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# A Monte Carlo-Quantum Mechanics Study of the Solvent-Induced Spectral Shift and the Specific Role of Hydrogen Bonds in the Conformational Equilibrium of Furfural in Water

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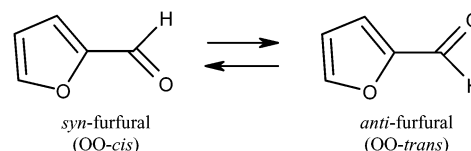
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The solvation shift of the lowest absorption transition of furfural in water is analyzed as a function of the rotation angle for the interconversion between the two conformations, OO-cis and OO-trans, of furfural. In total, 20 Monte Carlo NPT simulations are performed, corresponding to different rotation angles of the carbonyl group. The solvation shift of the  $n-\pi^*$  state is calculated to be  $1230 \pm 45 \text{ cm}^{-1}$  in the most stable OO-cis form. This calculated shift is found to be essentially independent of the rotation angle. The hydrogen bonds between furfural and water are also analyzed along the interconversion path. These hydrogen bonds are found to be equivalent, both in number and in binding energy, for all rotation angles. The results for the solvent-induced spectral shift and the hydrogen bond interactions confirm that in water they make no preference for any rotamer of furfural and lead to small contribution to the entropic activation barrier of furfural in protic solvents.

## Introduction

Conformation equilibrium of organic molecules in different solvents is a topic of great importance.<sup>1</sup> In this direction furfural is an interesting system that may exist in two possible conformations corresponding to a OO-cis and a OO-trans conformer<sup>2</sup> (Figure 1). In the gas phase it is known that the OO-trans is more stable than the OO-cis with an energy difference<sup>3</sup> that is less than 1.0 kcal/mol. Between these two forms there is a large interconversion barrier that has been determined<sup>3,4</sup> to be 9.3 kcal/mol. The conformational equilibrium of furfural, however, has a strong solvent dependence.<sup>5,6</sup> In neat furfural the barrier is<sup>3</sup> 11.0 kcal/mol. The barrier has also been determined for a few other solvents and it has been the subject of intense theoretical and experimental investigations.<sup>1–20</sup> The recent and interesting work of Baldrige, Jonas, and Bain<sup>7</sup> gives an overview of previous works on the energetics of furfural in the gas phase and in different solvents. The conformer with the larger dipole moment, OO-cis, dominates in polar solvents over the OO-trans conformer, which is, however, more stable in the gas phase or in low-polarity solvents (dielectric constant smaller than 5). The small energy difference between the two conformations and the activation barrier of furfural in different solvents have attracted both experimental<sup>2–15</sup> and theoretical investigations.<sup>15–20</sup> Bain and Hazendonk<sup>14</sup> have used combined NMR experiments to determine the activation barrier of furfural in toluene, acetone, and methanol. They have found that the behavior of the enthalpies of activation for the cis–trans process



**Figure 1.** Conformational equilibrium of furfural. The carbonyl group rotates relative to the furan ring.

does not obey a simple relationship with the dielectric constant. This, of course, indicates that the solvent effects are more complex than could be inferred by a simple reaction field. In addition, they also emphasized the existence of entropic aspects in the activation barrier. There is a large entropy activation in the case of toluene and acetone, for instance.<sup>14</sup> In the first solvent the variation is positive, indicating that the transition state is disordered compared to the planar form. For acetone, the reverse occurs, with the planar form more disordered than the transition state. For methanol, however, there is no significant entropy of activation, meaning that there is no preferred interaction between the solute and the solvent.<sup>14</sup> This is of great interest because one could at first expect that in protic solvents the hydrogen bonds, formed in the oxygen atoms of furfural should give a preferred structure along the rotation of the carbonyl group. This is the major interest of this present paper. Here we will give a very detailed theoretical analysis of the hydrogen bonds formed between furfural and water, a very protic solvent, along the cis-trans rotational interconversion, including the transition state. The selection for water is interesting because any hydrogen bond effect will be enhanced by this strong protic solvent. We shall consider the number of hydrogen bonds formed and the corresponding binding energies, as a function of the rotation

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angle. With this we analyze possible preferences of the solute form.

The solvent dependence of the UV–vis absorption spectrum of furfural is much less known despite its great importance as an additional aid to the conformation dynamics.<sup>21,22</sup> The ultraviolet absorption spectrum of furfural vapor is quite weak to be accurately measured, whereas in polar solvents the whole spectrum merges into a strong absorption.<sup>21,22</sup> The influence of polar solvents, e.g., water, on the  $n-\pi^*$  transition of furfural is known to give a blue shift, as normally expected. The  $\pi-\pi^*$  transition, instead, suffers a red shift.<sup>21,22</sup> It is important to understand the role of the conformers on the solvent-induced spectral shift of furfural during the internal rotation of the carbonyl group. In particular, the effect of the solvent on the  $n-\pi^*$  transition gives additional information on the possible preference of the solute form, because the lone pair of furfural is located in the same atom that is the proton acceptor of the hydrogen bond.

