Molecular Dynamics Simulation of the Reaction of Hydration of Formaldehyde Using a Potential Based on Solute−Solvent Interaction Energy Components

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Received: September 6, 2006; In Final Form: November 6, 2006

Molecular dynamics simulations of aqueous solutions at infinite dilution of the reaction of water with formaldehyde, $H_2O + H_2CO \rightarrow H_2C(OH)_2$, were performed using Lennard-Jones 12-6-1 potentials to describe the solute−solvent interactions, and TIP3P to describe the water−water interactions. The Morokuma decomposition scheme of ab initio interaction energies at the SCF level and the dispersion component at MP2 level were used to reproduce the molecular parameters of the solute−water interaction potential. The results show that the functions that use the EX-PL-DIS-ES interaction model to describe the solvation of the reactant and product systems lead to good values of the reaction (ΔG) and activation ($\Delta G^{\#}$) free energy as compared with those from using AMBER-derived parameters, and with the available theoretical and experimental data.

1. Introduction

The study, at microscopic level, of chemical reactions in solution is nowadays one of the topics of greatest interest in quantum chemistry.[1−15] One of the major difficulties in this type of study is the great number of interactions that take place, so that a full quantum mechanical treatment of both solute and solvent (using for example the CPMD method[16]) is costly, and recourse is made to approximate methods. Although there exist other procedures with an acceptable response to study the solvation of chemical systems (such as those which incorporate the effect of the solvent as a dielectric[17] or those which employed a mixed quantum/mechanical computational model, the QM/MM methods[18]), we shall use the classical method of molecular mechanics[19] using ab initio potentials to describe the solute−solvent interaction and the TIPnP potentials to describe the explicit solvent, allowing water molecules to take part in the reaction mechanism as takes place in a large number of the reactions in solution. The description of the solute−solvent interaction, however, will be based on the Lennard-Jones 12-6-1 analytical function whose molecular parameters are taken from fitting solute−solvent interaction energies calculated at the ab initio level,[20−27] instead of using the geometric-mean combining rules or parameter tables for model molecules. The solute charges are derived from a fit of the electrostatic component (ES) of the bimolecular solute−water interaction energy, which will henceforth be denoted as ESIE. With respect to the molecular parameters of the van der Waals terms in LJ-(12-6) interaction potential, we employed a fitting procedure based on using different components of the interaction energy— in particular, the repulsion-exchange (EX), polarization (PL), and dispersion (DIS) components—to describe the repulsive and attractive contributions.

Knowledge of the energy curves that guide fluctuations of the solvent is particularly important in the study of chemical processes in solution because it allows one to calculate the activation energy of the process without the necessity of determining the reaction path and the complex structure in the transition state. This is of special interest as reactions in solution do not follow simple reaction mechanisms as occur in gas phase, but more complex mechanisms where the molecules of the solvent are part of the intermediates and transition structures. Outstanding among the different theories proposed is the well-known Marcus relationship[28−31] which describes the free-energy curves of the reactant (R) and product (P) states as quadratic functions of the solvent polarization coordinate. The transition state is associated with the point of intersection of the two curves, and the reaction and reorganization energies are obtained directly from relationships between points of these two curves (see Figure 1). One of the most commonly used reaction coordinates is the difference in the solute−solvent interaction energy of a given set of solvent molecules in the presence of the reactant and product structures,[32] for which one only needs the potential function that suitable describes this interaction.

The present work is a continuation of previous studies in which the LJ(12-6-1) potential determined from the EX-PL-DIS-ES components was proposed to describe molecular solvation in aqueous solution at infinite dilution, the main objective now being to validate that model potential for chemical reactions in solution by obtaining energy properties related to reaction processes (in particular, the free energies of reaction and activation) but the goal is not to validate the simple Marcus' theory in reactions where the charge transfer and the atomic reorganization takes place, since we know that for a complete study of this system the solute reaction coordinate has to be included (i.e., multidimensional Marcus theory[33]). For this purpose, we chose the reversible hydration of formaldehyde since for this system there is sufficient theoretical and experimental information available for comparison with our results. We also carried out calculations with the AMBER force field[34] which applies quantum mechanically derived RESP charges[35] to calculate the electrostatic energy, and Lennard-Jones parameters derived from liquid properties[36] to calculate the van der Waals energy.

