Tautomerism in 7-Hydroxyquinoline: A Combined Experimental and Theoretical Study in Water

4 AUTHORS, INCLUDING:

Osama Kamal Abou-Zied

Sultan Qaboos University

**50** PUBLICATIONS   **947** CITATIONS

SEE PROFILE

Tautomerism in 7-Hydroxyquinoline: A Combined Experimental and Theoretical Study in Water

Najla Al-Lawatia, John Husband, Thomas Steinbrecher,[†] and Osama K. Abou-Zied*

Department of Chemistry, Faculty of Science, Sultan Qaboos University, P. O. Box 36, Postal Code 123, Muscat, Sultanate of Oman

ABSTRACT: Tautomerism in the ground and excited states of 7-hydroxyquinoline (7HQ) was studied in different solvents using steady-state and lifetime spectroscopic measurements, density functional theory (DFT) calculations, and molecular dynamics (MD) simulations. Equilibrium between the enol and the keto/zwitterion tautomers exists in 7HQ, which is solvent-dependent. Of the solvents used in this study, only in water does the absorbance spectrum of 7HQ show absorption from both the enol and zwitterion tautomers. In addition, in aqueous media, fluorescence is observed from the zwitterion tautomer only, which is attributed to self-quenching of the enol fluorescence by energy transfer to the ground-state zwitterion tautomer and energetically favorable excited-state proton transfer. Solvation of the hydrogen bonding sites of 7HQ was studied in binary mixtures of 1,4-dioxane and water, and three water molecules were estimated to connect the polar sites and induce intermolecular proton transfer. The results are confirmed by DFT calculations showing that three water molecules are the minimum number required to form a stable solvent wire. Mapping the water density around the polar sites using MD simulations shows well-defined hydrogen bonds around the amino and hydroxyl groups of the enol tautomer and slightly less well-defined hydrogen bonds for the zwitterion tautomer. The presence of three-member water wires connecting the polar centers in 7HQ is evident in the MD simulations. The results point to the unique spectral signatures of 7HQ in water, which make this molecule a potential probe to detect the presence of water in nanocavities of macromolecules.
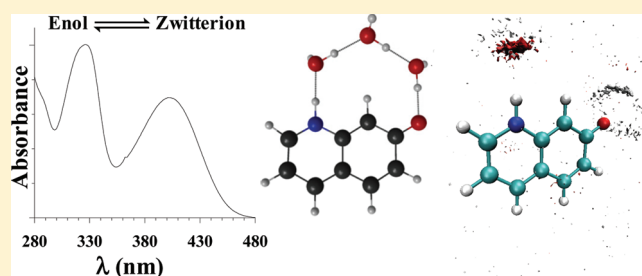
INTRODUCTION

A large number of low-molecular-weight compounds bind reversibly to proteins and are widely used as extrinsic probes to explore the interior properties of biological systems.[1,2] Molecules possessing one or more hydrogen bonds in their structure show a large sensitivity in their spectroscopy to solvent polarity. We have used some of these molecules to probe protein binding sites[3−7] and photoinduced tautomerization in DNA.[8−10] Recently, we examined one of the drug-binding sites of human serum albumin using 7-hydroxyquinoline (7HQ) as a local reporter.[11] The results point to the existence of water inside the binding site and to the role of water in molecular recognition and ligand binding. 7HQ is useful in this regard due to the high sensitivity of its spectroscopy to protic solvents and the unique spectroscopic signatures in aqueous solution. A molecule such as 7HQ that has both acidic and basic functional groups may serve as a model to study proton transfer in enzymes and proteins.[12−14] Herein, we characterize the spectroscopy of 7HQ in different solvents, particularly in aqueous medium, to understand the photophysics of the reversible interaction of 7HQ with water molecules.

7-HQ exists in equilibrium between the enol (E) and the keto (K) tautomer, which is solvent-dependent (Scheme 1). A zwitterionic species (Z) is stabilized in aqueous medium, which represents a valence bond resonance structure of the K tautomer that emphasizes its large dipole moment, as shown in Scheme 1. Considering the structure of 7HQ, direct intramolecular proton

Scheme 1. Tautomerization and Isomerization in 7HQ
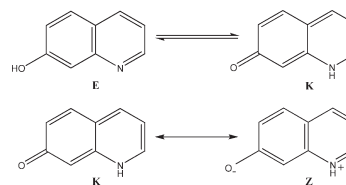
transfer is not possible, and thus, solvent-assisted proton transfer is the only mechanism linking together the tautomers in Scheme 1. Solvent-assisted excited-state proton transfer (ESPT) was proposed in protic solvents[15,16] in which the enol and imino groups become more acidic and basic, respectively, in the excited state than in the ground state.[17] As a result, the K resonance species was reported to form in nonaqueous protic solvents through a solvent chain,[18] whereas the Z resonance species was proposed to form in aqueous solvents via an anionic intermediate species.[19,20] Fluorescence was observed from the E tautomer only in nonprotic solvents, whereas in aqueous solution, fluorescence was observed from the Z tautomer only.[11,21,22] Dual fluorescence was observed in alcohols.[15,22,23] In the ground state, the E tautomer is the only
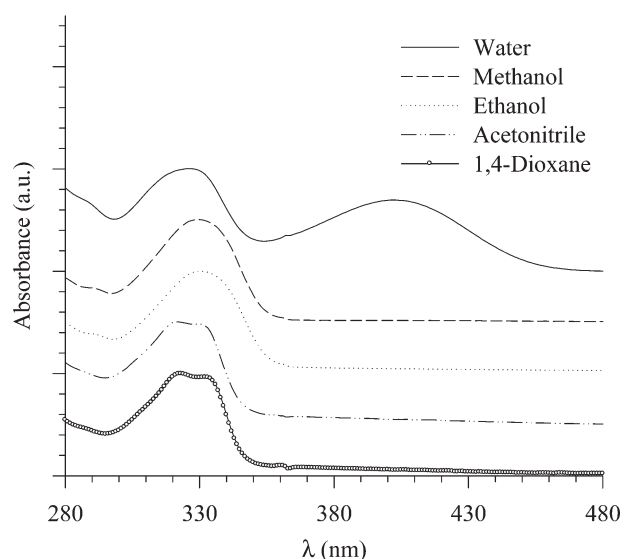
Figure 1. Absorption spectra of 7HQ in different solvents. The spectra are vertically spaced for clarity.