Thus, the major interest here is to investigate the hydrogen bonds formed between furfural and water and the solvent effects on the absorption spectrum of furfural in aqueous solution. We use a sequential Monte Carlo (MC) quantum mechanics (QM) methodology,<sup>23–25</sup> where we first generate the structures of the liquid by using MC simulations. The advantage of using a sequential procedure has been discussed before.<sup>25–27</sup> Supermolecular structures are extracted from the MC simulations and only statistically uncorrelated configurations are used. As we shall demonstrate, this leads to converged results for all calculations presented here.

The solvation shifts and the analysis of the hydrogen bonds are made for several rotation angles, starting with the OO-cis conformation and changing the dihedral angle until the OO-trans structure is reached (Figure 1). Note that the use of isolated cluster calculations is not recommended in this case. For one side there is no a priori indication of how many hydrogen bonds are formed. The change of the number of hydrogen bonds along the cis–trans interconversion is precisely the subject of interest here. On the other, geometry-optimized clusters cannot reproduce the liquid situation.<sup>26,28</sup> Instead, the use of computer simulation of liquids is more appropriate. We use MC simulation to generate the liquid structure. In total, 20 different conformations of furfural are used, with the dihedral angles changed by  $9^\circ$  between successive simulations. The QM calculations are performed in several supermolecular structures of each of these 20 conformations of furfural in aqueous solution obtained from the MC simulations. In every conformation singly excited configuration interaction calculations at the INDO/CIS<sup>29,30</sup> level are performed to obtain the solvatochromic shifts of the  $n-\pi^*$  and  $\pi-\pi^*$  electronic transitions during the conformational changes of furfural in water. Each supermolecule included in the QM calculation is composed of the solute furfural and all molecules up to the first solvation shell. The use of this supermolecular approach incorporates in a natural way the solute–solvent interaction because it is treated by quantum mechanics.

### Monte Carlo Simulation and Computational Details

Monte Carlo (MC) statistical mechanics simulations are carried out by employing standard procedures,<sup>31</sup> including the Metropolis sampling technique<sup>32</sup> and periodic boundary conditions using the minimum image method in a cubic box. The simulations are performed in NPT ensembles. The system consists of one furfural molecule plus 450 water molecules at temperature of 298.15 K and pressure of 1 atm. In total, 20

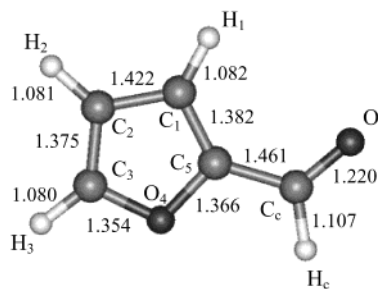


Figure 2. Geometrical parameters (Å) for the conformers of furfural.

TABLE 1: Potential Parameters Used in the Monte Carlo Simulations ( $q$  in Elementary Charge Unit,  $\epsilon$  in kcal/mol, and  $\sigma$  in Å)<sup>a</sup>

atom	$\epsilon$	$\sigma$	atomic charge $q$ in conformation:		
			OO-cis ( $\varphi = 0^\circ$ )	TS ( $\varphi = 90^\circ$ )	OO-trans ( $\varphi = 180^\circ$ )
O <sub>4</sub>	0.140	2.90	−0.113742	−0.140933	−0.186419
C <sub>1</sub>	0.070	3.55	−0.229589	−0.236743	−0.152939
C <sub>2</sub>	0.070	3.55	−0.092507	−0.109888	−0.182596
C <sub>3</sub>	0.070	3.55	−0.066166	−0.080331	0.013224
C <sub>5</sub>	0.070	3.55	0.093111	0.070219	0.096797
H <sub>1</sub>	0.030	2.42	0.154373	0.152396	0.150293
H <sub>2</sub>	0.030	2.42	0.123161	0.128195	0.146217
H <sub>3</sub>	0.030	2.42	0.160697	0.158236	0.141872
C <sub>6</sub>	0.105	3.75	0.378572	0.528755	0.382465
O <sub>5</sub>	0.210	2.96	−0.403259	−0.413801	−0.416096
H <sub>c</sub>	0.030	2.42	−0.004650	−0.056105	0.007182

<sup>a</sup> Atomic indices are defined in Figure 2. The parameters  $\epsilon$  and  $\sigma$  are taken from ref 16, and the atomic charges are obtained from CHELPG calculations using MP2/6-311+G(d).

