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REGULAR ARTICLE

Theoretically describing the ^{17}O magnetic shielding constant of biomolecular systems: uracil and 5-fluorouracil in water environment

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Abstract The nuclear magnetic resonance chemical shielding of ^{17}O is of great importance for biomolecular characterization in water environment. In these systems, oxygen atoms occupy important positions and are involved in hydrogen bonds with the water environment. In this work, different solvation models are used for the theoretical determination of the ^{17}O chemical shielding of the nucleobase uracil and the substituted 5-fluorouracil in aqueous environment. Continuum, discrete and explicit solvent models are used, and an analysis is made of the role played by the solute polarization due the solvent. The best results are obtained using the sequential quantum mechanics/molecular mechanics methodology using an iterative procedure for the solute polarization, but a good compromise is obtained by using the electronic polarization provided by the polarizable continuum model. Quantum mechanical calculations of the chemical shieldings are made using density-functional theory in two different exchange–correlation approximations. Using an iterative procedure for the solute polarization and the mPW1PW91/aug-pcS-2 model in the electrostatic approximation, we obtained magnetic shielding constants for the two O atoms of uracil within 2 ppm of the experimental results. For 5-fluorouracil, the theoretical results, with the same model, are again in good agreement with the experimental values. An analysis of the influence of the solute–solvent hydrogen bonds in the chemical shielding of uracil case is also made, and it is concluded that the most important contribution to the calculated shielding derives from the electrostatic contribution to the solute–solvent interaction.

Keywords Magnetic shielding · QM/MM methods · Solvent effects · Hydrogen bonds · DFT method

1 Introduction

Nuclear magnetic resonance (NMR) is one of the most important spectroscopic techniques in molecular characterization [1]. In recent years, it has been widely and successfully used to characterize biomolecular systems. In this vein, oxygen is one of the most important atoms in both, chemistry and biology. Oxygen is essential in most biomolecules occupying important positions and often involved in relevant intra- and intermolecular hydrogen-bonded interactions. These features make the oxygen spectrum of great importance in NMR experiments [2, 3]. The ^{17}O is the only naturally occurring oxygen isotope with nonzero nuclear spin. Its low natural abundance (0.04 %) is reported as the most experimental difficulty and justifies the restricted attention dedicated to this isotope. In fact, there are only few experimental NMR works dealing with ^{17}O magnetic constants [2–5]. There is then a clear importance in better understanding the magnetic properties of oxygen atoms in biomolecular systems. Although ^{17}O is found on several biomolecules, there are only a limited number of experimental works that use ^{17}O NMR to investigate biomolecular systems such as the nucleobases

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[4, 5]. This is the major interest of this present theoretical study where the NMR properties of ^{17}O in uracil and 5-fluorouracil are analyzed. We focus in the magnetic shielding of ^{17}O in both uracil and 5-fluorouracil, but have in mind also larger biological systems. Hence, the use of simplified models is analyzed in comparison with more elaborated procedures. As we will demonstrate for these two systems, the inclusion of the electrostatic interaction between the solute and the solvent is the major effect dominating the oxygen magnetic shielding, and in fact, very good results are obtained at this level.

The uracil molecule (Fig. 1) is a nucleobase naturally found in RNA making base pair with adenine. A simple change in uracil generates the 5-fluorouracil molecule (also shown in Fig. 1) that is used as an anticancer drug by blocking the RNA replication of disease cells [6]. For proper biological considerations, the interest is to study not the isolated biomolecule, but to consider the water environment. There is an early experimental work on the ^{17}O magnetic constants in uracil, and its derivatives performed by Chandrasekaran et al. [7]. A theoretical and experimental work [8] has clarified some aspects, using a microsolvation approach. In this present work, we consider in detail the role of the solute–solvent interaction and the water solvent environment using a combined and sequential classical simulation and quantum mechanics calculations, termed as sequential quantum mechanics/molecular mechanics methodology (S-QM/MM) [9–11].