Figure 2. Normalized fluorescence spectra of 7HQ in different solvents. λ_{ex} = 330 nm.

species that exists in nonprotic and nonaqueous protic solvents, but both the E and the Z tautomers are stable in comparable amounts in aqueous solution.[11,21]

We examine in this paper the spectroscopy of 7HQ in different solvents with emphasis on aqueous solvent to better understand the change in its spectra when incorporated in macromolecules. We investigate the mechanism of water solvation of the polar centers in 7HQ, experimentally in mixtures of binary solvents, and theoretically by density functional theory (DFT) and molecular dynamics (MD) simulations.

■ EXPERIMENTAL AND THEORETICAL METHODS

7HQ (99%) was obtained form Acros Organics and was recrystallized from ether, and the purity was checked with thin layer chromatography and from its absorption and fluorescence spectra in different solvents. Acetonitrile (spectroscopic grade), anhydrous 1,4-dioxane, and methanol were obtained from Sigma-Aldrich Chemical Co. Anhydrous ethanol was received from Acros Organics. Deionized water (Millipore) was used. The concentration of 7HQ in all solvents was 0.1 mM. For the study in binary mixtures, a stock solution of 7HQ in 1,4-dioxane (5 mM) was prepared. Equivolume amounts (20.0 μL) of 7HQ in 1,4-dioxane were pipetted into separate test tubes and diluted with the appropriate amounts of 1,4-dioxane/water to make volume/volume (v/v) mixtures.

Absorption spectra were obtained with an HP 845x Diode Array spectrophotometer. Fluorescence spectra were recorded on a Shimadzu RF-5301 PC spectrofluorophotometer. Lifetime measurements were performed using a TimeMaster fluorescence lifetime spectrometer obtained from Photon Technology International. Excitation was at 340 nm using an LED. The system response time as measured from the scattered light was estimated to be ~1.5 ns (fwhm). The measured transients were fitted to multiexponential functions convoluted with the system response function. The goodness of the fits was judged by the value of the reduced chi-squared (χ^2). The experimental time resolution (after deconvolution) was ~100 ps. In all the experiments,
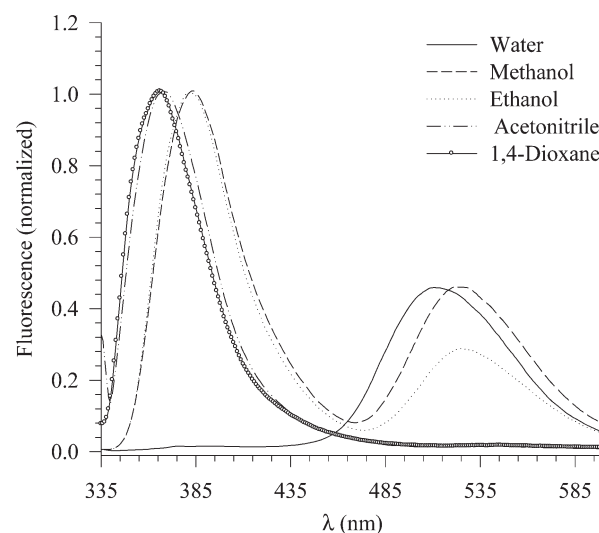
samples were contained in a 1 cm path length quartz cell, and the measurements were conducted at 23 ± 1 °C.

Geometry optimization and time-dependent calculations for the different tautomers of 7HQ uncomplexed and complexed with water molecules were carried out using the Gamess program.[24] Polarizable continuum model (PCM) calculations were carried out using Gaussian 03.[25] MD simulations were performed using the Amber 11 program.[26] The gaff forcefield with AM1BCC charges and the TIP4PEW water model were used.[27,28] Free energies of solvation were computed using the thermodynamic integration formalism in Amber, using 19 evenly spaced λ-points with independent 1 ns equilibration and 2 ns data collection phases for each substep. The simulation setup represents the removal of the solute from a box of water molecules, using soft core potentials[29] to facilitate an efficient transformation.