different MC simulations of furfural in water are performed for a fixed dihedral angle  $\varphi$  (O<sub>4</sub>C<sub>5</sub>C<sub>6</sub>O<sub>5</sub>, in Figure 2) with  $\Delta\varphi = 9^\circ$ , from  $0^\circ$  (OO-cis or syn-furfural) to  $180^\circ$  (OO-trans or anti-furfural). The intermolecular interactions are described by the standard Lennard-Jones plus Coulomb potential with three parameters for each atom  $i$  ( $\epsilon_i$ ,  $\sigma_i$ , and  $q_i$ ). The atomic parameters are combined by geometric average to generate the pair parameters  $\epsilon_{ij} = (\epsilon_i\epsilon_j)^{1/2}$  and  $\sigma_{ij} = (\sigma_i\sigma_j)^{1/2}$ . For the water molecules we use the SPC potential developed by van Gunsteren et al.<sup>33</sup> For furfural, we use the OPLS-AA potential previously used to study the free energy of its interconversion in different solvents.<sup>16,34</sup> The atomic charges of furfural have been obtained by fitting the electrostatic potential at points selected according to the CHELPG scheme,<sup>35</sup> using an ab initio second-order Møller–Plesset perturbation theory (MP2) with the 6-311+G(d) basis set,<sup>36,37</sup> as implemented in the Gaussian98.<sup>38</sup> The sets of intermolecular potential parameters employed in the simulations are shown in Table 1. As the atomic charges are different for the different rotational angles we obtain 20 sets of atomic charges from the MP2/6-311+G(d) calculations. In Table 1 we only show the charges for the planar OO-cis conformation ( $\varphi = 0^\circ$ ), the nearest conformation of the transition state ( $\varphi = 90^\circ$ ), and OO-trans conformation ( $\varphi = 180^\circ$ ). As can be seen, they do not differ much. However, it is interesting to note that the oxygen atom of the carbonyl has a larger negative charge than the oxygen in the furan ring. This aspect is seen here even when using other ab initio theoretical models. Thus the carbonyl group is more apt to make hydrogen bonds with the solvent water than the furan ring. In the 20 simulations, the averaged density has a small variation. The smaller value of the averaged density  $\rho = 1.045$  g/cm<sup>3</sup> was found to conformation at  $\varphi = 117^\circ$  and the larger value  $\rho = 1.055$  g/cm<sup>3</sup> was found at  $\varphi = 63^\circ$ . This means that in the average the smallest cubic box has size of  $L = 21.46$  Å and the largest 21.52 Å. The intermolecular interactions are spherically truncated within a center of mass

separation smaller than the cutoff radius,  $r_c = L/2$ . Long-range corrections were calculated beyond this cutoff distance.<sup>31</sup> The Lennard-Jones potential contribution is estimated assuming an uniform distribution  $G(r) \approx 1$  after the cutoff radius and the electrostatic potential contribution is estimated with the reaction field method of the dipolar interaction. In the simulation the molecules are kept with rigid geometries for the different conformations of furfural. The geometrical parameters used for furfural in the simulations are given in Figure 2. Using these parameters, we find that the dipole moments of the OO-cis and OO-trans configurations at the ab initio MP2/6-311G(d) level are 3.76 and 3.24 D, respectively. These compare very well with the corresponding experimental<sup>39</sup> values of 3.97 and 3.23 D. During the classical simulation the water molecules are kept in their  $C_{2v}$  structure with  $r_{OH} = 1.000$  Å and  $\theta(\text{HOH}) = 109.47^\circ$ .

The initial configurations are generated randomly, considering the position and orientation of each molecule. One MC step is performed after one water molecule randomly attempts to translate in the Cartesian directions and also attempts to rotate around a randomly chosen axis. The maximum allowed displacement of the molecules and of the box size are self-adjusted after 50 configurations to give an acceptance ratio of new configurations around 50%. The maximum rotation angle was fixed during the simulation in  $\delta\theta = \pm 15^\circ$ . The simulations consisted of a thermalization phase of  $2.0 \times 10^6$  MC steps, followed by an averaging stage of  $27.0 \times 10^6$  MC steps.

As quantum mechanical calculations will be performed on the configurations generated by the MC simulations it is very important to optimize the statistics. Successive configuration, which are statistically highly correlated, will not give important additional information. Therefore we calculate the interval of statistical correlation using the autocorrelation function of the energy.<sup>23–25,40,41</sup> Essentially, it gives the interval of MC steps in which the statistically uncorrelated configuration can be sampled. For the simulations presented here, we obtain that configurations separated by  $450 \times 10^3$  MC steps are statistically less than 10% correlated. Then, the total of  $27 \times 10^6$  successive configurations generated in each simulation can be drastically reduced to 60 nearly uncorrelated configurations without loss of statistical information.<sup>26,40,41</sup> Thus, after each simulation corresponding to the different rotation angles, 60 uncorrelated configurations are sampled to be used in further quantum mechanical supermolecular calculations. Each supermolecule is composed of the chromophore (furfural) and all solvent molecules up to the first solvation shell of the radial distribution function. This gives a number of 34 water molecules surrounding furfural. Then, for each QM calculation there are 308 valence electrons included. In total, 20 sets of configurations are generated by the MC simulations, corresponding to the different dihedral angles. This means that 60 QM calculations are performed for the supermolecules composed of one furfural and 34 water molecules. A more detailed discussion on the efficiency of the sampling procedure will be given below and demonstrate that statistically converged results are obtained.

All simulations are performed with the DICE<sup>42</sup> Monte Carlo statistical mechanics program. DICE is a general program for MC simulation with a graphical interface that calculates thermodynamic properties and generates structures for using in most conventional quantum chemistry program.