Solvation effects [9–11] are one of the primary focuses of developments in present computational quantum chemistry. Therefore, we have seen several theoretical works dedicated to NMR constants and its applications [12–26]. There are essentially two major possibilities for theoretical calculations of solvent effects. The first is the use of a continuum model such as the polarizable continuum model (PCM) [27, 28] that still dominates the theoretical applications. The second is the use of explicit solvent molecules with consideration of the thermodynamic condition. Both are used here. In the second, liquid configurations are generated by Monte Carlo (MC) simulation and used in subsequent calculations of the NMR properties. As the quantum mechanical (QM) calculations are made after the classical MC simulation, this uncoupling imposes the need for a proper consideration of the electronic polarization of the solute by the solvent. The solute polarization is a response of the electrostatic moments of the reference solute molecule due to its interaction with the solvent. This solute polarization has proven to be important in several previous studies [15, 29–31]. There are different possibilities available [29–35] for dealing with this. We have successfully used an iterative procedure [34, 35] bringing the solute into electrostatic equilibrium with the solvent. This is rather feasible for relatively small molecules such as uracil and 5-fluorouracil. Thus, it will also be used here. However, for larger solute molecules of biological interest, this procedure may become computationally inconvenient. Hence, in previous works [12, 13], we have also used a combination of PCM and S-QM/MM. In this, the atomic charges of the solute are obtained in the solvent environment using PCM. These charges are then used in the force field of the classical simulation. This is also used here. These iterative and PCM-QM/MM schemes have been successfully applied in the study of several molecular properties in solution [15], including magnetic constants [12–16].

In this work, we focus on the biologically important ^{17}O and therefore present an investigation of the oxygen nuclear magnetic chemical shielding of uracil and 5-fluorouracil in explicit aqueous environment with consideration of the solute polarization and analyzing different solvent models. The influence of the hydrogen bonds formed between the solute and the water solvent is also discussed.

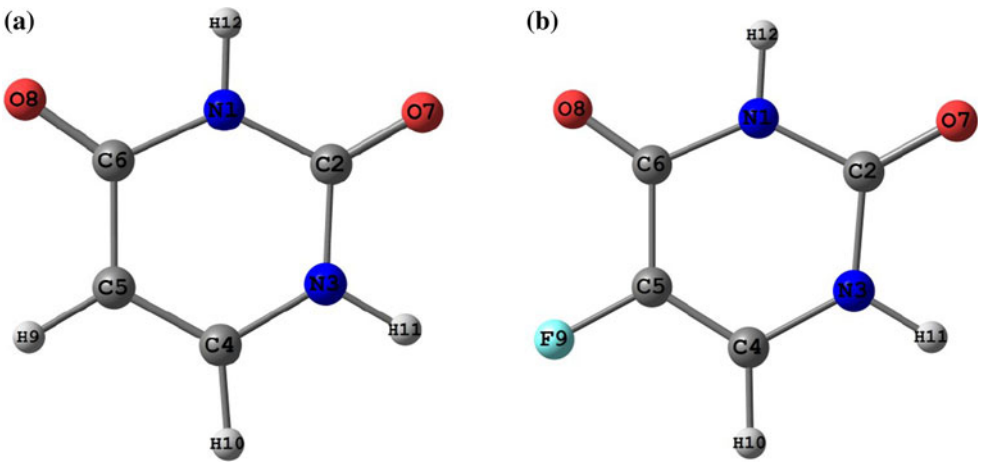

Fig. 1 Structures of **a** uracil and **b** 5-fluorouracil. The *labels* are used in the text and tables

2 Methods

We use a sequential QM/MM methodology where the liquid configurations are generated and structures are sampled for subsequent QM calculations. The liquid structure was then obtained using the Metropolis MC simulation in the NPT ensemble, where one solute molecule was solvated by 700 water molecules. The uracil and 5-fluorouracil geometries used were first obtained by optimizing the geometry at the MP2/aug-cc-pVTZ level.