The hydration of formaldehyde to give methylene glycol is a typical example of reactions of nucleophilic addition to the

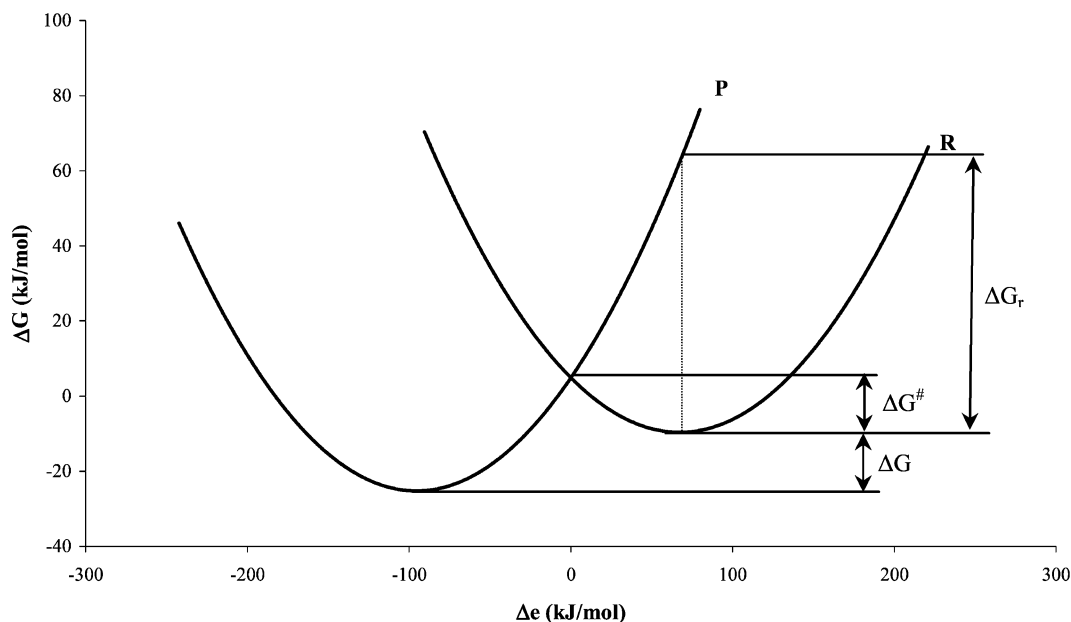* Corresponding author. Telephone: +34-924289401. Fax: -34-924275576. E-mail: santi@unex.es.
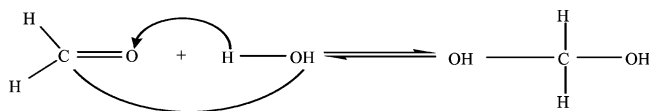
Figure 1. Free energy curves for R and P simulations using the ΔE_s energies.

carbonyl group and has been studied by various authors.[36-39] This reaction, which usually does not take place in the gas phase, in solution can be regarded as an example of protonic addition processes in an aqueous environment and as a model reaction in physical organic chemistry since it provides a great amount of information about chemical reactivity in solution. The reaction can be schematized as the transfer of a water hydrogen (with the rupture of an Ow−Hw bond) to the carbonyl oxygen to form a bond (O−Hw), and the formation of a covalent bond between the water oxygen and the carbon of the aldehyde (C−Ow).

The theoretical and experimental study of this reaction provides thermodynamic and kinetic data (i.e., the equilibrium and rate constants) that can be compared with those given by applying our model potential. We can thus validate the goodness of our proposed model for the theoretical study of chemical reactions in aqueous solution.

2. Formalism And Calculation Details

2.1. Formalism for the Study of Reaction Processes. In order to study reaction processes, it is necessary to define a reaction coordinate which must contain the minima of the reactant and product states, respectively, and the most probable path between them. At a microscopic level, a suitable choice for reactions in solution is to use any of the solvent coordinates. For example, one can use the differences in the solute−water interaction energies (U_{sw}) between the diabatic states of solute in its product (P) and reactant (R) structures for a broad set of configurations of solvent molecules around the solute in a simulation (S).

$$\Delta E_S = U_{SW,P} - U_{SW,R} \qquad (1)$$

Thus, in the MD simulation of the reactant (S = R), we divide the trajectory into N equally separated steps. At each of these steps, the interaction energies of the solvent with the solute in

its reactant and product forms are calculated simultaneously ($U_{SW,R}$ and $U_{SW,P}$). In the same way, the interaction energies are calculated for the product simulation (S = P). In both cases, the difference ΔE_s fluctuates, and its values are collected as a histogram of the number of times, $n_S(\Delta e)$, that a particular value (Δe) of the macroscopic variable ΔE_S appears in the simulation.