■ RESULTS AND DISCUSSION

7HQ in Different Solvents. The absorption spectra of 7HQ in different solvents are shown in Figure 1 in the spectral region 280–480 nm. The peak at 330 nm is due to transition to the lowest $^1(\pi, \pi^*)$ excited state of the E tautomer.[18] This peak is structured in 1,4-dioxane which can be attributed to poor solute–solvent interaction. The peak is broad in polar protic solvents, indicating a strong interaction between the solvent and both the OH group and the N heteroatom of 7HQ. In water, a second peak at 400 nm is observed, which is due to absorption of the K/Z tautomer that gains its intensity at the expense of that of the E tautomer.

The corresponding fluorescence spectra of 7HQ in different solvents after excitation at 330 nm are shown in Figure 2. In 1,4-dioxane and acetonitrile, a sole peak at ~365 nm is due to fluorescence from the E tautomer. The peak is slightly red-shifted in acetonitrile. In alcohols, the E peak is red-shifted by ~1283 cm^{-1}, and a new peak at 525 nm emerges. The latter is fluorescence from the K/Z tautomer. The large red shift in the fluorescence of the enol tautomer in alcohols is a consequence of a polarity effect on $\pi^* \leftarrow \pi$ transitions. In water, the only peak in the spectrum is at 510 nm and is due to the K/Z tautomer.

Table 1. Fluorescence Lifetimes of 7HQ in Different Solvents

solvent	ε^a	π^{*a}	E_T^{Na}	τ^b	χ^2
1,4-dioxane	2.21	0.49	0.16	0.66	1.04
acetonitrile	35.94	0.66	0.46	1.82	0.94

^{a} Obtained from ref 32 (ε values were recorded at 25 °C). ^{b} Uncertainty in measurements is ±0.02 ns. λ_{ex} was 340 nm.

Comparing the fluorescence peak near 525 nm in water and alcohols (Figure 2), the peak in water is slightly broader and blue-shifted. The difference in shape and position of the two peaks may indicate two different species. In water, the fluorescence peak is expected to reflect a higher contribution from the Z resonance form due to the presence of highly polar water molecules. Although the two species are in resonance, the Z form can be viewed as a result of a proton transfer mechanism induced in the presence of water molecules, whereas the K form can be viewed as a result of a hydrogen atom dislocation in the presence of alcohol molecules.

A fair amount of work has been done on the excited state dynamics of 7HQ in different solvents covering the range from picoseconds to nanoseconds.[15,16,21,22,30,31] Multiexponential decays were reported in protic solvents with a strong correlation between the decay of the E* tautomer and the rise of the K*/Z* tautomers. The results prove the solvent-assisted role in the ESPT mechanism. Fluorescence from both the E* and the K* tautomers in alcohols (Figure 2) is then a manifestation of the existence of excited state equilibrium between the two species.

The above results show similar spectra of 7HQ in 1,4-dioxane and acetonitrile, although the two solvents are different in polarity (see Table 1 for the solvent dielectric constants (ε) and empirical parameters of solvent polarity (π^* and E_T^N).[32]). Both solvents share the inability to transfer a proton and the possible interaction with 7HQ is with its hydroxyl group.

We measured the fluorescence decay time of 7HQ in 1,4-dioxane and acetonitrile. In both solvents, the decay curves were best fitted to a single-exponential function (values are shown in Table 1). In contrast to the steady-state results, the measured fluorescence lifetime in acetonitrile is almost three times longer than that measured in 1,4-dioxane.

A solvent such as 1,4-dioxane, which appears to be nonpolar according to its static dielectric constant (ε = 2.21), has a high solvent polarity parameter (π^* = 0.49) and an E_T^N value of 0.16.[32] 1,4-Dioxane has two CH$_2$—O—CH$_2$ groups opposite to each other, which results in a net zero dipole moment. Hence, it is considered a nondipolar solvent. However, 1,4-dioxane exhibits a large quadrupole moment,[33,34] which is reflected in its π^* parameter that mainly takes into consideration the polarizability and the dipolarity of the solvent.[35] The corresponding E_T^N value indicates that 1,4-dioxane exhibits only 16% of the solvent polarity of water, which classifies 1,4-dioxane as an apolar, non-hydrogen-bond-donor solvent.[32] On the other hand, a dipolar, aprotic solvent such as acetonitrile tends to strongly solvate cations and electropositive atoms through its lone electron pairs.[32]

The longer fluorescence lifetime in acetonitrile is then an indication of a strong interaction between this solvent and the H-atom of the hydroxyl group of 7HQ. The free rotation of the OH group of 7HQ is expected to be restricted in the presence of acetonitrile molecules. Hindering the OH rotation will cause a longer fluorescence lifetime due to less contribution from this rotation to the overall nonradiative channel. Such interaction is less in the case of 1,4-dioxane.

In addition to the E and Z tautomers that exist in neutral aqueous medium, the cation (C) and the anion (A) species were reported to exist in the ground state in a small percentage (estimated 3% and 1%, respectively).[17,21] The spectral peak positions of the C and A species in the ground state were reported to be at 350 and 360 nm, respectively.[17] Both the E and the Z tautomers exist over a narrow range of pH $\approx$ 6−8 in the ground state. This range is widened in the first excited state (pH $\approx$ −2.7 − 13.5), which explains the absence of any fluorescence from either C* or A* in neutral aqueous solution. Fluorescence peaks from C* and A* were observed in the 430−450 nm range only in aqueous solution at extreme pHs ($<$−2.7 for C* or $>$13.5 for A*).[17]

Excitation anywhere in the absorption region of aqueous 7HQ yields a fluorescence peak at 510 nm, which is due to the Z* tautomer. No fluorescence was observed from the E* tautomer which was previously explained by efficient excited state reaction to yield the Z* species.[21] It is important to mention here that the stabilization of the Z tautomer in the ground state causes its absorption peak to overlap with the fluorescence peak of the E* tautomer. Such overlap is expected to cause an efficient energy transfer from the donor fluorescence (E*) to the Z tautomer absorption (acceptor). This is expected to deplete fluorescence from the E* species through a self-quenching mechanism.