The systems were treated at 95 °C and 1 atm corresponding to the experimental condition [7]. The intermolecular interactions were mediated by the standard Lennard-Jones (LJ) plus Coulomb potential. The LJ parameters of the solute correspond to the OPLS force field [36]. The water model used was the TIP3P [37]. The atomic charges for the solute Coulomb potential were obtained including the solute polarization by the solvent. Solute polarization is the change in the electrostatic moments due to its interaction with the solvent molecules. This is first included by using a simple PCM calculation and obtaining the solute atomic charges in the solvent environment. Another possibility used is an iterative procedure that brings the solute and the solvent into electrostatic equilibrium and has been described before [34]. The solute atomic charges are fitted with the CHELPG scheme [38] in MP2/aug-cc-pVTZ calculations and iterated until the dipole moment of the solute converges within 0. 01 D. The MP2/aug-cc-pVTZ level of calculation has been found to give good results for the dipole moment and atomic charges and has then been employed here [39]. The MC simulations were performed using the DICE program [40]. After equilibration, the liquid structures were generated using 3.51×10^8 MC steps. After concluding the MC simulation, configurations composed by the solute and the solvent are sampled for the QM calculations. Of course, it is not realistic the use of all structures generated by the MC simulation, and in fact, it is not necessary. The sampling can be optimized by using the autocorrelation function of the energy to systematically use statistically uncorrelated configurations [41]. A total of 100 configurations were then selected, with a correlation that is less than 13 %. These are the structures used in the quantum mechanics (QM) calculations, and the final result is taken as statistically converged averages. Part of the system is treated as explicit molecules, with a wave function that is antisymmetric and the remainder that are treated as point charges, only. The selection of the solvent molecules to be used in the QM part is based on the analysis of the solvation shells. In particular, we will pay special attention to the solvent molecules that are hydrogen bonded to the solute. In this case, both the solute and the HB solvent molecules are treated quantum mechanically. If all solvent molecules are treated as point charges, only the electrostatic solute–solvent interaction is included. In this specific case, it is possible to obtain the same statistically converged average value with only one QM calculation performed using an average configuration. This has been termed before as the average solvent electrostatic configuration (ASEC) [42]. The ASEC is a configuration counterpart of the average potential used by Aguilar and co-workers and termed ASEP [43]. Including the HB solvent molecules requires a proper identification of the hydrogen bonds. We use both geometrical and energetic criteria [44, 45] to select the water molecules making hydrogen bond (HB) with the solute, as successfully used before [46]. The geometrical criterion is obtained from the radial distribution function and the energetic one from the pairwise energy interaction [46]. Hence, we use here $r(O_{\text{solute}}–O_{\text{w}}) < 4.0$ Å, $E < -4.0$ kcal/mol and $\theta_{\text{O–(OH)w}} < 40.0°$. The calculations that use only the solute and the HB solvent molecules are termed as HB model. In addition to this, we have considered the bulk effect and used the remaining solvent molecules as an electrostatic embedding thus using 350 nearest water molecules treated as point charges. This model is then called HB + PC with the solvent and hydrogen-bonded water molecules treated quantum mechanically and the entire system embedded in the electrostatic field of the remaining water molecules.