The probability $P_S(\Delta e)$ of finding the system in a particular configuration with an energy Δe can be expressed in a region close to the minimum by a Gaussian-type function

$$P_S(\Delta e) = \sqrt{2\pi \langle (\Delta E)^2 \rangle_S} \, \exp\left[\frac{-(\delta \Delta e)^2}{2\langle (\delta \Delta E)^2 \rangle_S} \right] \qquad (2)$$
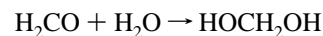
where $\delta \Delta E = \Delta E - \langle \Delta E \rangle_S$ represents the fluctuations of the energy ΔE in the S state.

The free energy $G_S(\Delta e)$ is computed from the normalized probability distribution of the variable Δe:

$$G_S(\Delta e) = -k_B T \ln P_S(\Delta e) \qquad (3)$$

A graphical representation is then used to obtain the free energies of reaction ΔG, reorganization ΔG_r, and activation $\Delta G^{\#}$.

2.2. Geometry and Net Charge of the Molecules. For this work, we chose the formaldehyde−water system as reactant and the methylene glycol molecule as product:

$$H_2CO + H_2O \rightarrow HOCH_2OH$$

The geometries of the formaldehyde, water, and methylene glycol involved in the simulations were determined at the HF level with the "split-valence" 6-31G* basis of Pople et al.[41,42] using the Gaussian/92 package.[43] The separation and relative orientation of the two solute molecules that form the reactant system (formaldehyde and water) are shown in Figure 2 for two different structures: (a) the optimum geometry in which the oxygen of the water molecule is placed near the carbon atom to favor the nucleophilic attack followed by a proton transfer (structure A); (b) the optimum geometry in which the hydrogen of the water molecule is placed near the oxygen to favor the proton addition followed by the nucleophilic attack (structure B).
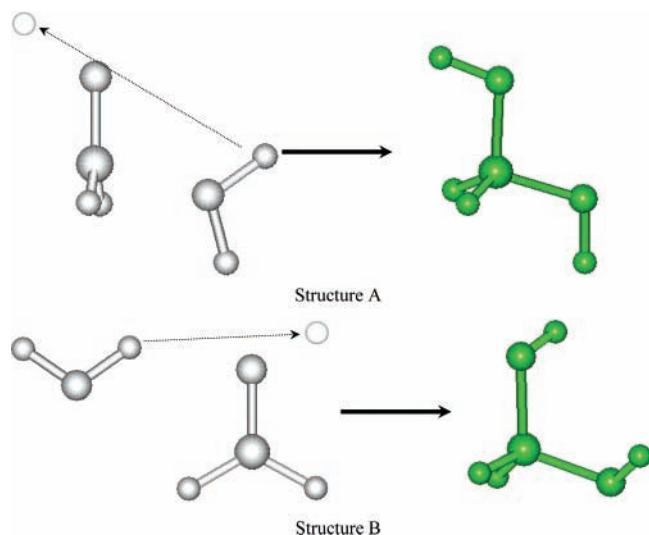
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Figure 2. Geometries of the reactant and product systems in the reaction process.
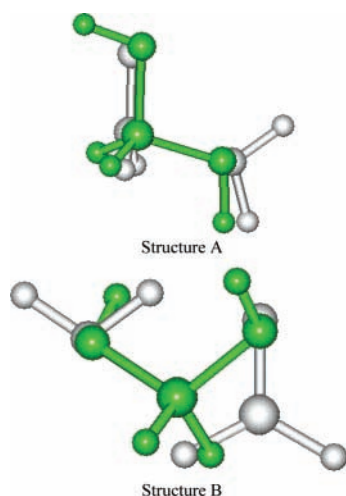

Figure 3. Overlapping reactant and product molecules for the free energy curves.

