Water-Catalyzed Excited-State Double Proton Transfer in 3-Cyano-7-azaindole: The Resolution of the Proton-Transfer Mechanism for 7-Azaindoles in Pure Water

Pi-Tai Chou,* Wei-Shan Yu, Ching-Yen Wei,
Yi-Ming Cheng, and Chan-Yi Yang

*Department of Chemistry, The National Chung-Cheng
University, Chia Yi, Taiwan R.O.C.*

7-Azaindole (7AI) and its analogues have been intensively studied toward probing solvation (e.g. water, alcohols) and/or protein dynamics.[1–8] However, in pure water the mechanism of ESDPT in 7AI has been an issue of long-standing controversy. In contrast to its dual emission behavior in alcohol solvents, consisting of normal and tautomer emission, 7AI in water apparently exhibits only a single fluorescence band with a maximum at 385 nm. The peak represents a red shift of ∼4200 cm⁻¹ with respect to the normal emission maximum in hydrocarbon solvents. This emission band initially assigned to a strongly red-shifted normal emission[1b] has been alternatively suggested to result from an exciplex (7AI/water) formation.[2] Later, Negrerie et al.[6a] reassigned the entire 385 nm band to the tautomer emission resulting from ESDPT. Subsequently, Chou and co-workers[8] investigated 7AI in ethers titrated by water and resolved a weak emission maximum at ∼510 nm that was proposed to originate from ESDPT of the 1:1 cyclic 7AI/water hydrogen-bonded complex. They further suggested that the polyhydrated 7AI, which are prevalent in water, inhibit tautomerization during the excited-state lifetime. By analyzing the relaxation dynamics of the entire emission band in water Chapman and Maroncelli[5b] were able to extract a nonnegligible portion of a rapid rise component (∼200 ps) in the longer wavelength region and concluded that the entire 7AI normal fluorescence lifetime of ∼800 ps is dominated by the ESDPT reaction. The rapid rise time is associated with the fast, dominant nonradiative decay rate of the excited tautomer. The much slower N* → T* ESDPT rate (see Scheme 1) and rapid nonradiative decay rate of T* account for a lack of the steady-state tautomer emission in pure water. Conversely, Petrich and co-workers[6b–d] interpreted their observations of the 7AI reaction in water as indicating that only a small fraction (<20%) of the 7AI reaction in pure water is correctly solvated to tautomerize within a relatively rapid time frame of <80 ps, while the majority

Scheme 1. (a) Structures of 7AI, 3CAI and Its Corresponding Derivatives and (b) the Proposed ESDPT Mechanism and Hydrogen-Bonded Structures for 3CAI (or 7AI) in Water
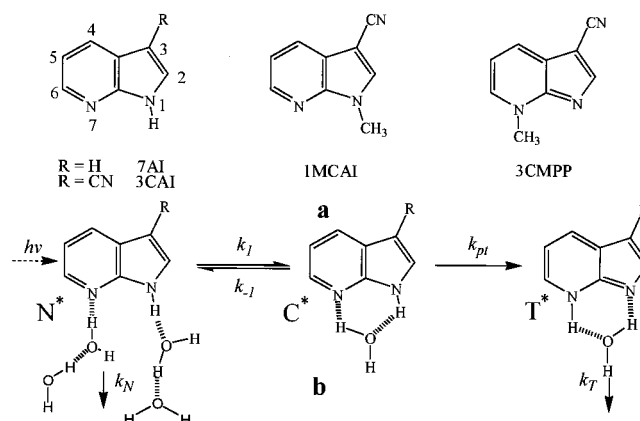
(>80%) of the solutes are in a polysolvated configuration that blocks tautomerization for times much longer than the ∼800 ps lifetime of the excited normal state. They further suggested that negligible tautomer emission for 7AI in water is due to the rapid protonation of the tautomer species, resulting in a tautomer cationic emission hidden inside the dominant 385 nm normal emission band. The water-solvated 7AI has also received considerable attention theoretically. Chaban and Gordon[9] concluded that the tautomer is more stable than the normal 7AI by ∼20 kcal/mol in the S_1 state, and the presence of one water molecule significantly reduces the proton-transfer barrier to ≤6 kcal/mol. The addition of more than one water molecule should result in a further lowering of the activation energy. Siebrand and co-workers[10] shared the same viewpoint and suggested that model studies involving more solvent molecules are needed before reaching a basic understanding of the proton-transfer process in water. In another approach, a computer simulation performed by Mente and Maroncelli[11] led to a conclusion in favor of the slow ESDPT reaction dynamics from the entire 7AI solvated species which exists predominantly as a "neighbor-bonded" structure (i.e. structure N).