Water Solvation of 7HQ. The selective stabilization of the Z tautomer in the presence of water is due to solute−solvent interactions that not only determine the relative stability of the tautomeric forms but can also influence the interconversion mechanism. A protic solvent such as water, a strong hydrogen bond donor/acceptor, can accept a proton from the donor site of the solute molecule and transfer a different proton to the acceptor site of the solute. Water-assisted proton transfer mechanism studies have shown that the assistance of a water molecule significantly lowers the free energy barriers in proton-transfer-related reactions.[36,37] The dynamics in such proton transfer reactions can be greatly influenced by the presence of water molecules through short-range hydrogen-bonding interactions. In this case, an explicit interaction with a limited number of water molecules could influence the whole reaction path by lowering the energy barrier due to the direct participation of water molecules in the proton transfer process. The absence of the Z absorption in other protic solvents, such as methanol and ethanol, may indicate that, unlike water, short-range interaction between solvent molecules and the polar centers in 7HQ is not enough to stabilize the Z tautomer in the ground state.

The tendency of water molecules to strongly associate with each other through intermolecular hydrogen bonds allows more than one molecule of water to form a solvent network or a solvent wire along which proton transfers can take place to and from the solute. Such proton transfer mechanisms through a water bridge have been formulated theoretically.[36−40] We have recently estimated the number of water molecules solvating the hydrogen bonding centers of several systems experimentally in binary mixtures of 1,4-dioxane/water[7,41,42] and theoretically using ab initio methods.[41,42]

We quantify the number of water molecules solvating 7HQ by measuring the spectral changes in binary mixtures of 1,4-dioxane and water. The choice of 1,4-dioxane is convenient because it is miscible with water in all proportions and thus provides an opportunity to study the effect of a broad range of solvent polarity (see the discussion above regarding the polarity of 1,4-dioxane). In this regard, 1,4-dioxane is a better choice than a
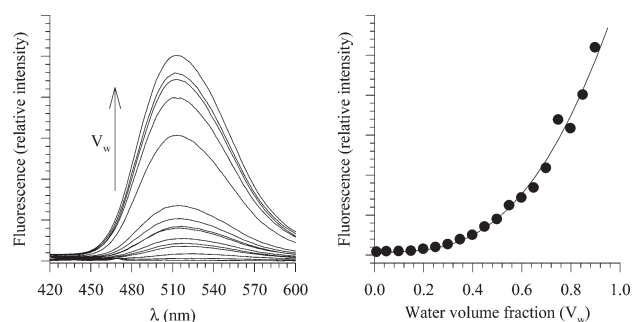
Figure 3. Selected fluorescence spectra of 7HQ (left panel) in 1, 4-dioxane/water binary mixtures. The right panel shows the intensity change of the peak at 510 nm as a function of water volume fraction (V_w), and the solid line is the best nonlinear least-squares fit to eq 3. $\lambda_{ex} = 400$ nm.

solvent such as acetonitrile, which possesses a high polarity. Mixtures of 1,4-dioxane and water were also proposed as media to study probes in nanoenvironments similar to those encountered in vesicles and at interfaces.[7,41−45]

Selected fluorescence spectra of 7HQ in the 1,4-dioxane/water binary mixtures are shown in Figure 3 for different water contents after excitation at 400 nm. No fluorescence intensity was detected in anhydrous 1,4-dioxane. As the water content increases, the fluorescence intensity grows at 510 nm. The results confirm that the excited species at 400 nm is the Z tautomer only.

We can then write the following equilibrium as a result of solvation by water:

$$7HQ + nH_2O \overset{K_{eq}}{\rightleftharpoons} 7HQ{:}(H_2O)_n \qquad (1)$$
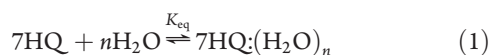
Equation 1 assumes that increasing the water content leads to local solvation of the polar parts in 7HQ by n water molecules. In this case, water molecules in the first solvation shell will participate by only a certain number (n), and the rest of the water molecules will have the same effect as bulk water molecules. In this equation, $K_{eq} = [BS_n]/[B][S]^n$, where K_{eq} is the equilibrium binding constant, $[BS_n]$ represents the concentration of 7HQ solvated by n water molecules, $[B]$ is the concentration of unsolvated 7HQ, and $[S]$ is the water concentration. An expression relating the relative concentrations to the observed fluorescence (F_{obs}) and to the fluorescence of solvated 7HQ (F_{BS_n}) and unsolvated 7HQ (F_B) can be written as[7,41,42,46,47]

$$\frac{[BS_n]}{[B]} = \frac{(F_{obs} - F_B)}{(F_{BS_n} - F_{obs})} \qquad (2)$$

Using eq 2 to rewrite the equilibrium constant, one obtains the following expression:

