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# A Monte Carlo-quantum mechanics study of the lowest $n-\pi^*$ and $\pi-\pi^*$ states of uracil in water†

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Received 21st March 2007, Accepted 2nd July 2007

First published as an Advance Article on the web 17th July 2007

DOI: 10.1039/b704335j

The solvatochromic shifts of the  $n-\pi^*$  and  $\pi-\pi^*$  states of uracil in water are analyzed using a combined and sequential Monte Carlo/quantum mechanics (MC/QM) approach. The role of the solute polarization and electronic delocalization into the solvent region are investigated. Electronic polarization of the solute is obtained using the HF/6-31G(d), the polarizable continuum model (PCM) and an iterative procedure using MP2/aug-cc-pVDZ in the MC/QM. The in-water dipole moment of uracil is obtained, respectively, as 5.12 D, 6.12 D and  $7.01 \pm 0.05$  D. This latter result, corresponding to an increase of 60% with respect to the gas phase value, is used in the classical potential of the MC simulation to obtain statistically uncorrelated configurations for subsequent QM calculations of the ultraviolet-visible absorption spectrum of uracil in water. QM calculations are performed at the time-dependent density-functional theory (TD-DFT) combined with the B3LYP and B3PW91 functionals, multiconfigurational (CASSCF) and the semi-empirical all-valence electron INDO/CIS methods. Using 60 solute-solvent configurations with the explicit inclusion of 200 water molecules the solvatochromic shift is obtained as a blue shift of 0.50 eV for the  $n-\pi^*$  state and a red shift of 0.19 eV for the  $\pi-\pi^*$  state, in good agreement with experimentally-inferred values. These results are compared with TD-DFT results in conjunction with PCM approaches and the importance of solute polarization and wave function delocalization over the solvent region is discussed. Our results suggest that the elusive  $n-\pi^*$  state of uracil in water lies around 255 nm hidden by the intense and broad  $\pi-\pi^*$  transition with a maximum at 260 nm, inverting the relative locations of these states compared to the gas phase. This is further supported by considering the in-water dipole moment changes upon excitation, as obtained from CASSCF calculations.

## Introduction

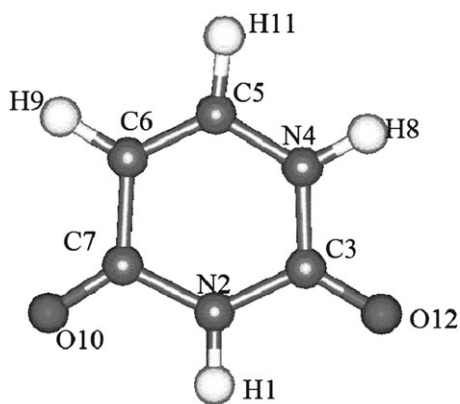
In recent years efforts have been made in the study of the photophysical and photochemical properties of nucleic acid bases.<sup>1</sup> A detailed understanding of the spectroscopic properties of the DNA and RNA bases in water environment is very important because of their biological significance. Uracil, in particular, has attracted interest because of its characteristic absorption and emission spectra in solution.<sup>2–5</sup> An interesting aspect is that the two lowest transitions in the gas phase are a  $n-\pi^*$  transition followed by a  $\pi-\pi^*$  one. In water the first would increase in energy (a blue shift) whereas the second would decrease (a red shift) thus bringing the two states very close. In fact, this close proximity, or the possible inversion of the states in polar solvents, would have important consequences in the photophysics of uracil in water, an aspect that has been examined recently.<sup>6</sup> However, whereas the  $\pi-\pi^*$

transition of uracil has been observed both in gas and in water the location of the  $n-\pi^*$  excitation in water seems to be elusive.