For the calculation of the magnetic shielding constants, we have used density-functional theory (DFT). Based in successful previous results for shielding constants [13, 47–49] and indirect spin–spin coupling [14, 50], all NMR parameters were calculated using B3LYP [51, 52] and mPW1PW91 [53, 54] functionals with the appropriate aug-pcS-n [55] basis set, specially designed for chemical shielding calculations. For the gas-phase calculations and both the PCM and ASEC solvation models, the aug-pcS-2 basis set was used. In the case of HB and HB + PC models, this is computationally more involved and we compromised still using the aug-pcS-2 basis set on the oxygen atom but the pcS-2 on the other atoms. To avoid the gauge problem, we have used the gauge-included atomic orbital method (GIAO) [56–61]. Finally, for better comparison, the chemical shift (δ) was converted to the theoretical magnetic shielding (σ) by using the absolute shielding scale of Wasylishen and Bryce [62] for oxygen:

$$\sigma_{\text{liquid}} = 287.5 \pm 0.6 \text{ ppm} - \delta_{\text{liquid}} \quad (1)$$

All quantum mechanics calculations were carried out in the Gaussian 03 program [63].

Table 1 The electronic charges (e) of oxygen obtained with the CHELPG scheme and the calculated dipole moments μ(D) of uracil (5-fluorouracil) in gas phase and in aqueous environment

Atom	Gas	PCM[a]	PCM/PCM[b]	Iterative
O_7	−0.575 (−0.567)	−0.685 (−0.674)	−0.698 (−0.689)	−0.743 (−0.726)
O_8	−0.566 (0.176)	−0.687 (0.214)	−0.702 (0.215)	−0.747 (0.195)
μ	4.34 (3.93)	6.03 (5.60)	6.36 (5.91)	6.45 (5.92)

Results obtained at the MP2/aug-cc-pVTZ level

[a] For this calculation, we used $\varepsilon = 55.6$, which is the dielectric constant of water at 100 °C

[b] PCM/PCM means that the geometry was optimized considering the solute involved by PCM, and subsequently, it was used to fit the charges, again considering the molecule involved by PCM

3 Results and discussion

3.1 Solute polarization

First, we discuss the electronic polarization of the solute due to the solvent. Table 1 shows the calculated charges on the oxygen atoms and the dipole moments of uracil and 5-fluorouracil. For the isolated uracil, the dipole moment computed here is 4.34 D. This value agrees with the previous result of 4.39 D, which was calculated at the MP2/aug-cc-pVDZ level [64]. These results are in good agreement with the results of 4.51, 4.29 and 4.33 D [65], respectively, obtained using DFT/PBE1PBE, MP2 and CCSD(T) calculations with the Dunning aug-cc-pVDZ basis functions. An early experimental result indicates a value of 3.87 D for uracil in gas phase [66], a value that seems too low considering the theoretical calculations, as noted before [64]. We obtained a dipole moment of isolated 5-fluorouracil as 3.93 D (Table 1), but apparently there are no experimental results for comparison.

For hydrated uracil, the iterative procedure yields a dipole moment of 6.45 D. This value is in fair agreement with the result obtained by describing the solvent using PCM (6.03 D). In water solution, the iterative method and PCM predict that polarization effects increase the dipole moment by about 50 and 40 % from its value in theoretical gas phase (Fig. 2). A recent work [64] also used the S-QM/MM method to calculate the dipole moment and found a value of 7.01 D for uracil in water at the different thermodynamic condition of 25 °C and 1 atm.

Similarly, in the case of 5-fluorouracil, we obtained a dipole moment of 5.60 D using PCM and 5.92 D using the iterative procedure corresponding to about 43 and 51 % larger than the gas-phase value, respectively.

To consider how the geometry change induced by the solvent affects the charges, the geometry of both uracil and 5-fluorouracil was re-optimized including solvent effects using PCM (named as PCM/PCM, Table 1). In this case, the calculated dipole moments were 6.36 D for uracil and 5.91 D for 5-fluorouracil, very close to the values obtained using the gas-phase geometry (Table 1). Thus, the contribution of the geometry relaxation to the electronic polarization of the solute is only 0.3 D for both uracil and 5-fluorouracil.