## Results and Discussion

**Hydrogen Bond Analysis.** In this section we analyze the number of hydrogen bonds formed between furfural and water

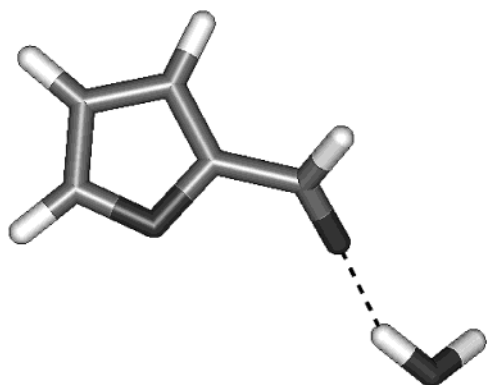
**TABLE 2: Statistics of the Hydrogen Bonds Formed between Furfural and Water**

no. of HB	OO-cis ( $\varphi = 0^\circ$ )		TS ( $\varphi = 90^\circ$ )		OO-trans ( $\varphi = 180^\circ$ )	
0	23%		28%		8%	
1	58%		60%		72%	
2	17%		12%		18%	
3	2%				2%	
average	0.97		0.84		1.13	
proton acceptor	O <sub>c</sub>	O <sub>4</sub>	O <sub>c</sub>	O <sub>4</sub>	O <sub>c</sub>	O <sub>4</sub>
	0.87	0.10	0.82	0.02	1.13	0.00

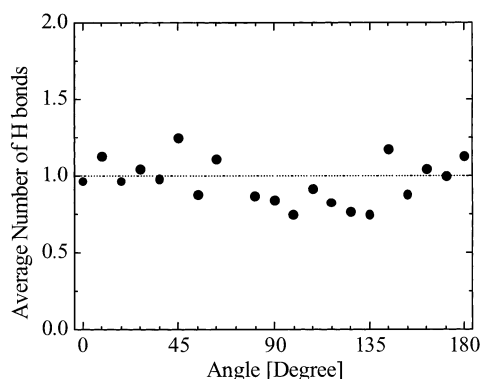
and the energy of these bonds for each of the 20 different conformations used here. These will give microscopic detailed information of the specific interaction involving the proton acceptor furfural and the proton donor water clarifying the specific role played by the hydrogen bonds in the rotational interconversion between the two extreme OO-cis and OO-trans conformers.

A common procedure to identify hydrogen bonds is by using the radial distribution function. In this case spherical integration of the first peak of the radial distribution function between the oxygen atom of furfural and the hydrogen atom of water would give the coordination number; i.e., the number of hydrogen bonds formed. The uncertainty associated with this procedure is that it cannot be assured that all nearest-neighbor structures are indeed associated with hydrogen bonds.<sup>24,26,43</sup> An efficient and more correct way to extract the hydrogen-bonded structures has been presented by Stlinger and Rahman<sup>44–46</sup> and Mezei and Beveridge.<sup>47</sup> They have discussed the directional and energetic aspects of hydrogen bonds and its usefulness in identifying hydrogen bonds in computer simulation of liquids. Hydrogen bonds are indeed better obtained using the geometric and energetic criteria.<sup>24,26,43,48</sup> We consider a hydrogen bond formation when the distance  $R(\text{O} - \text{O}_w) \leq 3.7$  Å, the angle  $\theta(\text{OO}_w\text{H}_w) \leq 36^\circ$ , and the binding energy is positive. Again, as there are 20 simulations performed, corresponding to the 20 rotation angles selected, it is cumbersome to give detailed information for all cases. Let us then first consider the most important cases of the OO-cis, OO-trans, and the transition state. It is of great importance to clarify the specific role played by the hydrogen bonds in the rotational interconversion between the two extreme OO-cis and OO-trans forms. Table 2 gives the detailed statistics of the hydrogen bonds. In the OO-cis case 23% of the configurations make no hydrogen bonds, 58% makes one, 17% makes two, and 2% makes even three hydrogen bonds. Table 2 shows that out of the 60 configurations selected there are 58 hydrogen bonds in the OO-cis conformation, thus making, on average, 0.97 hydrogen bond. These are averages for the liquid. Almost all the hydrogen bonds formed have the oxygen of the carbonyl as the proton acceptor. For instance, in this case of OO-cis, 0.87 is formed in the oxygen of the carbonyl, the O<sub>c</sub> site, and a negligible number of 0.10 in the oxygen atom O<sub>4</sub> of the furan ring. Similar results can be obtained for the OO-trans and even for the transition state. In these cases we find that furfural makes, on average, 1.13 hydrogen bonds in the OO-trans case and a slightly smaller number of 0.84 for the transition state. In the case of OO-trans 72% of the configurations make one hydrogen bond. In total, there are 1.13 hydrogen bonds and all these have the O<sub>c</sub> site as the proton acceptor. Figure 3 illustrates the hydrogen bond formed between furfural and water for an arbitrarily selected angle ( $\varphi = 36^\circ$ ). This is very indicative that the hydrogen bonds do not contribute to any preferred orientation of furfural in water. To have the overall picture of the number of hydrogen bonds in the different conformations, Figure 4 shows the average number as a function of the rotation angle. As can be seen the total number of hydrogen bonds is