In the gas phase, the ultraviolet absorption spectrum of uracil (Fig. 1), is characterized by a very broad band in the region of 240 nm. The vapor-phase spectra of uracil have been determined by Clark *et al.*<sup>7</sup> that characterized a  $\pi-\pi^*$  transition at 5.08 eV. In the same work<sup>7</sup> this transition was seen at 4.77 eV in water. The location of this  $\pi-\pi^*$  transition in water was confirmed by Voet *et al.*<sup>8</sup> More recently this transition was reported in water at 4.80 eV.<sup>9</sup> This leads to the conclusion that the spectral shift of the  $\pi-\pi^*$  transition in changing from vapor to water is a red shift of magnitude between 0.28 and 0.31 eV. None of the above experimental studies could find a  $n-\pi^*$  excitation. Fujii *et al.*<sup>10</sup> reported the electronic spectrum of uracil in a supersonic jet and identified the 0–0 band system at 4.37 eV and assigned it to the low-lying  $n-\pi^*$  excitation. Eaton and Lewis<sup>11</sup> studied the absorption spectrum of the related crystalline 1-methyluracil and identified a  $n-\pi^*$  excitation at a larger transition energy of 4.63 eV. Theoretically, this transition has been obtained at 4.55 eV.<sup>12</sup> In water, however, this  $n-\pi^*$  transition has not been conclusively located experimentally. It should be a low intensity transition very close to the broad and very intense  $\pi-\pi^*$  transition. Apparently the only report available is an uncertain assignment from the CD spectra of uracil derivatives in water solution that would place

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† Electronic supplementary information (ESI) available: Sixty statistically uncorrelated configurations composed of one central uracil molecule surrounded by the 200 nearest water molecules. See DOI: 10.1039/b704335j



**Fig. 1** Uracil molecule. Atomic indices are used to define the electrostatic parameters.

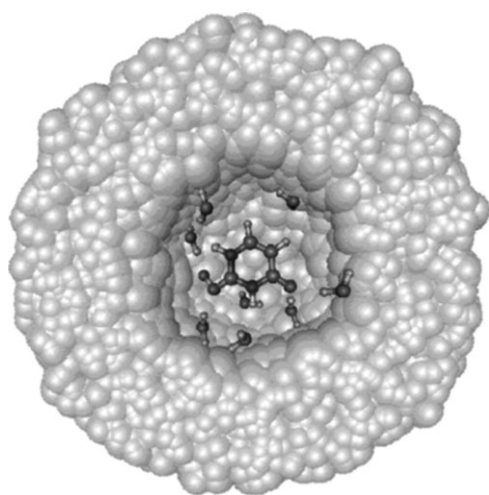
this transition at 5.17 eV.<sup>13</sup> If one accepts this result it would imply a substantial blue shift of the  $n-\pi^*$  excitation, in going from gas to water environment, of 0.54 or 0.80 eV. The latter is very unlikely for the blue shift of uracil, being a value more typical of betaine systems. Recent theoretical studies<sup>6,14</sup> have considered this blue shift to be 0.50 eV.

On the theoretical side there have been several studies of the absorption spectrum of uracil in gas<sup>12</sup> and in water environment.<sup>6,14–16</sup> Some of these studies use a continuum approach for the inclusion of the solvent effect. However, the importance of a specific solute–solvent interaction has been emphasized.<sup>6</sup> Aschi and co-workers<sup>14</sup> utilize instead the perturbed matrix method (PMM) where the solvent interaction is included in a perturbed electronic Hamiltonian that is diagonalized in each step of a molecular dynamics simulation.<sup>17</sup> Recently Barone and coworkers made extensive explorations on excited state surfaces of the Franck–Condon region for uracil and 5-fluorouracil in acetonitrile and water solutions.<sup>18</sup> The relative energies of the low-lying excited state of uracil in water and in acetone were also reported in this work.