When building the free energy curves, it is necessary to keep in mind that in the configurations stored during the simulation of one of the molecules, the other molecule must be displaced to the position that occupies the first and reoriented with the aim of reproducing the distribution of their atoms, i.e., when a molecule is replaced by the other in each simulation, the atoms of the two systems must match, avoiding that any solvent molecule overlaps with the solute (see the motion of the methylen glycol molecule, drawn as dark spheres in Figure 3, to the zone of the reactant, drawn as white spheres).

The net charges on each solute atom q_i^s were obtained using the aforementioned ESIE procedure, which has been extensively described in previous work.[22-27] It can be summarized as fitting the values of the Coulomb electrostatic component of the interaction energy $U_{sw}(ES)$, using the variational scheme of Morokuma and co-workers[44,45] implemented in the GAMESS package,[46] with the expression

$$U_{sw}(ES) = \sum_{ij} \frac{q_i^s q_j^w}{r_{ij}} \qquad (4)$$

where the TIP3P charges of the solvent water (as well as those of the water molecule that forms part of the solute) q_i^w are pre-assigned.

2.3. Potential Function for the Solute—Solvent Interaction. Once the solute and solvent atomic charges q_i^s and q_i^w had been determined, several hundred values of the SCF (used in the calculation of the charges q_i^s) and MP2 solute—solvent interaction energy were used to obtain the interaction parameters of the chosen potential energy function. In the present study, this was a Lennard-Jones 12-6 potential function that includes a Coulomb term in addition to the van der Waals terms:

$$U_{sw} = \sum_{ij} \frac{A_{ij}^{sw}}{r_{ij}^{12}} - \sum_{ij} \frac{B_{ij}^{sw}}{r_{ij}^6} + \sum_{ij} \frac{r_{ij}}{q_i^s q_j^w} \qquad (5)$$

The parameters to be determined are hence the corresponding A_{ij}^{sw} and B_{ij}^{sw}. These are obtained in a similar way to q_i^s, but now the energies used in the fits are those that describe the exchange (EX) and polarization (PL) components of the interaction energy at the SCF level, and the dispersion (DIS) component related to the MP2 correlation energy:[47]

$$U_{sw}(EX) = \sum_{ij} \frac{A_{ij}^{sw}}{r_{ij}^{12}} \qquad (6)$$

$$U_{sw}(PL + DIS) = -\sum_{ij} \frac{B_{ij}^{sw}}{r_{ij}^6} \qquad (7)$$

The parameters A_{ij}^{sw}, B_{ij}^{sw} and q_i^s are listed in Table 1 for the formaldehyde—water and methylene glycol systems. They were obtained either from the EX-PL-DIS-ES components or from the AMBER(ff99) force field, and will henceforth be denoted as ABQ and AMBER respectively.

2.4. Simulation Details. Molecular dynamics simulations on an *NVT* ensemble of a solute molecule in an aqueous environment formed by several hundred of water molecules were carried out at 298 K using the AMBER program.[36] The time considered for the simulations was 1100 ps with time steps of 0.1 fs. The first 1000 ps were taken to ensure that the equilibrium is reached completely, and the last 100 ps were stored to evaluate the positions and velocities of the water molecules. The water molecules that are initially located at distances less than 1.6 Å from any solute atom were eliminated from the simulations. The long-range electrostatic interactions were treated by the Ewald method,[48] and the solutes were kept rigid using the shake algorithm.[49] A cutoff of 5 Å was applied to the water—water interactions to simplify the calculations, and periodic boundary conditions were used to maintain constant the number of solvent molecules. The solute—solvent interactions were calculated with the potential function LJ(12-6-1), using the parameters obtained from fitting the EX-PL-DIS-ES components or those from the AMBER(ff99) field forces, while for the solvent—solvent interactions the potential TIP3P of Jorgensen[50] was employed.

Results and Discussion

Inspection of Table 1 shows that our ABQ potential led to systems with higher charges and to A_{ij}^{sw} and B_{ij}^{sw} interaction parameters that give van der Waals components slightly greater than those obtained with the AMBER potential, in the cases both of the reactant and of the product. Thus, from the minima in the contour maps calculated with the reactant and the product described with our potential (Figure 4) we can see that they are similar for structure A, but quite different for structure B.