$$F_{obs} = \frac{F_B + F_{BS_n}K_{eq}[S]^n}{1 + K_{eq}[S]^n} \qquad (3)$$

Equation 3 represents a binding isotherm between species in equilibrium. The measured change in the fluorescence intensity of 7HQ as a function of water volume fraction is displayed in Figure 3 (assuming the density of water = 1.0 g mL^{-1}, $V_w = [S] \times$ molecular weight of water). The best fit to eq 3 is also shown. The calculations from the best fit show that three water molecules solvate the polar groups in the 7HQ molecule $(n = 3)$. The estimated value for K_{eq} from the fit is $(4.5 \pm 1) \times 10^{-5}$ M^{-3}. It
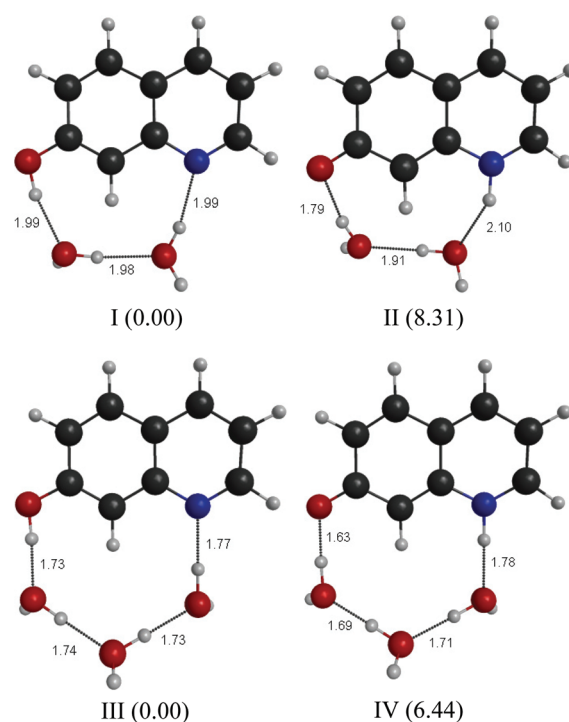

Figure 4. Structures of the most stable ground-state minimum configurations of the *cis*-E and Z tautomers with two and three water molecules. The structures were obtained from DFT calculations described in the text. The values in parentheses are relative energies in kcal/mol. The lengths of the hydrogen bonds are shown (in Å).

should be noted here that K_{eq} represents an equilibrium constant for the binding of three water molecules.

Structures of the 7HQ:(H₂O)ₙ Complexes. The structures of the E and Z tautomers with two and three water molecules were calculated in their ground states using the DFT-B3LYP method with the 6-311++G(2d,p) basis set. The calculations were also carried out for each of the two tautomers without water molecules to predict the most stable conformer for the bare tautomers. The structures were fully optimized without any symmetry constraint. For the bare tautomers (without water molecules), the optimized structures were found to be planar in all cases, with the *cis*-E tautomer 11.6 kcal/mol more stable than the Z tautomer. The *trans*-E isomer (in which the O−H bond points away from the amino group) is calculated to be 1.1 kcal/mol less stable that the *cis*-E isomer. Similar results were obtained at the HF/6-31G(d,p) level of calculations.[48] The calculations agree with the experimental results in supersonic jets in which the trans rotamer is barely populated for free 7HQ, as well as for 7HQ complexed with one water molecule.[48] Accordingly, we proceed with structural optimizations for only the *cis*-E and the Z tautomers.

By adding two water molecules to the polar sides of both tautomers and optimizing the total structures (Figure 4), the water molecules interact with the hydroxyamino region of the *cis*-E tautomer (structure I) and with the oxoamino region of the Z tautomer (structure II). For the enol tautomer with two water molecules (*cis*-E:(H₂O)₂), the optimized structure is calculated to be more stable than Z:(H₂O)₂ by 8.31 kcal/mol. The optimized geometry of the *cis*-E:(H₂O)₂ complex shows the formation of a short water network solvating both the hydroxyl group and the tertiary nitrogen heteroatom. However, the results suggest that two water molecules are not quite sufficient to span the gap

Table 2. Summary of DFT Calculations

	bare	+2 H$_2$O	+3 H$_2$O	PCM
	normalized ΔE (kcal/mol)			
cis-E tautomer	0	0	0	0
Z tautomer	11.56	8.31	6.44	1.63
	S$_1$ ← S$_0$ (nm)			
cis-E tautomer	303		329	310
Z tautomer	440		430	413

between the hydrogen-donating and -accepting moieties in 7HQ. For the molecular skeleton to remain planar, the hydrogen-bond network is somewhat distorted: the HOC angle associated with the hydroxyl group is relatively acute at 108.7° (cf. 109.7° in the bare molecule), and the O—H bond makes a dihedral angle of ∼10° with respect to the plane of the molecule. An even larger dihedral angle of ∼17° is found for the hydrogen bond to the amino group. The XOX angles of the hydrogen bonds are all significantly nonlinear, with angles ranging from 167° to 170°. Finally, the calculated lengths of the hydrogen bonds are also relatively long, as indicated in Figure 4. The hydrogen-bond network is similarly distorted in the Z:(H$_2$O)$_2$ tautomer.