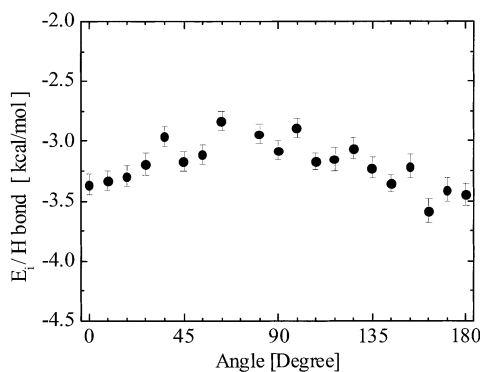




**Figure 3.** Illustration of the hydrogen bond formed between furfural and water for a rotation angle of  $36^\circ$ .



**Figure 4.** Calculated number of hydrogen bonds between furfural and water as a function of the rotation angle.



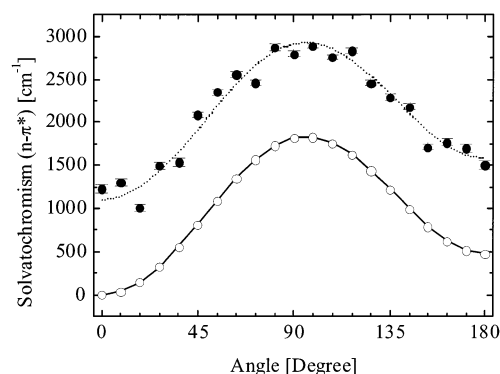
**Figure 5.** Binding energy per hydrogen bond as a function of the rotation angle.

remarkably stable, varying between a minimum of 0.75 hydrogen bonds (for  $\varphi = 135^\circ$ ) and a maximum of 1.25 hydrogen bonds (for  $\varphi = 45^\circ$ ). A consequence of this result is, of course, that hydrogen bonds do not contribute much to the energy change along the rotational interconversion. Hence, hydrogen bonds do not give rise to any preferred solute–solvent structure. To make this assertion even more emphatic, we show in Figure 5 the hydrogen bond energies. In the OO-cis case the binding energy is calculated as 3.36 kcal/mol. The maximum binding is  $3.58 \pm 0.10$  kcal/mol, obtained for  $\varphi = 162^\circ$ . For comparison, the minimum binding is  $2.83 \pm 0.10$  kcal/mol, obtained for  $\varphi = 63^\circ$ . In complement, the binding energy for the OO-trans case is  $3.45 \pm 0.10$  kcal/mol, 0.1 kcal/mol stronger than in the case of the OO-cis case. As the statistical error in the calculations is 0.1 kcal/mol, we cannot, in fact, distinguish between the OO-cis and OO-trans cases. For the transition state the binding energy is only 0.5 kcal/mol weaker than in the planar forms. The conclusion is that hydrogen bonds between furfural and

**TABLE 3: Calculated Solvatochromic Shifts ( $\text{cm}^{-1}$ ) and Comparison with Experimental Data<sup>a</sup>**

transition	solvatochromism	experiment
$n \rightarrow \pi^*$ (OO-cis)	$1230 \pm 45$	$1200,^a$ $1350^b$
$n \rightarrow \pi^*$ (OO-trans)	$1130 \pm 43$	
$\pi \rightarrow \pi^*$ (OO-cis)	$-1005 \pm 64$	$-1300^c$
$\pi \rightarrow \pi^*$ (OO-trans)	$-950 \pm 64$	

<sup>a</sup> From cyclohexane to water, ref 22. <sup>b</sup> From isooctane to water, ref 22. <sup>c</sup> From *n*-hexane to water, ref 21.

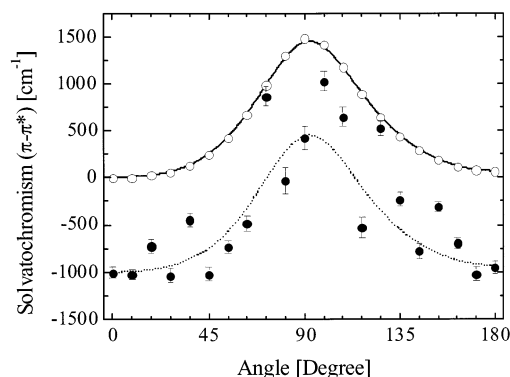


**Figure 6.** First absorption transition of furfural in the gas phase and in water as a function of the rotational angle. Lines shown are best fits to the calculated points. The lower curve corresponds to the transition shift of furfural in gas phase. The upper curve is the same transition shift in explicit water environment.

water are essentially equivalent for all rotation angles and therefore they make no contribution to a particular preference for any rotamer. This is in agreement with what could be expected from the experimental NMR measurements of Bain and Hazendonk.<sup>14</sup>

**Solvatochromic Shifts.** Now we analyze the solvation shifts of furfural in water. The UV–vis absorption spectrum of furfural in the gas phase shows a very weak  $n-\pi^*$  and a strong  $\pi-\pi^*$  electronic transitions.<sup>21,22</sup> The solvation shift of the  $n-\pi^*$  in water is thus measured from cyclohexane and isooctane, leading to an observed blue shift of  $1350 \pm 150 \text{ cm}^{-1}$ . As both solvents have a low polarity and low dielectric constant, we compare these values with those obtained here for the gas phase. For the  $\pi-\pi^*$  electronic transition the shift from *n*-hexane to water has been measured as  $-1300 \text{ cm}^{-1}$ . Again, we take this value for a comparison of our results for the solvation shift from gas to water. Table 3 shows a comparison of our calculated results and the experimental values available for the OO-cis conformation for both the  $n-\pi^*$  and  $\pi-\pi^*$  electronic transitions. As can be seen, the agreement is very good. The blue shift of the  $n-\pi^*$  transition is calculated as  $1230 \pm 45 \text{ cm}^{-1}$ , whereas the red shift of the  $\pi-\pi^*$  electronic transition is calculated as  $-1005 \pm 64 \text{ cm}^{-1}$ . These compare very well with the above-quoted experimental results of 1350 and  $-1300 \text{ cm}^{-1}$ , respectively.