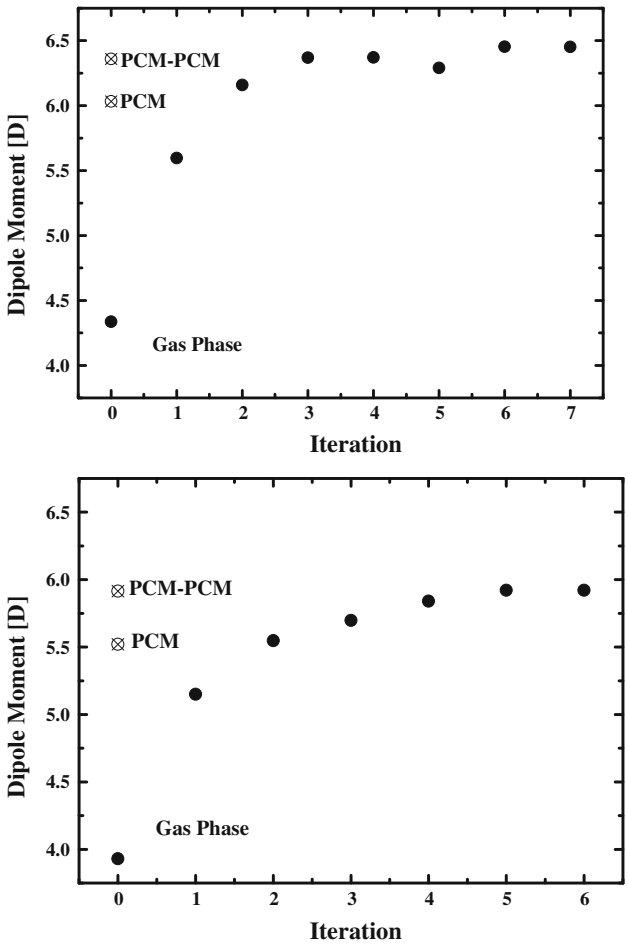

Fig. 2 The dipole moment for hydrated uracil (*top*) and 5-fluorouracil (*bottom*) versus the number of iterations. *PCM* means the value was obtained in the optimized gas-phase geometry and the solvent represented by the PCM model. PCM–PCM means the geometry and charges were obtained considering the solute in the solvent environment described by the PCM model

Table 2 The mPW1PW91/aug-pcS-2 magnetic shielding σ (ppm) constants of uracil and 5-fluorouracil in water solution

Property		Gas	PCM[a]	ASEC(PCM)[b]	ASEC(Iter)[c]	HB	HB+PC	Exp. ref. [7]
Uracil								
O_7	σ	−7.8 (−11.6)	35.5 (33.0)	50.6 (47.3)	57.2 (54.1)	30.8 ± 1.0 (25.8 ± 1.0)	55.3 ± 1.1 (50.3 ± 1.1)	55.5
	$\Delta\sigma_{GL}$	–	43.3 (44.6)	58.4 (58.9)	65.0 (65.7)	38.6 ± 1.0 (37.6 ± 1.0)	63.1 ± 1.1 (61.9 ± 1.1)	
O_8	σ	−113.5 (−117.1)	−41.1 (−43.1)	−17.2 (−20.4)	−13.5 (−16.4)	−55.5 ± 1.5 (−61.8 ± 1.7)	−10.4 ± 1.6 (−14.9 ± 1.6)	−13.5
	$\Delta\sigma$	–	72.4 (74.0)	96.3 (96.7)	100.0 (100.7)	58. 0 ± 1.5 (55.3 ± 1.7)	103.1 ± 1.6 (102.2 ± 1.6)	
5-Fluorouracil								
O_7	σ	3.6 (−0.2)	43.7 (41.0)	49.4 (45.9)	56.5 (53.3)	–	–	57.5
	$\Delta\sigma_{GL}$	–	40.1 (41.3)	45.8 (46.2)	52.9 (53.5)	–	–	
O_8	σ	−93.5 (−96.4)	−25.5 (−27.0)	−13.6 (−16.4)	−12.6 (−15.1)	–	–	−6.5
	$\Delta\sigma_{GL}$	–	68.0 (69.4)	79.9 (80.0)	81.0 (81.3)	–	–	