The determination of the solvatochromic shifts of the low-est-lying states of uracil in water is thus very important for understanding the location of the elusive  $n-\pi^*$  of uracil and to rationalize the photophysics in water. Therefore the blue shift of the  $n-\pi^*$  and the red shift of the  $\pi-\pi^*$  states are the subject of this work. Using a combined and sequential Monte Carlo/quantum mechanics (MC/QM) approach we first generate statistically uncorrelated solute–solvent configurations for *a posteriori* QM calculations.<sup>19,20</sup> We paid special attention to the role played by the solute polarization and the wave function delocalization into the solvent region. The solute polarization is obtained from an iterative procedure, previously described.<sup>21</sup> The delocalization of the wave function is analyzed by incorporating a varied number of explicit solvent molecules, a procedure that is becoming common practice, even in continuum solvation models, and has shown to be important for uracil.<sup>6</sup> Here a relatively small number of explicit water molecules is first considered. To analyze the importance of the wave function delocalization we next explicitly include all water molecules within a distance of *ca.* 11 Å from the solute.

## Methodology

MC simulations are carried out employing the Metropolis sampling technique and periodic boundary conditions using the minimum image method in a cubic box.<sup>22</sup> The simulations are performed in the canonical  $NVT$  ensemble. The system consists of one uracil molecule and 700 water molecules at room temperature ( $T = 300$  K) and density of  $0.9966 \text{ g cm}^{-3}$ . The intermolecular interactions are described by standard Lennard-Jones plus Coulomb potentials with three parameters for each site  $i$  ( $\epsilon_i$ ,  $\sigma_i$  and  $q_i$ ). For uracil, the  $\epsilon_i$  and  $\sigma_i$  parameters of the potential were obtained from the OPLS force field<sup>23</sup> and the charges are obtained from an electrostatic fit (CHELPG)<sup>24</sup> using the MP2/aug-cc-pVDZ method. The geometry of uracil was obtained at this same level of calculations. For the water molecules we used the simple point charge (SPC) potential.<sup>25</sup> The solute geometry was kept frozen during the simulation. This may lead to small deviation in our results. The MC simulations were performed with the program DICE<sup>26</sup> and consisted of a thermalization phase of  $2.8 \times 10^7$  MC steps, followed by an averaging stage of  $1.05 \times 10^8$  MC steps. After calculating the auto-correlation function of energy<sup>19,20</sup> a total of 60 structures were selected with less than 12% of statistical correlation. To obtain the solute polarization due to the electrostatic field of the solvent an iterative procedure, previously described,<sup>21</sup> was employed. The first iteration consists of the atomic charges obtained from the CHELPG fit of the MP2/aug-cc-pVDZ calculation of isolated uracil. After the MC simulation using these atomic charges, 60 uncorrelated structures are sampled for use in the QM calculations and an average dipole moment and atomic charges were obtained. These charges are then used in another simulation to obtain new structures and values of the atomic charges. This procedure is carried out until a convergent value is obtained for the dipole moment of the solute. Using these electrostatic parameters of the solute, now in electrostatic equilibrium with the solvent, another MC simulation is performed to generate the solute–solvent configurations for the *a posteriori* QM calculations of the absorption spectrum of uracil. The solute–solvent configurations are extracted from the MC simulation with a varied number of explicit solvent molecules. Using explicit solvent molecules means that the wave function is anti-symmetric with respect to the electrons both in the solute and in the solvent molecules considered and thus it delocalizes over the solvent region. The QM calculations were performed on solute–solvent structures and three different models were used to obtain the solvatochromic shift of the lowest electronic state of uracil in water: (1) the uracil surrounded by 300 water molecules (all solvent molecules within the center-of-mass distance of 13 Å) represented only by point charges, termed as 300 H<sub>2</sub>O(SPC); (2) the solvent effects were modeled by explicitly including nine water molecules (corresponding to a distance of 4.5 Å away from the center of mass of the uracil molecule), embedded in the other 291 SPC solvent molecules. The average result is obtained after considering 60 of these configurations, as described above. This model is illustrated in Fig. 2 and is named 9 H<sub>2</sub>O + 291 H<sub>2</sub>O(SPC); (3) long-range interaction and the bulk solvent effects were modeled by explicitly including all water molecules up to a distance of



**Fig. 2** One supermolecular structure showing 1 uracil and 9 water molecules surrounded by the solvent (291 SPC water molecules or PCM).