It is now of interest to analyze the solvation shifts for the different conformations of furfural. This is shown in Figure 6 for the  $n-\pi^*$  transition. In the gas phase (lower curve) the transition is blue shifted by as much as  $1700 \text{ cm}^{-1}$ , in going from the OO-cis to the transition state. This maximum in the transition state is not due to the solvent interaction because it occurs for the gas phase. This is only a structural effect. Next in the rotation, the gas-phase absorption decreases and reaches the value corresponding to the OO-trans case. Thus the gas-phase absorption  $n-\pi^*$  transition shows a clear structural dependence and reaches its maximum close to the transition state where the absorption increases by  $1700 \text{ cm}^{-1}$ . However, there is an interesting aspect in the analysis of the solvation

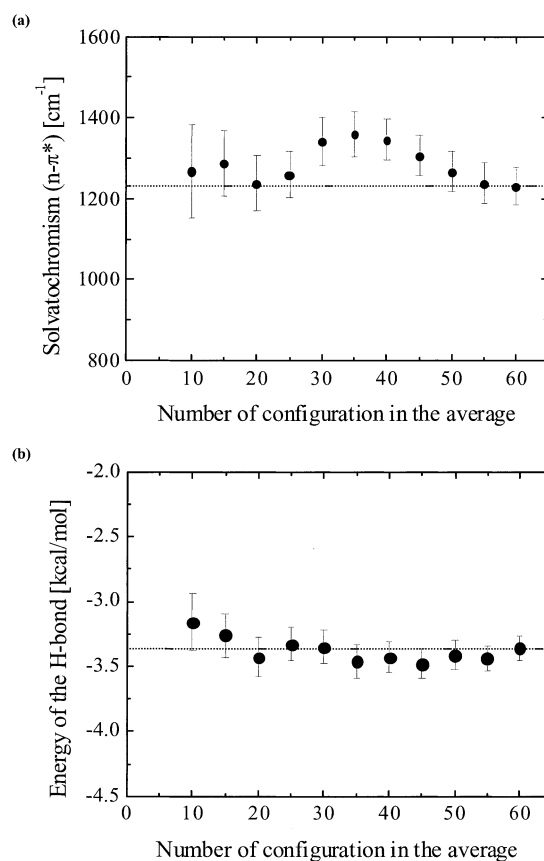


**Figure 7.** Second absorption transition of furfural in the gas phase and in water as a function of the rotational angle. Full line is the best fit for the transition in the gas phase. The dotted line is for visualization of a constant shift of  $-1000\text{ cm}^{-1}$  for the transition shift in explicit water environment. Comparison of the calculated points (full circles) with the dotted line shows the discrepancy from a constant solvation shift.

shift. As Figure 6 shows, the *solvation shift* (difference between the two curves) is essentially independent of the conformation. This is not surprising because, as noted in the previous section, the solvent environment in the oxygen atom of the carbonyl is not very dependent on the rotation angle. As the lone pair of this atom is the one involved in the promotion of the  $n-\pi^*$  transition, it follows the same pattern along the rotation and gives a constant shift of about  $1200\text{ cm}^{-1}$ . Even in the other extreme, the OO-trans conformation, the shift is  $1130\text{ cm}^{-1}$ , only  $100\text{ cm}^{-1}$  less than in the more favorable OO-cis conformation. The constant solvatochromic shift of the  $n-\pi^*$  transition is thus related to the nonexistence of a preferred angle for the interaction of hydrogen bonds and the carbonyl group. Therefore, this should not occur in the strong  $\pi-\pi^*$  transition. Indeed, as shown in Figure 7, the  $\pi-\pi^*$  transition shows a more erratic behavior. The  $\pi^*$  orbital is more localized in the furan ring but during the rotation of the carbonyl group the occupied  $\pi$  orbital becomes less defined and is not delocalized over the entire molecule because it loses planarity. The largest variations form a constant shift (dotted line) are found close to the transition state. At the other extreme, the OO-trans planar conformation, the solvation shift is a red shift of  $1130\text{ cm}^{-1}$ , only  $100\text{ cm}^{-1}$  less than in the case of OO-cis.

Every point in Figures 6 and 7 is the result of an average over 60 quantum mechanical calculations. It is clear that if each of these numbers is not properly converged a wrong picture could emerge. We shall show below that the use of an efficient sampling procedure, as adopted here, guarantees converged results for a relatively small number of quantum mechanical calculations. This is of course an important point not only for the general QM/MM methodology but also because using 20 different simulations each entry in Figures 6 and 7 requires an average value for each rotation angle, amounting here to a total of 1200 quantum mechanical calculations.