In parenthesis, results obtained using B3LYP. $\Delta\sigma_{GL}$ is the difference between the values obtained in gas and in solution

[a] For this calculation, we used $\varepsilon = 55.6$, which is the dielectric constant of water at 100 °C

[b] In this model, the electronic polarization of the solute is included by using PCM

[c] In this model, the solute electronic polarization effect was obtained by using an iterative procedure (see text)

3.2 ^{17}O magnetic shielding constants in uracil

Now we will discuss the ^{17}O shielding constants in uracil. Table 2 contains our theoretical results, as well as the experimental results available. Uracil and 5-fluorouracil have two non-symmetric oxygen atoms, which experience different environmental effects (see Fig. 1). This feature originates two different peaks in the ^{17}O NMR spectrum. Experimental measurements for the chemical shielding on O_7 and O_8 in water at 95 °C [7] show, respectively, resonances at 55.5 and −13.5 ppm. We investigated these magnetic shielding using different solvent models.

Combining the PCM representation for the solvent and mPW1PW91/aug-pcS-2, we calculated the shielding constants of 35.5 and −41.1 ppm on O_7 and O_8. These PCM values differ from the experiment by ∼20 ppm in the case of O_7 and ∼30 ppm in the case of O_8 (Table 1).

Considerable improvement is obtained including electronic polarization of the solute and describing the solvent by the ASEC model. Using the iterative polarization, we obtained a result of 57.2 ppm for O_7 (ASEC(Iter), Table 2), in very good agreement with experiment, differing by less than 2 ppm. The same level of calculation yields a shielding constant of −13.5 ppm for O_8, again in very good agreement with the experimental result. To verify the dependence of the results with the functional, B3LYP was also used and found again to be in good agreement with experiment differing by only 2–3 ppm from those obtained with mPW1PW91. These results show that the electrostatic interaction between the solute and the solvent water molecules is dominant and good agreement with experimental values for the ^{17}O chemical shift is obtained using the ASEC model and treating accurately the solute polarization.

Figure 3 shows the $\sigma(^{17}O_7)$ as a function of the iterative step. It is clear that the solute electronic polarization is very important and increases the shielding constant from gas to liquid leading to a value in very good agreement with experiment. The polarization increases the net charge on the oxygen site. Witanowski et al. [67] discussed a possible relation between the magnetic shielding and the charge on atomic sites. It is naturally expected that the increase in the electronic charge on a given atom increases its magnetic shielding, as discussed by Pople and Karplus [68] for the ^{13}C case. The Fig. 4 then shows the shielding constant and the corresponding electronic charges calculated on O_7 in each iterative step and confirms this expectation.

The iterative method used to obtain the electronic polarization demands several classical simulations and quantum mechanical calculations. Thus, it is worth analyzing a simpler method previously described [12, 15, 35]. We consider now a simplified approach where the solute

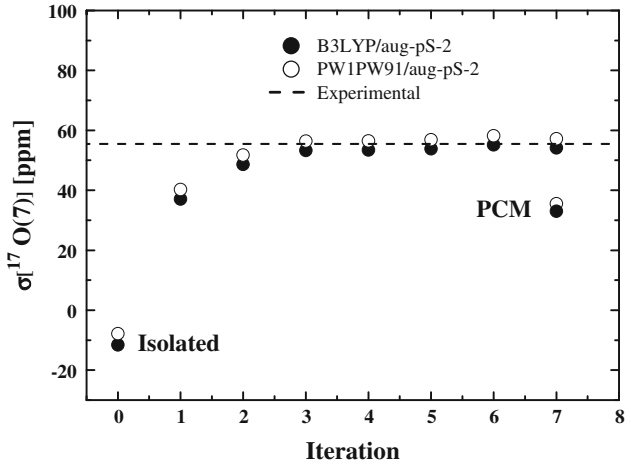

Fig. 3 The isotropic magnetic chemical shielding for $^{17}O_7$. The *bold* and *blank circles* correspond, respectively, to B3LYP and mPW1PW91 data for an iterative procedure. *The dotted line* corresponds to the experimental value (see text)