11 Å. This leads to 200 explicit water molecules and it is termed 200 H<sub>2</sub>O. For this very large system consisting of a total of 1642 valence electrons a semi-empirical method will be adopted. Additionally, for comparison, we also substitute the configurations of charges by the polarizable continuum model (PCM) using the IEF-PCM version.<sup>27,28</sup> These calculations were done at the non-equilibrium regime using the united atom model (UAM) for the radius calculation.<sup>28</sup>

The quantum chemical calculations of the first and second models above were done using the time-dependent DFT (TD-DFT) level. Two different hybrid functionals were used to describe the low-lying excited states; the exchange correlation functional of Becke–Lee–Yang and Parr (B3LYP)<sup>29,30</sup> and the Becke–Perdew and Wang (B3PW91).<sup>31</sup> The basis set used in our TD-DFT calculations is a combination of the 6-31G(2p,2d) basis for the solute and the 6-31G basis for the solvent molecules. Additionally, a combination of the 6-31+G(d,p) and 6-31G(d) was used in the B3PW91 functional. This includes some diffuse functions on the solute

molecule. The QM calculations were performed with the Gaussian 03 program.<sup>32</sup> For the semi-empirical calculations, in the third model, we used the INDO/CIS method with the spectroscopic parametrization<sup>33</sup> implemented in the ZINDO program.<sup>34</sup> For additional support, in some specific points, CASSCF<sup>35</sup> calculations were made using the MOLCAS program.<sup>36</sup>

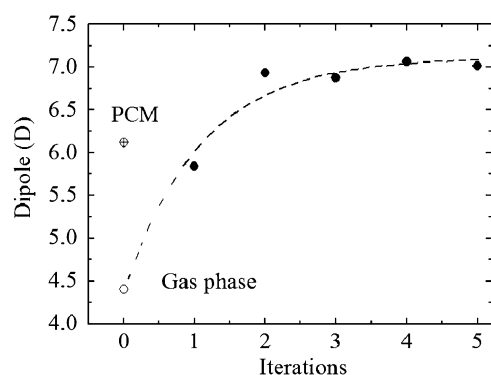
## Results and discussions

We first discuss the polarization of uracil in water. Table 1 summarizes the results for the electrostatic parameters and dipole moments of uracil in water environment. For the isolated molecule, the dipole moment is calculated here as 4.39 D using MP2/aug-cc-pVDZ. This value seems overestimated compared to the experimental gas phase value of 3.87 D.<sup>37</sup> The experimental dipole moment of uracil has also been reported in dioxane solution, leading to the value of 4.13 D.<sup>38</sup> Our value of 4.39 D for the gas phase dipole moment, however, is in line with the recent values<sup>16</sup> of 4.51, 4.29 and 4.33 D, respectively, obtained using DFT/PBE1PBE, MP2 and CCSD(T) theoretical levels with the same aug-cc-pVDZ basis functions. Using the B3LYP/6-31G(2d,2p) model the calculated result is obtained here as 4.33 D, similar to the MP2/aug-cc-pVDZ value. Based on these results and the expected accuracy of the MP2/aug-cc-pVDZ model to reproduce dipole moments within 10% and also on the relatively accurate CASSCF/CASPT2 value of 4.4 D<sup>12</sup> it would not be very unlikely that the experimental gas phase dipole moment is slightly underestimated.

The iterated calculated values of the dipole moment of uracil in the presence of the water solvent molecules are shown in Fig. 3. After five iterations the dipole moment converges to the in-water value of  $7.01 \pm 0.05$  D. In Fig. 3 every calculated result (black circle) represents an average over 60 MP2/aug-cc-pVDZ calculations of one uracil molecule surrounded by 300 SPC water molecules. For comparison the calculated PCM dipole moment of uracil is also shown in Fig. 3, representing a value of 6.12 D. The converged in-solution dipole moment of  $7.01 \pm 0.05$  D represents a considerable solute polarization leading to an increase of 60% compared to