**Statistical Convergence Analysis.** The question of sampling configurations from statistical simulations has been recognized to be a very important issue and it is crucial for the efficiency of QM/MM methods. We have addressed this issue several times before.<sup>23–27</sup> Instead of performing a quantum mechanical calculation on every configuration generated by the MC simulation, we use the interval of statistical correlation and the statistical inefficiency, to select the configuration that gives relevant statistical information.<sup>23–27,40,41,48</sup> We have shown numerically that performing average over thousands of successive configurations generated in the MC simulation, gives the



**Figure 8.** Convergence of the (a) calculated solvation shift and (b) hydrogen binding energy for the OO-cis case.

same result as averaging over only a few statistically uncorrelated configurations.<sup>40</sup> This is a very efficient way to sample configurations. It is statistically sound, and as we demonstrate, now it gives statistically converged results.

Now we analyze the dependence of our calculated average values on the set of values used in the calculation. As discussed before, the configurations separated from the MC simulation are statistically uncorrelated and therefore the average value should converge fast and systematically and should be independent of the particular choice of the set of MC configurations selected for the QM calculations. The statistical error of the average, however, depends on the total number of uncorrelated configurations ( $l$ ) used to calculate the average; i.e., on the total size of the simulation. Figure 8a shows the calculated average solvation shift of the  $n-\pi^*$  transition of the OO-cis conformation of furfural in water as the number of configurations used for the average is increased. This corresponds to the zero rotation angle of Figure 6. There are 20 averages of this type obtained for the analysis of the rotation effect on the  $n-\pi^*$  transition. Of course, only one case is given for illustration. Figure 8a clearly shows that the solvatochromic shift reported is a statistically converged value. In complement, Figure 8b shows the same convergence analysis for the hydrogen binding energy of the OO-cis case. The results clearly demonstrate that all average values considered here are statistically converged with only 60 uncorrelated structures of the MC simulation. This is again a demonstration of the efficiency of the sampling procedure used here that only  $l = 60$  instantaneous values give statistically converged results. Increasing further the number of calculations does not change the average, but of course, the statistical error, which depends on  $1/\sqrt{l}$ , decreases.

## Summary and Conclusions

The conformation equilibrium of furfural has been of great interest and the subject of several theoretical and experimental studies. It is known that it may exist in two conformations, the OO-cis and the OO-trans conformers, that are separated by a large interconversion barrier. In water, the conformer with the higher dipole moment, the OO-cis, is the most stable. In this investigation we have considered the role of hydrogen bonds in the conformational equilibrium and in the solvation shift of the  $n-\pi^*$  and  $\pi-\pi^*$  transitions of furfural in water.

A detailed analysis is made of the hydrogen bonds formed. To verify the dependence on the rotation angle, 20 different rotamers were considered. Thus 20 different Monte Carlo simulation were performed. On average one hydrogen bond is formed in the most stable OO-cis form. The number and strength of these hydrogen bonds do not vary much along the interconversion, thus suggesting that this interaction makes no preference for any particular rotamer. This is in agreement with experimental results obtained for furfural in a protic solvent.

Using a combined Monte Carlo and quantum mechanics methodology, the structure of the liquid composed of one furfural molecule and the first solvation shell of water is subjected to the calculation of the absorption spectrum. From the 20 different Monte Carlo simulations a total of 60 structures are sampled for each case for subsequent quantum mechanical calculations. It is found that the  $n-\pi^*$  absorption transition shifts by  $1230 \pm 45 \text{ cm}^{-1}$  in the OO-cis form, in good agreement with the experimental result of  $1350 \text{ cm}^{-1}$ . The solvatochromic shift of this  $n-\pi^*$  transition does not depend on the particular rotation angle. This is supplementary strong evidence that the hydrogen bonds have no preference for any particular rotamer of the solute and leads to small contribution to the entropic activation barrier. Before concluding, we should mention that the selection of water for this study is also related to the existence of the UV-vis experiment of furfural in water. Similar to the case of water we also found that the number and strength of hydrogen bonds formed between chloroform (a weaker protic solvent) and furfural is essentially constant along the rotational interconversion giving again no contribution to the entropic activation barrier.