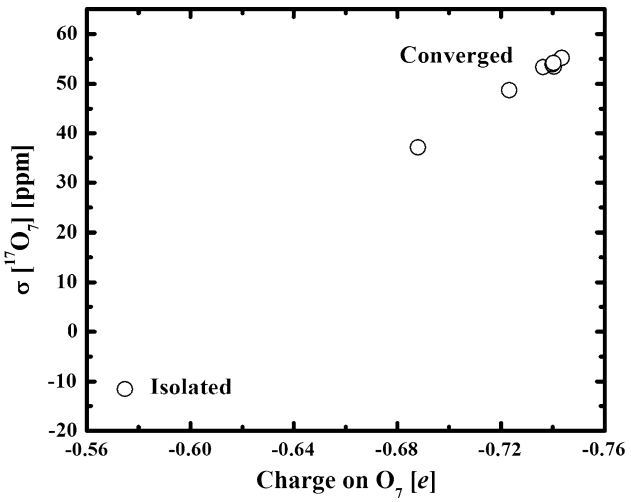

Fig. 4 The nuclear magnetic shielding on O_7 as function of the electron density on the atom. The magnetic shielding and atomic charges are simultaneously computed at each iteration step

geometry and, subsequently, the charges are obtained using the PCM approach. Next, we use these parameters in a single simulation generating the ASEC to be used in the calculations of the NMR constants. These results are also shown in the Table 2 and termed as ASEC(PCM). One can see that in general the results represent a good compromise differing by less than 7 ppm from the fully iterated result. Table 1 and Fig. 2 show that the solute polarization obtained by this procedure is close to that obtained by the iterative procedure. This confirms that this discrete polarized model is an interesting alternative for large biomolecular systems, corroborating our previous results [15, 35].

Next, we consider the effect of explicitly including some solvent water molecules in the calculation. We focus now in the solute–solvent hydrogen-bonded (HB) water molecules. We first identify the water molecules that are hydrogen bonded to the solute. This is made using the geometrical and energetic criteria, described before [15]. These criteria are $r(O_{solute}–O_{water}) < 4.0$ Å, $\theta_{O–(OH)w} < 40.0°$ and $E < -4.0$ kcal/mol and are obtained from the distribution functions and the pairwise energy interaction. For instance, the radial distribution function between oxygen of uracil and oxygen of water completes the hydrogen bond shell at 4.0 Å. Using these criteria, an average of 1.44 and 1.73 hydrogen bonds are formed on O_7 and O_8, respectively. This is in line with early works [69, 70] that pointed two water molecules hydrogen bonded with the O_8 atom. Table 2 shows in addition, the NMR results after including explicitly the water molecules involved in the hydrogen-bonding (HB) uracil–water on O_7 and O_8. The results obtained with the mPW1PW91 functional are a magnetic shielding of 30.8 ± 1.0 ppm on O_7 and a shielding of -55.5 ± 1.7 ppm on O_8. This indicates clearly that the sole inclusion of the hydrogen-bonded water is not sufficient to describe the magnetic shielding. The reason is that the electrostatic interaction with the bulk water molecules is very important as seen above. The results improve considerably after including the electrostatic embedding (HB + PC) of 350 waters molecules treated as simple point charges. This corresponds to including all solvent water molecules up to 13.5 Å from the center-of-mass of the solute. Explicitly considering the hydrogen-bonded water molecules precludes the use of the average configuration (ASEC), and thus, 100 QM calculations are needed to obtain statistically converged results. This increases considerably the computational effort, thus we compromised by still using the aug-pcS-2 basis set on oxygen but the pcS-2 on the other atoms. The explicit use of the HB molecules surrounded by the electrostatic embedding for uracil gives results of 55.3 ± 1.1 and -10.4 ± 1.6 ppm on O_7 and O_8, respectively. These results are also in very good agreement with experiment.