**Table 1** Calculated values of the atomic charges obtained from CHELPG and dipole moments (D) from MP2/aug-cc-pVDZ calculations using PCM and iterative MC/QM with 60 statistically uncorrelated configurations. *Implicit* is the calculated value using HF/6-31G(d). See Fig. 1 for definition of the atomic types. The statistical error is shown for the converged iterated dipole moment

Atom	Gas phase		In-water	
	MP2/aug-cc-pVDZ	<i>Implicit</i> HF/6-31G(d)	PCM MP2/aug-cc-pVDZ	Iterative MP2/aug-cc-pVDZ
H1	0.3443	0.3737	0.3980	0.4343
N2	−0.6105	−0.7181	−0.6572	−0.7294
C3	0.7651	0.8945	0.8497	0.9688
N4	−0.4728	−0.5549	−0.5173	−0.5844
C5	0.1409	0.2149	0.1884	0.2613
C6	−0.4380	−0.5554	−0.5080	−0.5295
C7	0.7946	0.9349	0.8693	0.9782
H8	0.3253	0.3509	0.3942	0.4264
H9	0.1664	0.1954	0.1943	0.1999
O10	−0.5668	−0.6394	−0.6890	−0.8070
H11	0.1236	0.1432	0.1602	0.1499
O12	−0.5721	−0.6397	−0.6826	−0.7685
$\mu$	4.39	5.12	6.12	$7.01 \pm 0.05$



**Fig. 3** Calculated average values of the dipole moments with respect to the number of iterations. The cross open circle represents the value of 6.12 D obtained using the PCM.

the calculated value in the gas phase. The PCM model for the solvent represents a very economical procedure to obtain a reasonable approximation, leading to a solute polarization of *ca.* 40% compared to the calculated *in vacuo* dipole moment value. In previous studies<sup>39</sup> it has been suggested that a very simple estimate of the solute polarization could be obtained by performing one HF/6-31G(d) calculation. This originates in the usual tendency of this theoretical model to overestimate the dipole moment by *ca.* 20%. Table 1 compares these procedures to incorporate the solute polarization. It can be seen that whereas the implicit polarization of the HF/6-31G(d) method is insufficient the PCM model gives around 2/3 of the polarization obtained in the iterative procedure. It may also be seen that the PCM calculated atomic charges are intermediary between the gas phase and the in-solution values. This suggests that for more complex systems the use of PCM could initiate the iterative process or even be used as a reasonable approximation for generating the atomic charges to represent the polarized solute.

Before discussing the results for the transition energy shifts of uracil in water we first briefly discuss the results obtained for the gas phase absorption spectra. Our TD-DFT results give the first excited state as a  $\pi-\pi^*$  state and the second excited state as an  $n-\pi^*$  state. For the B3PW91/6-31+G(d,p) the  $n-\pi^*$  state was located at 4.57 eV and the  $\pi-\pi^*$  was found at 5.14 eV. Similar results were obtained for the 6-31G(2p,2d) basis function for the B3LYP and B3PW91 functionals, the  $n-\pi^*$  was located at 4.51 and 4.54 eV and the  $\pi-\pi^*$  at 5.16 and 5.18 eV, respectively, for B3LYP and B3PW91 functionals. This indicates that for the isolated molecule the changes in the functional form and in the basis set have little effect on the excitation energies. This is in line with the observation in a recent review.<sup>40</sup> These values and the corresponding assignment of each state are in agreement with gas phase experiments<sup>7,10,11</sup> and CASPT2 calculations<sup>12</sup> and with the more recent investigations.<sup>6,14,16</sup> Using INDO/CIS the corresponding  $n-\pi^*$  and  $\pi-\pi^*$  transitions are calculated, respectively, at 4.09 and 5.37 eV. We note that the INDO/CIS separation between the two states is overestimated, being about twice as large as experiment.

Using the configurations generated by the MC simulation with the converged solute polarization different QM calcula-

tions were performed to obtain average values of the gas-to-water solvatochromic shifts. In the following discussion we assume that the  $\pi-\pi^*$  transition in water is red-shifted by 0.28–0.31 eV, as obtained from the experimental results discussed in the Introduction. This compares with the red shift of 0.3 eV considered in ref. 16 but is larger than the red shift value of 0.20 eV assumed in ref. 6 and 14.

