contact ion pair between Cl$^-$ and a solvated H_3O^+ cation or a $H_5O_2^+$ polarized by the anion. The departure of the proton is expected to imply a second activated process which would be a jump of proton H_4 from the neighborhood of oxygen O_5 to the neighborhood of another oxygen atom like O_2, thus giving rise to a Cl$^-$/H_3O^+ ion pair separated by one water molecule.

In brief, the ionic dissociation of HCl appears to require at least one pair of water molecules, in accordance with Librovich's proposal (24-26). The resulting proton can then be present in solution in presumably various transient solvated forms which differ from each other by the number of water molecules (27).

Conclusion

We have focused our attention on two typical reactions occuring in an aqueous solution: hydrolysis and ionic dissociation. Both examples emphasize the prominent role of the water dimer which appears to be very important chemical species among the many possible multimers which may be considered as individual components of liquid water (28). The results reported here confirm the reasoning proposed in part III after having analyzed the properties of the liquid dimer in solution. In particular, the dimerization magnifies the acid-base properties of the water molecule and gives rise to a deformable species which reduces the possible geometric constraints occuring when the reaction requires a positively charged hydrogen atom and a nucleophilic oxygen atom simultaneously. This explains the efficiency of bifunctional catalytic (or water-assisted) hydrolysis. In the example that we have considered here, the role of the surroundings appears to be less decisive, which may probably be a general trend in such reactions which do not involve large charge transfers. One must, therefore, keep in mind that the

observed effects, which are quite important when one considers energy variations, are less marked on free energy differences because of the low entropy associated to the transition state.

In contrast with what one have might expected in the case of the ionic dissociation of hydrogen chloride, the influence of the high dielectric permittivity of the medium, which is here very important, is not the only factor that influences the process. Again, the strong interaction between the oxygen atom of the water molecule and the hydrogen atom of hydrogen chloride plays such a role that a single water molecule appears not to be basic enough, and that a dimer is required for the dissociation to occur.

A question then arises immediately: what about higher multimers, and in particular, trimers which are expected to occur in liquid water? Two kinds of trimers can be considered: a linear trimer or a bifurcated one, as represented on Figure 5.

In the case of bifunctional catalysis, these species are expected not to be very important because the modifications of the atomic charges in the linear trimer are not greater than in the dimer, the charge transfer occuring mainly between the two terminal molecules *(29)*. In addition the entropy variations are expected to be greater than for the dimer. As for the bifurcated trimer, the basicity or proton affinity of the central oxygen atom is known to be increased by an electron transfer from the two hydrogen-bonded molecules, but the resulting positive charge is shared between the four terminal hydrogen atoms.

This interesting property of the bifurcated trimer may become of greater importance when only the properties of oxygen are involved in the process. This is the case of the ionic dissociation of Brønsted acids. Indeed, the complex $(H_2O)_3HCl$ exhibits, in the case of the bifurcated trimer, all the features of a stronger interaction. At the same computational level as for the dimer, carried out in a *vacuum*, the optimized geometry
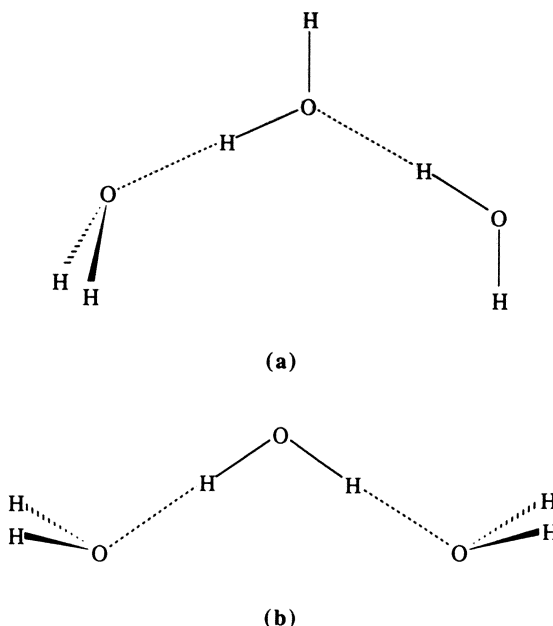

(a)

(b)

Figure 5 : linear (a) and bifurcated (b) water trimers.

of the complex between HCl and the bifurcated dimer shows a longer H-Cl bond: 1.300 Å instead of 1.291 Å and a shorter O-H bond: 1.732 Å instead of 1.809 Å in the case of the $(H_2O)_2HCl$ complex (Chipot, C. unpublished results). The assistance of two water molecules, or more, may, therefore, become crucial for the ionic dissociation of weaker acids *(30-32)*. These examples show that, in aqueous solution, the number of water molecules chemically involved in a reaction (*i.e.* participating to the exchange of electrons) may be larger than one would anticipate, just by considering the stoichiometry of the process.

In addition, the quantum chemical computations have to take the electron correlation into account, since the Hartree-Fock approximation favors the ionic structures and may lead, as in the H_2O-HCl complex to spurious minima.

This, of course, may complicate to a large extent a realistic simulation of reactions in aqueous media. The approximation which consists of considering the solvent as a *continuum*, although it has some obvious limitations, allow us to undertake these sophisticated computations on a rather small subsystem. It is, therefore, still a very useful tool for exploring a rather complex reality.

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