Finally, for obtaining the solvent effect on the magnetic shielding, we consider gas-phase results. Apparently, experimental values are not available. For uracil O_7, we obtain a gas-phase shielding constants of -7.8 ppm with mPW1PW91/aug-pcS-2 model. Considering our best results, ASEC(Iter), these calculations predict a gas–liquid shift of $\Delta\sigma_{GL} \sim 60.0$ ppm on O_7. In the case of O_8, the solvent effect of 100.0 ppm shows a larger contribution of the aqueous environment.

3.3 ^{17}O magnetic shielding constants in 5-fluorouracil

Now we will briefly discuss the 5-fluorouracil results. Table 2 shows the main theoretical and experimental reports. The experiment reports chemical shielding

constants of 57.5 and −6.5 ppm on O_7 and O_8, respectively. The HB and HB + PC solvent models are not used here, and only the PCM and ASEC models with the mPW1PW91 and B3LYP functionals are considered. The PCM results of 43.7 and −25.5 ppm for O_7 and O_8, respectively, differ appreciably from experiment, being ~20 ppm apart from the experimental values. The ASEC(PCM) presents results in better agreement with the experiments. Shielding constants of 49.4 and −13.6 ppm were calculated on O_7 and O_8. The best results are again obtained using the ASEC(Iter) method that gives shielding constants of 56.5 and −12.6 ppm on O_7 and O_8, respectively. Again the solvent effect is very strong with a gas–liquid shift ($\Delta\sigma_{GL}$) of 52.9 ppm on O_7. The O_8 chemical shielding is more sensitive to solvent effects giving 81.0 ppm for the gas–liquid shift.

4 Conclusions

Theoretical studies of the chemical shielding of the oxygen atom are very important because of its great biological interest and can complement the interpretation of experiments. In this study, we have performed a systematic investigation of the magnetic shielding constants $\sigma(^{17}O)$ of uracil and 5-fluorouracil in water. Because of the solute–solvent interaction, the electrostatic moments of the reference solute molecule changes. Thus, we have first paid attention to this electronic polarization effect. This is large and changes the dipole moment of uracil from a gas-phase value of 4.34 D into an in-water value of 6.45 D. For 5-fluorouracil, similar sizable effect is observed and changes the dipole moment from 3.94 into the in-water value of 5.92. These polarizations are incorporated in the force field for the Monte Carlo simulation that generated the liquid configurations. Chemical shielding calculations were made using these configurations generated by the MC simulation. Continuum, discrete and explicit solvent models were applied in combination with two DFT models to estimate the ^{17}O shielding constants of uracil and 5-fluorouracil under the influence of a liquid water environment. Our best results were obtained using the mPW1PW91 density functional using the aug-pcS-2 basis set. Using the iterative polarization in the pure electrostatic model, we obtained magnetic shielding constants of 57.2 and −13.5 ppm for uracil in very good agreement with the experimental results of 55.5 and −13.5 ppm, respectively. For 5-fluorouracil, the theoretical results with the same model are 56.5 and −12.6 ppm, again in good agreement with the experimental values of 57.5 and −6.5 ppm. A combined use of PCM and QM/MM was also considered with good results. This combination where PCM is used for the electronic polarization of the solute and incorporated into the QM/MM calculations is very promising for treating larger solute molecules, as also noted before [12, 15, 35]. Using PCM to introduce the polarization effects and then using the ASEC model to represent the solvent in the magnetic shielding calculations leads to a good computational performance with a minor compromising in the accuracy of the results. Thus, it becomes an interesting alternative also for the study of ^{17}O shielding constants on larger biological systems.

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