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## References and Notes

- (1) Abraham, R. J.; Bretschneider, E. *Internal Rotational Molecules*; Orville-Thomas, W. J., Ed.; John Wiley: New York, 1974; Chapter 13.
- (2) Miller, F. A.; Fateley, G. G.; Witkowski, R. E. *Spectrochim. Acta* **1967**, 23A, 891.
- (3) Abraham, R. J.; Sivers, T. M. *Tetrahedron* **1972**, 28, 3015.
- (4) Little, T. S.; Qiu, J.; Durig, J. R. *Spectrochim. Acta* **1989**, 45A, 789.
- (5) Braathen, G. O.; Kveseth, K.; Nielsen, C. J.; Hagen, K. *J. Mol. Struct.* **1986**, 145, 45.
- (6) Salman, S. R. *Org. Magn. Reson.* **1982**, 20, 151.
- (7) Baldrige, K. K.; Jonas, V.; Bain, A. D. *J. Chem. Phys.* **2000**, 113, 7519.
- (8) Allen, G.; Bernstein, H. J. *Can. J. Chem.* **1955**, 33, 1055.
- (9) Benassi, R.; Folli, U.; Schenetti, L.; Taddei, F. *Adv. Heterocycl. Chem.* **1987**, 41, 75.
- (10) Roques, B.; Combrisson, S.; Riche, C.; Pascard-Billy, C. *Tetrahedron* **1970**, 26, 3555.
- (11) Martin, M. L.; Roze, J.-C.; Martin, G. J.; Fourmari, P. *Tetrahedron Lett.* **1970**, 39, 3407.
- (12) Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, 38, 3245.
- (13) Montaudo, G.; Caccamese, S.; Librando V.; Maravigna, P. *Tetrahedron* **1973**, 29, 3915.
- (14) Bain, A. D.; Hazendonk, P. *J. Phys. Chem. A* **1997**, 101, 7182.
- (15) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian J.; Frisch, M. J. *J. Phys. Chem.* **1996**, 100, 16098.
- (16) Kaminski, G. A.; Jorgensen, W. J. *J. Phys. Chem. B* **1998**, 102, 1787.
- (17) John, I. G.; Radom, L. *J. Am. Chem. Soc.* **1978**, 100, 3981.
- (18) Petrongolo, C. *Chem. Phys. Lett.* **1976**, 42, 512.
- (19) F. Birnstock, H-F. Hofmann and H-J. Kohler, *Theor. Chim. Acta* **1976**, 42, 311.
- (20) Miyahara Y.; Inazu, T. *J. Mol. Struct. (THEOCHEM)* **1996**, 364, 131.
- (21) Mora-Diez, N.; Montero, L. A.; Fabian, J. *J. Mol. Struct. (THEOCHEM)* **1998**, 453, 49.
- (22) Hiraoka, H.; Srinivasan, R. *J. Chem Phys* **1968**, 48, 2185.
- (23) Coutinho, K.; Canuto, S. *Adv. Quantum Chem.* **1997**, 28, 89.
- (24) Canuto, S.; Coutinho, K. *Int. J. Quantum Chem.* **2000**, 77, 192.
- (25) Coutinho, K.; Canuto, S.; Zerner, M. C. *J. Chem. Phys.* **2000**, 112, 9874.
- (26) Malaspina, T.; Coutinho, K.; Canuto, S. *J. Chem. Phys.* **2002**, 117, 1692.
- (27) Canuto, S.; Coutinho, K.; Trzesniak, D. *Adv. Quantum Chem.* **2002**, in press.
- (28) Coutinho, K.; Saavedra, N.; Canuto, S. *J. Mol. Struct. (THEOCHEM)* **1999**, 466, 69.
- (29) Ridley, J.; Zerner, M. C. *Theor. Chim. Acta* **1973**, 32, 111.
- (30) Zerner, M. C. *ZINDO: A Semiempirical Program Package*; University of Florida: Gainesville, FL, 1997.
- (31) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Clarendon Press: Oxford, U.K., 1987.
- (32) Metropolis, N.; Rosenbluth, A. W.; Rosenbluth, M. N.; Teller A. H.; Teller, E. *J. Chem. Phys.* **1953**, 21, 1087.
- (33) Berendsen, H. J. C.; Postma, J. P. M.; van Gunsteren, W. F. *Intermolecular Forces*; Pullman, B., Ed.; Reidel: Dordrecht, The Netherlands, 1981; p 331.
- (34) Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J. *J. Am. Chem. Soc.* **1996**, 118, 11225.
- (35) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, 11, 361.
- (36) Bartlett, R. J. *J. Phys. Chem.* **1989**, 93, 1697.
- (37) Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.
- (38) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
- (39) Mönnig, F.; Dreizler, H.; Rudolph, H. D. *Z. Naturforsch. A* **1965**, 20, 1323.
- (40) Coutinho, K.; Oliveira, M. J.; Canuto, S. *Int. J. Quantum Chem.* **1998**, 66, 249.
- (41) Rocha, W. R.; Coutinho, K.; Almeida, W. B.; Canuto, S. *Chem. Phys. Lett.* **2001**, 335, 127.
- (42) Coutinho, K.; Canuto, S. *DICE: A Monte Carlo Program for Molecular Liquid Simulation*; University of São Paulo: São Paulo, 1997.
- (43) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. *J. Chem. Phys.* **1983**, 79, 926.
- (44) Rahman, A.; Stiling, F. H. *J. Chem. Phys.* **1971**, 55, 3336.
- (45) Stiling, F. H.; Rahman, A. *J. Chem. Phys.* **1974**, 60, 1545.
- (46) Stiling, F. H. *Adv. Chem. Phys.* **1975**, 31, 1.
- (47) Mezei, M.; Beveridge, D. L. *J. Chem. Phys.* **1981**, 74, 622.
- (48) Almeida, K. J.; Coutinho, K.; De Almeida, W. B.; Rocha, W. R.; Canuto, S. *Phys. Chem. Chem. Phys.* **2001**, 3, 1583.