Adding a third water molecule to the optimized geometries (*cis*-E:(H$_2$O)$_2$ and Z:(H$_2$O)$_2$) results in structures in which the added water molecule is located in the second solvation shell. The third water molecule is stabilized through a hydrogen bond interaction with one of the two water molecules with no direct interaction with the 7HQ moiety (data not shown). On the other hand, adding three water molecules to the polar sides of both tautomers and optimizing the structures results in planar geometries with a stretched water network that reaches the two polar regions in each tautomer. The optimized structures are shown in Figure 4 with the corresponding hydrogen bonding lengths (III for *cis*-E:(H$_2$O)$_3$ and IV for Z:(H$_2$O)$_3$). As shown in the figure, the water network (or water wire) forms strong hydrogen bonds with each polar center in each tautomer. The dihedral angles between the molecular plane and the hydrogen bonds at each polar center in 7HQ are less than 2° in all cases, and all XOX angles are close to linearity (≥176°). These results support those concluded from the binary mixtures study mentioned above. The *cis*-E:(H$_2$O)$_3$ complex was calculated to be more stable than the Z:(H$_2$O)$_3$ complex by 6.4 kcal/mol.

It is noticed that by increasing the number of water molecules in the complex, the energy difference between the two solvated tautomers gets smaller. This may indicate that after complete solvation of the two tautomers by water, their relative stability is close to each other, or the Z tautomer may even become the most stable species, which explains the observation of its peak in the absorption spectrum of aqueous 7HQ. We clarified this point by estimating the effect of the polar medium (water) on the relative stabilities of the two tautomers of 7HQ by applying the PCM. The energy difference between the two tautomers in this case is only 1.6 kcal/mol (Table 2), with the E tautomer still the more stable.

The Franck—Condon transitions in the *cis*-E and Z tautomers (bare and solvated by three water molecules) were calculated using TD-DFT (B3LYP, 6-311++G(2d,p)). The results are included in Table 2. The calculated S$_1$ ← S$_0$ transitions are in good agreement with the measured absorption spectra shown in Figure 1, and the results indicate that the absorption peak at
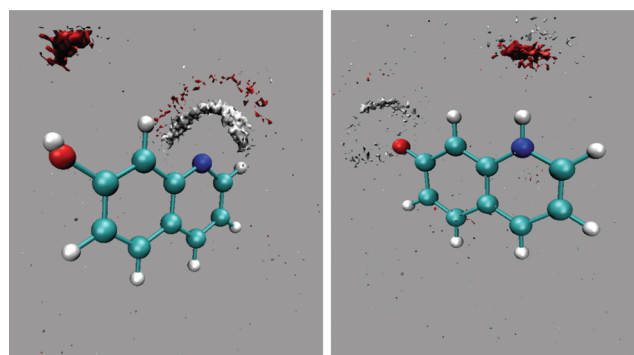

Figure 5. Mapping the water density around the polar sites of the E tautomer (left) and the Z tautomer (right) of 7HQ. The calculations were performed using MD simulations as described in the text. Red areas indicate increased oxygen density (H-bond acceptor position), white areas indicate hydrogen density (H-bond donor regions). The average structures of E and Z are superimposed onto the maps.

Table 3. Hydrogen Bonding Statistics (%)

	+1 H$_2$O	+2 H$_2$O	+3 H$_2$O
E tautomer	0	0	13.1
Z tautomer	0	0	3.7

400 nm is due only to the Z tautomer, whereas that at 330 nm is due to the *cis*-E tautomer with no contribution from the Z tautomer. The calculations also assign an observed absorbance at 260 nm in water to the Z tautomer. The calculated excitation energies, together with the relative ground state energies of the *cis*-E and Z tautomers, enable the relative energies of the S$_1$ states of the tautomers to be estimated. Using the PCM values, the Z* tautomer is calculated to be 21.38 kcal/mol more stable than the *cis*-E* tautomer. Thus, solvent-assisted excited-state proton transfer is suggested to be energetically favorable in water.

Further insight into the solvation of 7HQ by water can be obtained from MD simulations. Simulations were performed in explicit solvent for both the E and Z tautomers embedded in a 12 Å deep layer of TIP4PEW water molecules and equilibrated to room temperature and pressure using standard procedures. Parameterization of the 7HQ molecule was done using the gaff forcefield, and AM1BCC charges were assigned. After equilibration, 10 ns of unrestrained MD simulations were conducted, and the ptraj module of Amber was used to produce the water density maps shown in Figure 5. The maps show well-defined hydrogen bonds about the amino and hydroxyl groups of the E tautomer and slightly less well-defined hydrogen bonds, especially around the oxygen, for the Z tautomer. Significantly, although some rotation of the OH group is indicated by the shown averaged position of the hydrogen relative to the oxygen, the hydrogen bonding is clearly defined in only one direction, suggesting a preference for the *cis* isomer.

Directly analyzing the number of hydrogen bonds gives more information: Table 3 gives statistics that count the likelihood of finding networks of one, two, or three water molecules connecting the two polar sites in the tautomers. The results show that in these simulations, networks of less than three molecules are never formed, but chains, or wires, of three molecules are, indeed, occasionally present, supporting the results previously discussed herein. Three-member water wires are found to be significantly

4199

dx.doi.org/10.1021/jp201649z |*J. Phys. Chem. A* 2011, 115, 4195–4201

more common for the E tautomer than the Z. It should be noted that the occurrence of four-member or larger networks would be expected to quickly increase to close to 100%, as the number of possible pathways increases. Thus, a three-member water wire is suggested to be the shortest direct link sterically possible between the hydrogen donating and accepting sites and, therefore, the most likely to be involved in solvent-assisted proton (hydrogen) transfer.