First we used 300 H<sub>2</sub>O(SPC) where 300 water molecules around uracil are treated as simple point charges. In the TD-DFT approach the  $n-\pi^*$  was shifted to higher energies by 0.80 eV while the  $\pi-\pi^*$  state was shifted by –0.02 eV, to lower energies (Table 2). Compared to experiment, we note that the  $\pi-\pi^*$  transition shift is too small. Using only PCM the results improve for the  $n-\pi^*$  transition (0.40 eV) but is still very small (–0.04 eV) for the  $\pi-\pi^*$  transition.

We now consider the wave function delocalization. The delocalization of the wave function over the solvent region contributes to a red shift.<sup>41,42</sup> Including explicitly 9 water molecules together with uracil as the solute in PCM indeed improves the description of the  $\pi-\pi^*$  shift. The calculated value of –0.17 eV (obtained using either B3LYP or B3PW91) is now in better agreement with the experimental result, as seen in Table 2. This has been noted in a previous report of this transition where 4 explicit water molecules were included.<sup>6</sup> These 4 water molecules were placed at optimized positions. As a liquid is characterized by a statistical distribution our results with 9 water molecules were extracted from the MC simulation and the shift reported is an average value. Using these same structures, an even better result for the  $\pi-\pi^*$

**Table 2** The lowest  $n-\pi^*$  and  $\pi-\pi^*$  solvent shifts (eV) calculated with different theoretical methods using different representation of the water solvent

Present results	$n-\pi^*$	$\pi-\pi^*$
TD-B3LYP 300 H <sub>2</sub> O(SPC) <sup>a</sup>	0.80	–0.02
TD-B3LYP PCM	0.40	–0.04
TD-B3LYP 9 H <sub>2</sub> O + PCM <sup>a</sup>	0.62	–0.17
TD-B3PW91 9 H <sub>2</sub> O + PCM <sup>a</sup>	0.64	–0.16
TD-B3PW91 9 H <sub>2</sub> O + PCM <sup>ab</sup>	0.59	–0.17
TD-B3LYP 9 H <sub>2</sub> O + 291 H <sub>2</sub> O(SPC) <sup>a</sup>	0.75	–0.20
INDO-CIS 200 H <sub>2</sub> O <sup>ac</sup>	0.28	–0.07
INDO-CIS 200 H <sub>2</sub> O <sup>a</sup>	0.50	–0.19
INDO-CIS 9 H <sub>2</sub> O + 291 H <sub>2</sub> O(SPC) <sup>ac</sup>	0.55	–0.24
CASSCF/ANO-L/4s3p2d <sup>ad</sup>	0.48	–0.36
CASSCF/6-31G(d,p) <sup>ad</sup>	0.42	–0.35

*Previous results*

TD-PBE0-PCM <sup>6</sup>	0.29	–0.09
TD-PBE0-PCM + 4 H <sub>2</sub> O <sup>6</sup>	0.48	–0.10
PMM/TD-B3LYP <sup>14</sup>	0.38	–0.18
PMM/TD- PBE0 <sup>14</sup>	0.54	–0.10
TD-B97-1 PCM <sup>16</sup>	—	–0.08
Experiment <sup>e 7–11,13</sup>	0.54	–0.28, –0.31

<sup>a</sup> Obtained as a converged statistical average using 60 uncorrelated configurations. All the statistical errors found in the average analysis were less than 0.02 eV for the  $n-\pi^*$  state and 0.01 eV for the  $\pi-\pi^*$  state. <sup>b</sup> Obtained at 6-31+G(d,p)-uracil and 6-31G(d)-water bases set. <sup>c</sup> Results without the solute polarization. <sup>d</sup> Obtained from the dipole moment variations, as given in eqn (1). See text. <sup>e</sup> For the  $n-\pi^*$  transition the experimental value is inconclusive. See text. Previous calculations<sup>6,14</sup> have assumed the value of 0.50 eV.