We have been focusing on the design and synthesis of 7AI derivatives. Our goal is aimed at searching for 7AI analogues that are expected to exhibit high-yield, long-lived tautomer emission in water so that both steady state and dynamical approaches are feasible. It turns out that 3-cyano-7-azaindole (3CAI)[12] provides an ideal model to achieve this goal. Instead of a single fluorescence for 7AI in pure water (pH 7.0), dual emission for 3CAI was observed with maxima at 355 (the F_1 band) and 472 nm (the F_2 band, see Figure 1a). The intensity ratio for the F_2 versus the F_1 band is independent of the studied concentration in the range of $10^{-5}–10^{-4}$ M, eliminating the possibility that the dual emission results from the aggregate of 3CAI. For the F_1 band, single-exponential decay kinetics[14] were resolved with a lifetime fitted to be 905 ps ($\chi^2 = 1.055$), while the F_2 band is apparently composed of rise and decay components which are fitted to be

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(12) 3CAI was synthesized according to ref 13. The product was purified by repeated recrystallization from (1:1 v/v) aqueous ethanol. ¹H NMR (400 MHz): 6.6 (s, 1H), 7.38 (t, *J* = 6.21, 6.0 Hz, 1H), 7.75 (d, *J* = 8.02 Hz, 1H), 8.59 (d, *J* = 4.8 Hz, 1H).
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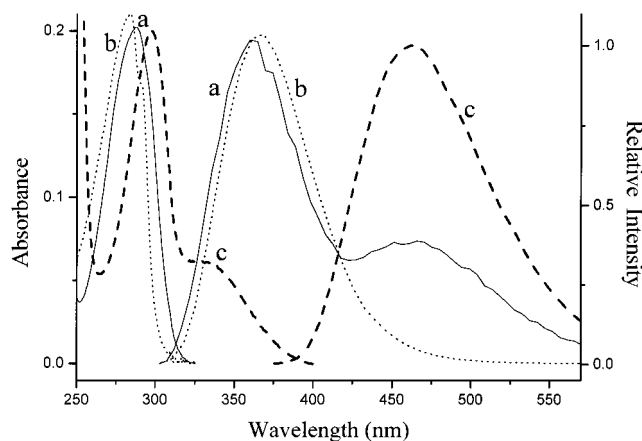
Figure 1. The absorption and emission spectra of (a) 3CAI (—), (b) 1MCAI (···), and (c) 3CMPP (- - -) in pure water (pH 7.0). The excitation wavelength is 280 nm.
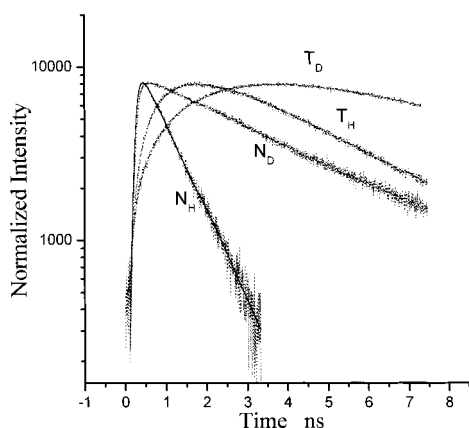

Figure 2. The time-dependent fluorescence of 3CAI (4.0×10^{-5} M) (a) in H_2O monitored at N_H = 340 nm ($\tau = 9.05 \times 10^{-10}$ s, $\chi^2 = 1.055$) and T_H = 500 nm ($\tau_1 = 9.10 \times 10^{-10}$ s (rise), $\tau_2 = 3.25 \times 10^{-9}$ s (decay), $\chi^2 = 1.005$) and (b) in D_2O monitored at N_D = 340 nm ($\tau = 3.47 \times 10^{-9}$ s, $\chi^2 = 1.035$) and T_D = 500 nm ($\tau_1 = 3.50 \times 10^{-9}$ s (rise), $\tau_2 = 6.80 \times 10^{-9}$ s (decay), $\chi^2 = 1.095$). The excitation wavelength is 270 nm.

910 ps and 3.25 ns, respectively ($\chi^2 = 1.005$, see Figure 2). The rise time of the 910 ps component of the F_2 band, within experimental error, is identical with the decay time (905 ps) of the F_1 band. A remarkable deuterium isotope effect was observed in D_2O in which the 3.50 ns rise time of the F_2 band correlates well with the decay time of 3.47 ns monitored at the normal emission (e.g. 340 nm), while the lifetime of the tautomer emission increases to 6.80 ns (Figure 2). In a comparative study 1-methyl-3-cyano-7-azaindole (1MCAI),[15] which serves as a non-proton-transfer model, exhibits a normal Stokes shifted emission maximum at ~360 nm (τ_f = 13.5 ns). Conversely, the tautomer analogue 3-cyano-7-methyl-7H-pyrrolo[2,3-b]pyridine (3CMPP)[16] in water reveals a single fluorescence maximum at 475 nm (Figure 1c) of which the spectral features and decay dynamics (τ_f = 5.25

ns) are similar to that of the F_2 band of 3CAI. The possibility that the F_2 band originates from the 3CAI protonated cation or deprotonated anion emission has been excluded by the observation of their corresponding emission maxima at 440 (τ_f = 0.67 ns, in 2.0 M HCl) and 425 nm (τ_f = 4.7 ns, in 2.0 M NaOH), respectively, with system-response-limited (~30 ps) rise dynamics. Furthermore, pK_a and pK_a^* of N_1H^+ for 3CMPP were determined to be 4.8 and 0.2, respectively. Assuming that the proton-transfer tautomer of 3CAI exhibits similar photoacidity with 3CMPP, the F_2 band in pure water (pH 7) with a Stokes shift of ~10 000 cm^{-1} can be unambiguously ascribed to the imine tautomer emission resulting from ESDPT.