Comparing the total free energy of solvation (ΔG_{solv}) of the compounds gives an indication of how the tautomerization equilibrium is shifted in water. Calculations with the explicit inclusion of the TIP4PEW water molecules give a ΔG_{solv} of -9.1 and -12.2 kcal/mol for the E and Z tautomers, respectively. Thus, both tautomers are well solvated in water, and upon solvation, the E−Z equilibrium is shifted in favor of the Z tautomer. The latter point is in accord with the DFT results. The value of ΔG_{solv} of -9.1 kcal/mol for the E tautomer corresponds to a solubility constant of 4.7×10^{6}.

■ CONCLUSIONS

The spectroscopy of 7HQ was studied in different solvents to characterize the different tautomers in the ground and excited states. An absorption peak at 400 nm was observed in aqueous solution, which is attributed to a Z tautomer. In addition to direct excitation, the Z tautomer is formed in the excited state after a proton transfer process from the E tautomer. Fluorescence from both tautomers was observed in alcohol solvents, indicating the existence of an equilibrium between the two species in the excited state. The absence of fluorescence from the E tautomer in water is attributed to both self-quenching of the fluorescence of this tautomer by energy transfer to ground-state Z tautomer, and energetically favorable excited-state proton transfer. In nonprotic solvents, fluorescence was observed from the E tautomer only.

Solvation of the hydrogen bonding sites of 7HQ was studied in binary mixtures of 1,4-dioxane and water, and three water molecules were estimated to connect the polar sites and induce intermolecular proton transfer. The results were confirmed by carrying out DFT calculations in which three water molecules are the minimum number required to form a stable solvent wire. Mapping the water density around the polar sites using MD simulations shows well-defined hydrogen bonds around the amino and hydroxyl groups of the E tautomer and slightly less well-defined hydrogen bonds for the Z tautomer. The MD simulations also indicate the preference of the *cis* isomer over the *trans* isomer of the E form in the presence of water.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: (+968) 2414-1468. Fax: (+968) 2414-1469. E-mail: abouzied@squ.edu.om.

Present Addresses

†Universität Karlsruhe (KIT), Inst. f. Phys. Chemie, Abt. Theor. Chem. Biol., Kaiserstrasse 12, 76131 Karlsruhe, Germany.

■ ACKNOWLEDGMENT

■ REFERENCES

(1) Royer, C. A. *Chem. Rev.* **2006**, *106*, 1769.

(2) Copeland, R. A. *Enzymes: A Practical Introduction to Structure, Mechanism, and Data Analysis*, 2nd ed.; Wiley: New York, 2000.

(3) Abou-Zied, O. K. *J. Phys. Chem. B* **2010**, *114*, 1069.

(4) Abou-Zied, O. K.; Al-Shihi, O. I. K. *J. Am. Chem. Soc.* **2008**, *130*, 10793.

(5) Abou-Zied, O. K. *J. Phys. Chem. B* **2007**, *111*, 9879.

(6) Abou-Zied, O. K. *Proc. SPIE−Int. Soc. Opt. Eng.* **2007**, *64490L*, 1.

(7) Abou-Zied, O. K. *J. Photochem. Photobiol. A* **2006**, *182*, 192.

(8) Wang, H.; Zhang, H.; Abou-Zied, O. K.; Yu, C.; Romesberg, F. E.; Glasbeek, M. *Chem. Phys. Lett.* **2003**, *367*, 599.

(9) Abou-Zied, O. K.; Jimenez, R.; Romesberg, F. E. *J. Am. Chem. Soc.* **2001**, *123*, 4613.

(10) Ogawa, A. K.; Abou-Zied, O. K.; Tsui, V.; Jimenez, R.; Case, D. A.; Romesberg, F. E. *J. Am. Chem. Soc.* **2000**, *122*, 9917.

(11) Abou-Zied, O. K.; Al-Lawatia, N. *ChemPhysChem* **2011**, *12*, 270.

(12) Inoue, J.; Tomioka, N.; Itai, A.; Harayama, S. *Biochemistry* **1998**, *37*, 3305.

(13) Stoner-Ma, D.; Jaye, A. A.; Matousek, P.; Towrie, M.; Meech, S. R.; Tonge, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 2864.

(14) Garczarek, F.; Gerwert, K. *Nature* **2006**, *439*, 109.

(15) Itoh, M.; Adachi, T.; Tokumura, K. *J. Am. Chem. Soc.* **1984**, *106*, 850.

(16) Park, S.-Y.; Jang, D.-J. *J. Am. Chem. Soc.* **2010**, *132*, 297.

(17) Mason, S. F.; Philp, J.; Smith, B. E. *J. Chem. Soc. (A)* **1968**, 3051.

(18) Kwon, O.-H.; Doo, H.; Lee, Y.-S.; Jang, D.-J. *ChemPhysChem* **2003**, *4*, 1079 and references therein.

(19) Kwon, O.-H.; Kim, T. G.; Lee, Y.-S.; Jang, D.-J. *J. Phys. Chem. B* **2006**, *110*, 11997.