shift (−0.20 eV) is obtained with the configurations of 9 explicit water molecules in the electrostatic field of the 291 SPC water molecules. As Table 2 shows, however, the shift of the  $n\text{--}\pi^*$  transition (0.75 eV) becomes very large. These results for the  $\pi\text{--}\pi^*$  shift show the same trend of those obtained by Improta and Barone.<sup>6</sup> Using only PCM the result is unsatisfactory (too small) for the  $\pi\text{--}\pi^*$  shift but improves when the solute wave function is allowed to delocalize over 4 nearest water molecules. Using the PMM Zazza and co-workers<sup>14</sup> were able to obtain a good description of the shifts. Millefiori and Alparone<sup>16</sup> in a study of the polarizability of uracil have also considered the red shift of the  $\pi\text{--}\pi^*$  transition. Their result using TD-DFT in the PCM approximation is −0.08 eV, a value that is very small, but in line with the results discussed above, that have not delocalized the wave function over the solvent region.

A better description can now be made by explicitly including all water molecules up to a distance of 11 Å. This leads to 200 water molecules. It thus includes a total of 1642 valence electrons of the solute and the solvent. Such a large calculation requires the use of semi-empirical methods. One advantage of these calculations is that the wave function is fully allowed to delocalize over the solvent leading to a red shift contribution to the excitation energy.<sup>41,42</sup> These calculations were done with the INDO/CIS method. As shown in Table 2, the shifts improve to 0.50 eV for the  $n\text{--}\pi^*$  state and to −0.19 eV for the  $\pi\text{--}\pi^*$  state. These results suggest that for the  $\pi\text{--}\pi^*$  shifts it is important to delocalize the solute wave function over the solvent region. Table 2 also shows the INDO/CIS results obtained using the MC configurations generated without considering the solute polarization (*i.e.* the atomic charges used in the MC simulation were obtained from gas phase calculation). This leads to a polarization contribution to the solvatochromic shift of −0.12 eV for the  $\pi\text{--}\pi^*$  state and 0.22 eV for the  $n\text{--}\pi^*$  state. Comparing to the total calculated shift we conclude that the solute polarization is responsible for 60% of the total solvatochromic shift for the  $\pi\text{--}\pi^*$  state and 45% of the total solvatochromic shift for the  $n\text{--}\pi^*$  transition. Including both wave function delocalization and the solute polarization induced by the solvent the calculated shift is in good agreement with the experimental results. The TD-B3LYP result using explicitly 9 water molecules in the PCM also gives satisfactory results for the shifts. Using explicit solvent molecules has been found to be important not only in solvatochromic shifts<sup>6,19,43</sup> and NMR shieldings<sup>44,45</sup> but also in stabilizing different molecular conformations in water.<sup>46</sup> Although the present TD-B3LYP calculations have given a reasonably good description of the solvent shifts in the absorption spectrum a recent suggestion has been made that includes a Coulomb-attenuated exchange–correlation functional (CAM-B3LYP) which shows promising results for electronic excitation energies, particularly in the case of Rydberg and charge-transfer transitions.<sup>47–49</sup>

The solvatochromic shifts can also be approximately obtained considering the changes in dipole moments upon excitation.<sup>50</sup> One possibility for obtaining this theoretical shift is by using a Lippert-type relation<sup>51</sup> such as that derived by Karelson and Zerner<sup>43</sup> on the basis of the reaction

field theory. Accordingly, the shift is given by

$$\Delta\bar{\nu}(\text{cm}^{-1}) = 22679 \times \frac{d}{\text{MM}} \left[ \frac{\varepsilon - 1}{2\varepsilon + 1} (\mu_g \mu_g - \mu_e \mu_e) + \frac{\eta^2 - 1}{2\eta^2 + 1} (\mu_e \mu_e - \mu_g \mu_g) \right] \quad (1)$$