The well-resolved tautomer emission discards the proposed mechanism of the prohibition of ESDPT during the lifetime of the excited 7AI in pure water.[1b,2,8] The unique rise time of the tautomer emission correlating well with the entire decay of the normal emission discounts the proposed mechanism that only a minor part of the nearly correct 1:1 cyclic complex is undergoing ESDPT, while the normal emission originates from the polysolvated 7AI.[6b−d] Alternatively, the experimental results can be plausibly rationalized by the mechanism proposed by Maroncelli and co-workers[5b,11] that ESDPT dynamics associate with completely solvated, neighbor-bonded 3CAI (structure N* in Scheme 1) where the kinetic scheme can be described within the framework of 7AI in alcohols. Under the assumption of a fast excited-state equilibrium between N* and 1:1 cyclic hydrogen-bonded 3CAI/H_2O (C*), the overall rate of ESDPT (k_{PT}) in pure water is expressed as $k_{PT} = (k_1/k_{-1})k_{pt}$, where k_{pt} is deuterium isotope dependent and may be governed by a tunneling mechanism.[11] On the basis of the results, $k_{PT}^H/k_{PT}^D \sim k_{pt}^H/k_{pt}^D$ = 910 ps^{-1}/3.50 ns^{-1} = 3.85 is deduced for 3CAI at 298 K.

Knowing that cyano-substitution on aromatic molecules may possibly lead to the dramatic change of acidity,[17] pH-dependent absorption and fluorescence lifetime studies have been performed. pK_a and pK_a^* of N_1H for 3CAI were determined to be 11.5 and ~12.8, respectively, which are only slightly more acidic than that of 12.1 and ~13 for 7AI.[6c] In addition, the reaction center for ESDPT is between the pyrrolic hydrogen and pyridinic nitrogen sites, which is far away from the cyano-substitution. It is thus believed that the electronic configuration and geometrical environment of 3CAI in water should not be drastically different from those of 7AI in water. The lack of tautomer emission in 7AI is due to the slow (~800 ps^{-1}) ESDPT rate in combination with a much faster nonradiative decay rate of the excited tautomer.[5b] In the case of 3CAI the rate of ESDPT is also slow (~910 ps^{-1}). However, the much longer tautomer lifetime, i.e., small non-radiative decay rate and hence large quantum yield,[18] makes 3CAI a unique model to resolve the mechanism of ESDPT for 7-azaindoles in pure water.

(14) Pico- to nanosecond measurements were performed by using an Edinburgh OB 900-L time-correlated single photon counting system coupled with the third harmonic (257−270 nm, fwhm ~ 100 fs) of the Ti-Sapphire oscillator as an excitation source.

(15) A suspension of 3CAI (0.14 g, 1 mmol) and sodium hydride (57%, 0.17 g, 4 mmol) in THF (3 mL) was stirred under argon atmosphere at 0 °C for 20 min. Methyl iodide (0.11 mmol) was then added and the resulting mixture was stirred for 1 h to obtain 1MCAI. ^{1}H NMR (400 MHz) 3.50 (s, 3H), 6.4 (s, 1H), 7.38 (t, J = 6.33, 6.25 Hz, 1H), 7.75 (d, J = 8.1 Hz, 1H), 8.59 (d, J = 4.7 Hz, 1H).

(16) 3CMPP was synthesized by dissolving 3CAI (100 mg) in dry THF. To the solution was added 0.08 mL of CH_3I and the mixture was refluxed for 3 h. After cooling, the solution containing precipitates was filtered, and the precipitate was collected followed by the dissolution with the addition of excess potassium carbonate. The resulting solution was then extracted by ethyl acetate. The ethyl acetate layer was dried and filtered and the product was obtained after evaporating the solvent. ^{1}H NMR (400 MHz) 2.47 (s, 3H), 5.9 (s, 1H), 5.2 (d, J = 8.3 Hz, 1H), 6.5 (t, J = 6.50, 6.35 Hz, 1H), 6.56 (d, J = 4.1 Hz, 1H).

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(18) The quantum yield of 3CMPP is determined to be ~0.07 (τ_{obs} ~ 5.25 ns), while it is only 0.0024 (τ_{obs} ~ 0.49 ns) for 7MPP in water.[5b] The result may be rationalized by the larger energy gap for the tautomer emission in 3CMPP (λ_{max} ~ 475 nm) than that in 7MPP (λ_{max} ~ 522 nm), resulting in a reduction of the radiationless deactivation.