TABLE 1: Interaction Parameters[a,b]

		ABQ			AMBER		
system	atom	A_{ij}	B_{ij}	q_i	A_{ij}	B_{ij}	q_i
formaldehyde–water	C	444851.5	−122.9	0.553	696790.7	564.5	0.420
	HC	113294.1	307.3	0.004	60959.2	107.9	0.015
	HC	113294.1	307.3	0.004	60959.2	107.9	0.015
	OC	567908.6	466.2	−0.562	472934.6	581.3	−0.450
	Ow	581935.5	594.8	−0.834	581935.5	594.8	−0.834
	Hw	0.0	0.0	0.417	0.0	0.0	0.417
	Hw	0.0	0.0	0.417	0.0	0.0	0.417
methylene glycol	C	358701.7	−262.8	0.345	785890.0	636.7	0.403
	HC	88880.2	274.8	0.000	32323.5	79.5	−0.007
	HC	88880.2	274.8	0.000	32323.5	79.5	−0.007
	O	298807.9	415.2	−0.659	582511.3	645.5	−0.596
	O	298807.9	415.2	−0.659	582511.3	645.5	−0.594
	H	0.0	0.0	0.501	0.0	0.0	0.400
	H	0.0	0.0	0.501	0.0	0.0	0.399

[a] The parameters and charges in the reactant water are the same as the TIP3P parameters of the solvent water. [b] In these fits, the water solvent has been considered to have the oxygen as the only interaction center.
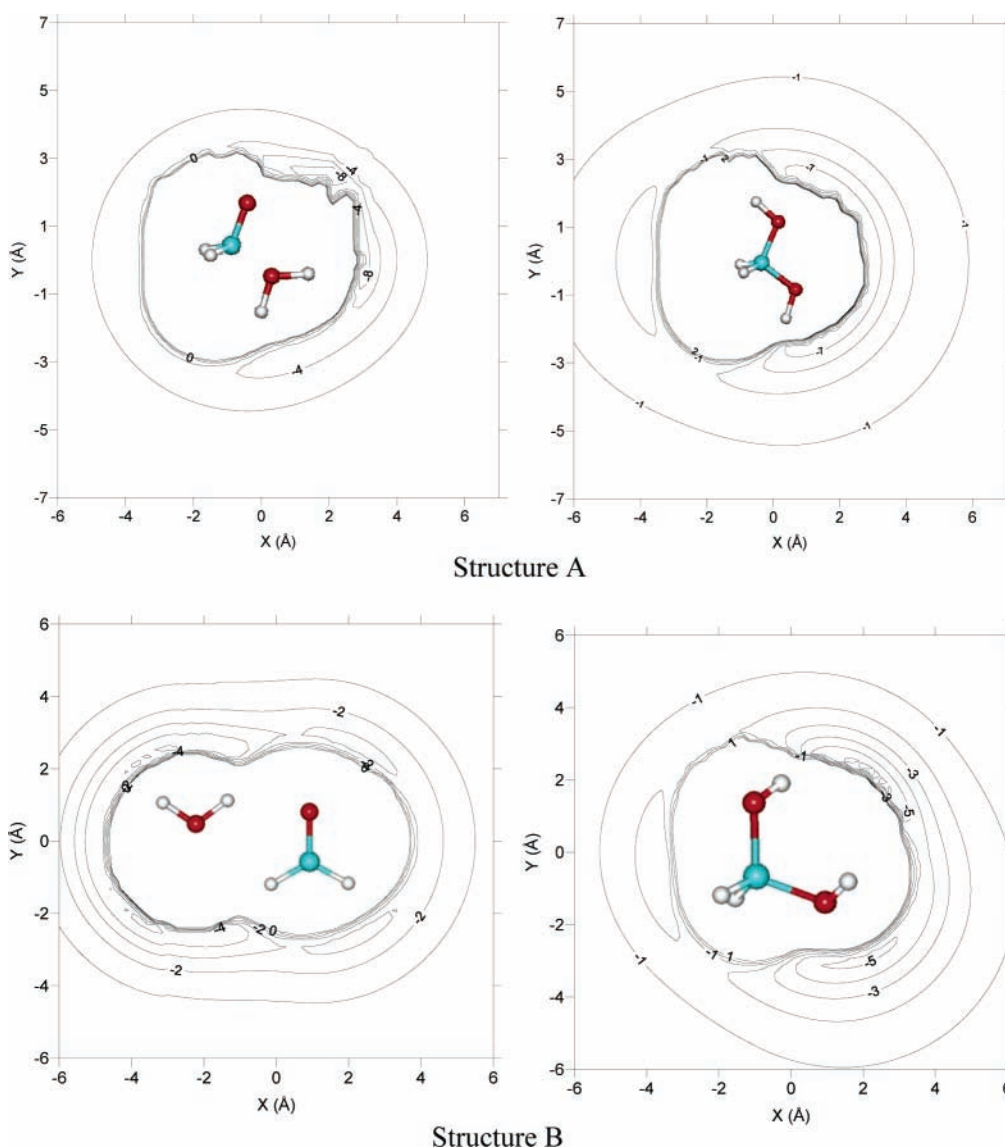