where  $\mu_g$  is the ground state dipole moment,  $\mu_e$  is the excited state dipole moment,  $\varepsilon$  is the dielectric constant of the medium ( $\varepsilon = 80$ ),  $\eta$  is the index of refraction of the medium ( $\eta = 1.33$ ),  $d$  is the density of the solute (taken as  $d = 1.03 \text{ g cm}^{-3}$ ) and MM is the molar mass of the solute (MM = 112 amu). Again, using the structures generated by the MC simulation the in-water dipole moments were calculated using the CASSCF<sup>35</sup> level of theory employing the C, N, O[4s3p2d]/H[2s1p] ANO-L basis set contractions<sup>52</sup> and imposing the  $C_s$  point group symmetry, with the molecule placed in the  $yz$  plane. For the  $\pi\text{--}\pi^*$  state, the active space included all  $\pi$  valence electrons, comprising a total of 10 orbitals and 10 electrons, labeled as (0, 10), corresponding to zero orbitals of  $a'$  symmetry and ten of  $a''$  symmetry. The active space was enlarged with two lone-pair orbitals of  $a''$  symmetry for the  $n\text{--}\pi^*$  states, leading to (2, 10). For comparison, CASSCF/6-31G(d,p) are also performed. The results are also shown in Table 2 and these are averages over 60 configurations but using the statistically converged *average configuration* described before.<sup>53</sup> The solvatochromic shift of −0.36 eV for the  $\pi\text{--}\pi^*$  state is in good agreement with the experimental result (see Table 2). The blue shift of 0.48 eV for the  $n\text{--}\pi^*$  state corroborates an experimental blue shift of *ca.* 0.50 eV.

Before concluding, we should note that whereas the INDO/CIS calculations including explicitly a very large number of solvent water molecules give a good description of the *solvatochromic shifts* it cannot adequately handle the relative position of the two excited states. Because of the failure to reproduce accurate gas-phase transition energies, as opposed to the shifts, the INDO/CIS calculations in water still place the  $n\text{--}\pi^*$  state below the  $\pi\text{--}\pi^*$  state. The reversal in solution, however, is obtained by the TD-DFT methods and the CASSCF considerations, where the calculated  $\pi\text{--}\pi^*$  state is located *ca.* 0.1 eV below the  $n\text{--}\pi^*$  state, as estimated before for uracil in water.<sup>6</sup>

## Conclusions

The two lowest-lying excited states of uracil in water are studied theoretically using different theoretical models. The polarization of the solvent onto the solute ground state is first analyzed using Monte Carlo and MP2/aug-cc-pVDZ calculations. The statistically converged dipole moment of uracil in-water is  $7.01 \pm 0.05 \text{ D}$ . A large polarization (6.12 D) is also obtained using the polarizable continuum model. The solvatochromic shifts of the  $\pi\text{--}\pi^*$  and  $n\text{--}\pi^*$  transitions are then analyzed. Whereas the experimental red shift of the  $\pi\text{--}\pi^*$  transition is well characterized the blue shift of the  $n\text{--}\pi^*$  transition is not available because the transition has never been conclusively identified in water. The spectral shifts are analyzed using different procedures for the quantum mechanical calculations of the solvent effects. These procedures include super-molecular calculations on configurations

generated by Monte Carlo simulations, with a varying number of explicitly included solvent molecules. The role of the delocalization of the wave function into the solvent region is analyzed. The importance of the solute polarization is also analyzed. Comparison is made with previous calculations and also with results obtained with the polarizable continuum methods. Different results are obtained depending on the different methods but for the red shift of the  $\pi$ - $\pi^*$  transition they all give slightly lower values than experiment although still in reasonably good agreement. For the  $n$ - $\pi^*$  transition, the theoretical results point to a blue shift of *ca.* 0.5 eV, suggesting its location in water at 255 nm, lying beneath the intense and broad  $\pi$ - $\pi^*$  transition seen experimentally at 260 nm. This prediction is further supported by considering the in-water dipole moment change upon excitation, as obtained by additional CASSCF calculations. These results confirm the reversal of the relative location of these two excited states in water, compared to the gas phase.

## Acknowledgements

This work has been partially supported by CNPq, CAPES and FAPESP (Brazil).

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