(20) Poizat, O.; Bardez, E.; Buntinx, G.; Alain, V. *J. Phys. Chem. A* **2004**, *108*, 1873.

(21) Lee, S.-I.; Jang, D.-J. *J. Phys. Chem.* **1995**, *99*, 7537.

(22) Kang, W. K.; Cho, J. S.; Lee, M.; Kim, D. H.; Ryoo, R.; Jung, K. H.; Jang, D.-J. *Bull. Korean Chem. Soc.* **1992**, *13*, 140.

(23) Lavin, A.; Collins, S. *Chem. Phys. Lett.* **1993**, *204*, 96.

(24) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Rev. B.01*, Gaussian Inc.: Pittsburgh, PA, 2003.

(26) Case, D. A.; Darden, T. A.; Cheatham, III, T. E.; Simmerling, C. L.; Wang, J.; Duke, R. E.; Luo, R.; Walker, R. C.; Zhang, W.; Merz, K. M.; Roberts, B.; Wang, B.; Hayik, S.; Roitberg, A.; Seabra, G.; Kolossvary, I.; Wong, K. F.; Paesani, F.; Vanicek, J.; Wu, X.; Brozell, S.; Steinbrecher, T.; Gohlke, H.; Cai, Q.; Ye, X.; Wang, J.; Hsieh, M. J.; Cui, G.; Roe, D. R.; Mathews, D. H.; Seetin, M. G.; Sagui, C.; Babin, V.; Kollman, P. A. *AMBER 11*; Univeristy of California: San Francisco, 2010.

(27) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. *J. Comput. Chem.* **2004**, *25*, 1157.

4200

dx.doi.org/10.1021/jp201649z |*J. Phys. Chem. A* 2011, 115, 4195–4201

(28) Horn, H. W.; Swope, W. C.; Pitera, J. W.; Madura, J. D.; Dick, T. J.; Hura, G. L.; Head-Gordon, T. *J. Chem. Phys.* **2004**, *120*, 9665.

(29) Steinbrecher, T.; Mobley, D. L.; Case, D. A. *J. Chem. Phys.* **2007**, *127*, 214108.

(30) (a) Itoh, M.; Adachi, T.; Tokumura, K. *J. Am. Chem. Soc.* **1983**, *105*, 4828. (b) Tokumura, K.; Itoh, M. *J. Phys. Chem.* **1984**, *88*, 3921. (c) Konijnenberg, J.; Ekelmans, G. B.; Huizer, A. H.; Varma, C. A. G. O. *J. Chem. Soc., Faraday Trans. 2* **1989**, *85*, 39. (d) Nagakawa, T.; Kohtani, S.; Itoh, M. *J. Am. Chem. Soc.* **1995**, *117*, 7952. (e) Tokumura, K.; Natsume, M.; Nakagawa, T.; Hashimoto, M.; Yuzawa, T.; Hamahuchi, H.; Itoh, M. *Chem. Phys. Lett.* **1997**, *271*, 320.

(31) García-Ochoa, I.; Bisht, P. B.; Sánchez, F.; Martinez-Atáz, E.; Santos, L.; Tripathi, H. B.; Douhal, A. *J. Phys. Chem. A* **1998**, *102*, 8871.

(32) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 3rd ed.; VCH: Weinheim, Germany, 2003.

(33) Suppan, P. *Photochem. Photobiol. A* **1990**, *50*, 293.

(34) Suppan, P. *J. Lumin.* **1985**, *33*, 29.

(35) Reichardt, C. *Chem. Rev.* **1994**, *94*, 2319.

(36) Markova, N.; Enchev, V.; Timtcheva, I. *J. Phys. Chem. A* **2005**, *109*, 1981.

(37) Kyrychenko, A; Waluk, J. *J. Phys. Chem. A* **2006**, *110*, 11958.

(38) Carballeira, L.; Perez-Juste, I. *J. Mol. Struct. (Theochem)* **1996**, *368*, 17.

(39) Tian, Y.-C.; Fang, W.-H. *J. Phys. Chem. A* **2006**, *110*, 1170.

(40) Liao, R.-Z.; Ding, W.-J.; Yu, J.-G.; Fang, W.-H.; Liu, R.-Z. *J. Phys. Chem. A* **2007**, *111*, 3184.

(41) Abou-Zied, O. K. *Chem. Phys.* **2007**, *337*, 1.

(42) Abou-Zied, O. K.; Al-Shihi, O. I. K. *Phys. Chem. Chem. Phys.* **2009**, *11*, 5377.

(43) Melo, E. C. C.; Costa, S. M.; Maçanita, A. L.; Santos, H. *J. Colloid Interface Sci.* **1991**, *141*, 439.

(44) Belletête, M.; Lachapelle, M.; Durocher, G. *J. Phys. Chem.* **1990**, *94*, 5337.

(45) Belletête, M.; Lessard, G.; Durocher, G. *J. Lumin.* **1989**, *42*, 337.

(46) Connors, K. A. *Binding Constants. The Measurements of Molecular Complex Stability*; Wiley: New York, 1987.

(47) Abou-Zied, O. K.; Al-Hinai, A. T. *J. Phys. Chem. A* **2006**, *110*, 7835.

(48) Coussan, S.; Bach, A.; Leutwyler, S. *J. Phys. Chem. A* **2000**, *104*, 9864.