Figure 4. Isoenergy contour map for formaldehyde–water (left) and methylene glycol (right) obtained with the ABQ potential for A and B structures.

Besides, the product energy maps present minima deeper than that of the reactant molecule only for structure B.

These iso-energy maps are in consonance with the solute–solvent interaction energies given in Table 2 for the different cases studied. In general, the electrostatic (ES) contributions obtained with both potential are quite greater in absolute value than those obtained for the van der Waals (VDW) component. Comparing the interaction energy in the two systems, one can say that only for the structure B case is the reaction of formation of the methylene glycol accompanied by an increase in the

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TABLE 2: Solute−Solvent Interaction Potential Components[a]

system	components	formaldehyde−water		methylene glycol	
		ABQ	AMBER	ABQ	AMBER
structure A	$U_{s-w}(ES)$	−50.5	−38.5	−37.9	−27.1
	$U_{s-w}(VDW)$	11.9	6.6	5.9	4.4
	U_{s-w}	−38.6	−31.9	−32.0	−22.7
	ΔH_{s-w}[b]	−39.2	−32.5	−32.6	−23.3
structure B	$U_{s-w}(ES)$	−4.3	−31.5	−27.2	−36.1
	$U_{s-w}(VDW)$	0.7	4.7	6.5	5.2
	U_{s-w}	−3.6	−26.8	−20.7	−30.9
	ΔH_{s-w}[b]	−4.2	−27.4	−21.3	−31.5

[a] In kcal/mol and referred to 208 water molecules. [b] Obtained as $U_{s-w} - RT$.

TABLE 3: Free Energies Associated with the Reaction Process[a]

		AMBER	ABQ
structure A	ΔG	−2.74	−3.37
	$\Delta G^{\#}$	6.28 (8.77)[b]	3.47 (3.68)[b]
	ΔG_r	40.38	20.93
structure B	ΔG	0.27	−3.84
	$\Delta G^{\#}$	5.56 (3.95)[b]	0.89 (0.36)[b]
	ΔG_r	15.29	7.03

[a] In kcal/mol. [b] Value obtained when the Marcus relation $\Delta G^{\#} = (\Delta G_r + \Delta F)^2/4\Delta G_r$ is used.

molecular hydration, independently of the potential used. This increase is very significant when the ABQ potential is used, resulting in a change of −17 kcal/mol in the solvation enthalpy. On the contrary, when the structure A is used the reaction takes place with a loss of hydration, which is reflected in the decrease in the energy and solvation enthalpy that changes from −39.2 to −32.6 kcal/mol with our potential.

To calculate the reaction free energies, we constructed the R and P diabatic free energy curves of Figure 1 (obtained from their respective simulations and corrected according to the work of Tachiya[51] in which the product curve is vertically moved to cross the reactant curve at $\Delta e = 0$.). Except in the cases of the structure B with AMBER potential, the curves corresponding to the products are somewhat deeper than that of the reactant, leading to slightly exothermic reactions (see values ΔG in Table 3).

Given that the free energy of this reaction at 298 K is −4.23 kcal/mol when obtained from the experimental equilibrium constant $k_{eq}(T) = e^{3769/T−5.494}$ [52] and −4.64 kcal/mol when obtained from ultraviolet spectrophotometry,[53] we can conclude that for A and B structures the results with our electrostatic and van der Waals parameters describe the energies of this reaction better that when the AMBER parameters are used in the LJ(12-6-1) potential function. On the other hand, the higher hydration of the reactant in the case of structure A obtained with both potential justifies the high value of the reorganization energy ΔG_r. Also in this Table 3 is shown that the activation energy obtained from the crossing point of the two curves is similar to the result obtained from using Marcus' relationship, especially in the case of the ABQ potential.

However, comparing the values of the activation free energy in the methylene glycol formation with those from experimental studies, one observes an appreciable difference between the two results. From these experimental studies we highlight the work of Schecker and Schulz,[54] where they finds a temperature dependence of the rate constant given by $k_v(T) = 2.04 \times 10^5 \times e^{−2936/T}$ for the hydration of the formaldehyde and an free energy of activation of 14.85 kcal/mol, and the work of Winkelman[52] with $k_v(T) = 7800 \times e^{−1913/T}$ and $\Delta G^{\#} = 14.75$ kcal/mol. These

free energies of activation are very far from any of the theoretical values presented in this work.

To improve these disappointing results for the activation energy, we build new free energy curves for the formaldehyde reactant, where any water molecule can take part of the reaction mechanism. The obtained results lead to a substantial improvement of the activation barrier that increases up to 13.72 kcal/mol with the ABQ potential and up to 17.69 kcal/mol for the AMBER case.

Conclusions

In sum, the use of simple potentials of the type LJ(12-6-1) to describe the solute−solvent interactions in the molecular dynamics simulation of chemical reactions in aqueous medium and to obtain free energy curves leads to acceptable results when the interaction parameters are chosen appropriately. Thus, when one uses the ESIE charges and the A_{ij}^{sw} and B_{ij}^{sw} parameters, determined from the EX-PL-DIS components of the interaction energy, the results for the free energy of reaction are in very good agreement with the experiment. Moreover, the free energy of activation obtained with our model is also adequately described when in the simulation process the water molecules that surround to the formaldehyde can take part of the reaction mechanism. These good results are obtained when the reactant structure shows a water configuration that assists the protonation of the aldehyde.

References and Notes

(1) Cramer, C. J.; Truhlar, D. G. *Structure and Reactivity in Aqueous Solution*; American Chemical Society: Washington, DC, 1994.

(2) Warshel, A. *Computer Modeling of Chemical Reactions in Enzymes and Solutions*; Wiley & Sons: New York, 1991.

(3) Jorther, J.; Levine, R. D.; Pullman, B. *Reaction Dynamics in Cluster and Condensed Phases*; Kluwer Acad. Pub.: London, 1999.

(4) Moreau, M.; Turq, P. *Chemical Reactivity in Liquids. Fundamental Aspects*; Plenum: New York, 1988.

(5) Honeisel, C. *Theoretical Treatment of Liquids and Liquid Mixtures*; Elsevier: New York, 1993.

(6) Politzer, P.; Murray, J. S. *Quantitative Treatments of Solute-Solvent Interactions*; Elsevier: Amsterdam, 1994.

(7) Simkin, B. Y.; Sheikhet, I. I. *Quantum Chemical and Statistical Theory of Solutions. A Computational Approach*; Ellis Horwood: Madrid, 1995.

(8) Truhlar, D. G.; Isaacson, A. D.; Garret, B .C. *The Theory of Chemical Reaction Dynamics*; Baer, M., Eds.; CRC Press: Boca Raton, FL, 1985; Vol. 4.

(9) Muller, A.; Ratjczak, H.; Junge, W.; Diemann, E. *Electron and Proton Transfer in Chemistry and Biology*; Elsevier: New York, 1992.

(10) Bala, P.; Grocowski, P.; Lesyg, B.; McCammon, J. A. *Quantum Mechanical Simulation methods for Studying Biological Systems*; Bicout, D., Field, M., Eds.; Springer: Berlin, 1995.

(11) Gao, J. *Methods and Aplications of Combined Quantum mechanical and Molecular Mechanical Potentials*; Lipkowitz, K. B., Boyd, B. D., Eds.; VCH Review in Computational Chemistry 7; VCH, New York, 1996.

(12) Rivail, J. L. *New Theoretical Concepts for Understanding Organic Reactions*; Bertrán, J., Csizmadia, I. G., Eds.; Kluwer: Dordrecht, The Netherlands, 1989.

(13) Cramer, C. J.; Truhlar, D. G. *Solvent Effects and Chemical Reactivity*; Tapia, O., Bertran, J., Eds.; Kluwer: Dordrecht, The Netherlands, 1996.

(14) Hynes, J. T. *Solvent Effects and Chemical Reactivity*; Tapia, O., Bertran, J., Eds.; Kluwer: Dordrecht, The Netherlands, 1996.

(15) Truhlar, D. G. *The Reaction Path in Chemistry: Current Approaches and Perspectives*; Heidrich, D., Ed.; Kluwer: Dordrecht, The Netherlands, 1995.

(16) Car, R.; Parrinello, M. *Phys. Rev. Lett.* **1985**, *55*, 2471.

(17) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117.

(18) Gao, J. *J Chem. Phys.* **1992**, *96*, 537.

(19) Alder, B. J.; Winwright, T. E. *J. Chem. Phys.* **1959**, *31*, 459.

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(20) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Chem. Phys.* **2001**, 265, 207.

(21) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Chem. Phys. Lett.* **2002**, *357*, 279.

(22) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Recent Research Developments in Chemical Physics*; Transworld Research Network: Trivandrum, India, 2002.

(23) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Chem. Phys.* **2003**, *293*, 193.

(24) Tolosa, S.; Sansón, J. A.; Hidalgo, A. J. *Solution Chem.* **2005**, *34*, 407.

(25) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Chem. Phys.* **2005**, *315*, 76.

(26) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Mol. Simul.* **2005**, *31*, 549.

(27) Tolosa, S.; Sansón, J. A.; Hidalgo, A. *Chem. Phys.* **2006**, *327*, 187.

(28) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966.

(29) Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155.

(30) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891.

(31) Marcus, R. A.; Sutin, N. *Comments Inorg. Chem.* **1986**, *5*, 119.

(32) Carter, E. A.; Hynes, J. T. *J. Phys. Chem.* **1989**, *93*, 2184.

(33) Guthrie, J. P. *J. Am. Che. Soc.* **2000**, *122*, 5529.

(34) Case, D. A.; Darden, T. A.; Cheatham, T. E., III.; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Mert, K. M.; Wang, B.; Pearlman, D. A.; Crowley, M.; Brozell, S.; Tsui, V.; Gohlke, H.; Mongan, J.; Hornak, V.; Cui, G.; Beroza, P.; Schafmeister, C.; Caldwell, J. W.; Ross. W. S.; Kollman, P. A. AMBER 8, University of California, San Francisco, 2004.

(35) Shirts, M. R.; Pitera, J. W.; Swope, W. C.; Pande, V. S. *J. Chem. Phys.* **2003**, *119*, 5740.

(36) Jorgensen, W. L.; Tirado-Rives, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 1657.

(37) Kumpf, R. A.; Damenwood, J. R., Jr. *J. Phys. Chem.* **1989**, *93*, 4478.

(38) Williams, I. H.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 7832.

(39) Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31.

(40) Williams, I. H.; Spangler, D.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7717.

(41) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724.

(42) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.

(43) Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martín, R. L.; Fox, D. J.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. GAUSSIAN-92 Revision D.3, Gaussian Inc, Pittsburgh PA, 1992.

(44) Morokuma, K. *J. Chem . Phys.* **1970**, *19*, 553.

(45) Kitaura, K.; Morokuma, K. *Int. J. Quantum Chem.* **1976**, *10*, 325.

(46) Dupuis, M.; Spangler, D; Wendoloski, J. *National resource for Computations in Chemistry Software Catalog*; University of California: Berkeley, CA; GAMESS Program QG01, 1980.

(47) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(48) Ewald, P. *Ann. Phys.* **1921**, *64*, 253.

(49) Ryckaert, P.; Ciccotti, G.; Berendsen, J. J. C. *J. Comp. Phys.* **1977**, *23*, 237.

(50) Mahoney, M. W.; Jorgensen, W. L. *J. Chem. Phys.* **2000**, *20*, 8910.

(51) Tachiya, M. *J. Chem. Phys.* **1989**, *93*, 7050.

(52) Winkelman, J. G. M.; Voorwinder, O. K.; Ottens, M.; Beenackers, A. A. C. M.; Janssen, L. P. B. M. *Chem. Eng. Science* **2002**, *57*, 4067.

(53) Zavitsas, A. A.; Coffiner, M.; Wiseman, T.; Zavitsas, L. R. *J. Phys. Chem.* **1970**, *74*, 2746.

(54) Schecker, H. G.; Schulz, G. *Z. Phys. Chem. Neue Folge* **1969**, *65*, 221.