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ORIGINAL PAPER

Excited State Lactim to Lactam Type Tautomerization Reaction in 5-(4-Fluorophenyl)-2-Hydroxypyridine: Spectroscopic Study and Quantum Chemical Calculation

Anuva Samanta · Bijan Kumar Paul · Samiran Kar · Nikhil Guchhait

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Abstract The photophysical properties of 5-(4-fluorophenyl)-2-hydroxypyridine (FP2HP) have been studied by steady state and time resolved spectroscopy in combination with quantum chemical calculations. The molecule FP2HP exists as lactim and lactam form in the ground state due to small stability difference but does not undergo lactim to lactam isomerisation due to high barrier energy. Whereas in the excited state the lactim form undergoes tautomerization producing red shifted emission of the lactam tautomer along with the local emission of the lactim form. In polar protic solvents, the barrier for lactim-lactam tautomerization rapidly decreases forming the lactam tautomer only. Temperature has pronounced effect on the excited state tautomerization equilibrium and is clearly reflected in the measured equilibrium constant (K_{tau}^{0}) and free energy change (ΔG^{0}). Structural calculations at Hartree Fock and Density Functional Theory levels, calculated stability of the isomers in different solvents using Polarized Continuum Model and the theoretical potential energy surfaces for the ground and excited states along the proton transfer coordinate are reported for the tautomeric equilibrium of FP2HP.

Keywords Tautomerization · 5-(4-fluorophenyl)-2-hydroxypyridine · Fluorescence · Density Functional Theory (DFT) · Time Dependent Density Functional Theory (TDDFT)

A. Samanta · B. K. Paul · S. Kar · N. Guchhait (✉)
Department of Chemistry, University of Calcutta,
92 A. P. C. Road,
Kolkata 700009, India
e-mail: nguchhait@yahoo.com

Introduction

For long time the proton transfer (PT) reaction is found to be one of the most encountered photoinduced process studied both experimentally and theoretically due to its immense application in various fields of scientific research. The molecules capable of tautomerization via proton transfer reaction are used as fluorescence probes for the measurement of solvation dynamics [1] and biological environments [2], fluorescence recording [3], ultraviolet stabilizers [4], the development of laser dyes [5–7], metal ion sensors [8], radiation hard-scintillator [9] and organic light emitting devices [10].

Out of diversified molecular systems capable of PT reaction, studies on photoinduced proton transfer reaction in nitrogen heterocycles of pyridine class with a proton bridging between nitrogen and oxygen atom are one of the interesting problem [11, 12]. In this context, the photo-induced 2-hydroxypyridine (2HP) to 2-pyridone (2PY) tautomerism by proton transfer (PT) process [13–15] has drawn tremendous attention to biologists for many decades because this process plays an important role in the mutation of DNA [16, 17] and it is the representative of a large number of heterocyclic molecules that are relevant to biological function [18]. The tautomerism of purine and pyrimidine bases occur naturally in nucleic acids, neucleotides which play a key role in mutagenesis [19]. The molecule 2HP exhibits two stable tautomeric forms: the lactim form 2HP and the lactam form 2PY. This tautomeric equilibria has been extensively studied experimentally in condensed and gas phases [13–15] as well as theoretically. In the 2HP-2PY equilibrium the energy difference between the two tautomers is sufficiently small and hence both species observed in the ground state, but proton transfer does not proceed in the ground state

because of a high energy barrier (16,000–20,000 cm^{-1}) [13, 20–23], whereas in polar solvents the lactam- form predominates over the lactim- form [24, 25]. Experiment in supersonic jet expansion [13] reveals that the S_0-S_1 band origin were observed at 36,123 cm^{-1} and 29,831 cm^{-1} which were identified as a $\pi \rightarrow \pi^*$ transition for the 2HP and 2PY form, respectively [15]. In the $\pi\pi^*$ excited singlet state, the large exothermicity (≈6,500 cm^{-1}) of the lactim to lactam reaction should decrease the barrier for proton transfer, thus allowing lactim to lactam transformation after photoexcitation [26].

In the present work, we have synthesized 5-(4-fluorophenyl)-2-hydroxypyridine (FP2HP), quite similar to that of 2HP having one substitution at fifth position and carried out its photophysical studies by steady state absorption and emission in combination with time resolved spectroscopy. The molecule is an important synthetic precursor for the synthesis of compounds having anxiolytic activity [27]. Interestingly, this molecule is suitable for enol-keto tautomerization along the five member hydrogen bonding ring. Therefore, tautomerization of this synthetic precursor could be important for both the ground and excited states. The para substituted fluorophenyl unit (electron deficient center) can be used as electron acceptor from the parent pyridine unit (electron donor) and may influence the hydrogen bond strength at the proton transfer site and thus affect the isomerisation reaction. The possibility of photo-induced electron transfer (PET) from the parent pyridine unit to electron deficient fluorophenyl unit can compete with the PT reaction. Lastly, this molecule can be used as multi-dentate ligand binding sites for making complex with metal ions so that this molecule can be used as transition metal ions sensor. The effect of temperature on the tautomerization reaction has been explored by following fluorescence spectra. Quantum mechanical calculations have been performed for structural and potential energy curve calculations along the proton transfer coordinate for the ground state and first excited singlet state at Density Functional Theory (DFT) and Time-Dependent Density Functional (TDDFT) levels of theory to correlate the experimental results with theoretical data. The effect of solvents on lactim-lactam equilibrium has also been explored theoretically for a correlation with the experimental results.

Experimental section

To a solution of the Vilsmeier reagent at 10°C, 4-fluorophenyl acetic acid was added. The mixture was stirred and heated at 70°C for 7 h. After cooling to room temperature, the mixture was added slowly to a mixture of ice and water and then a solution of Na_2CO_3 was added

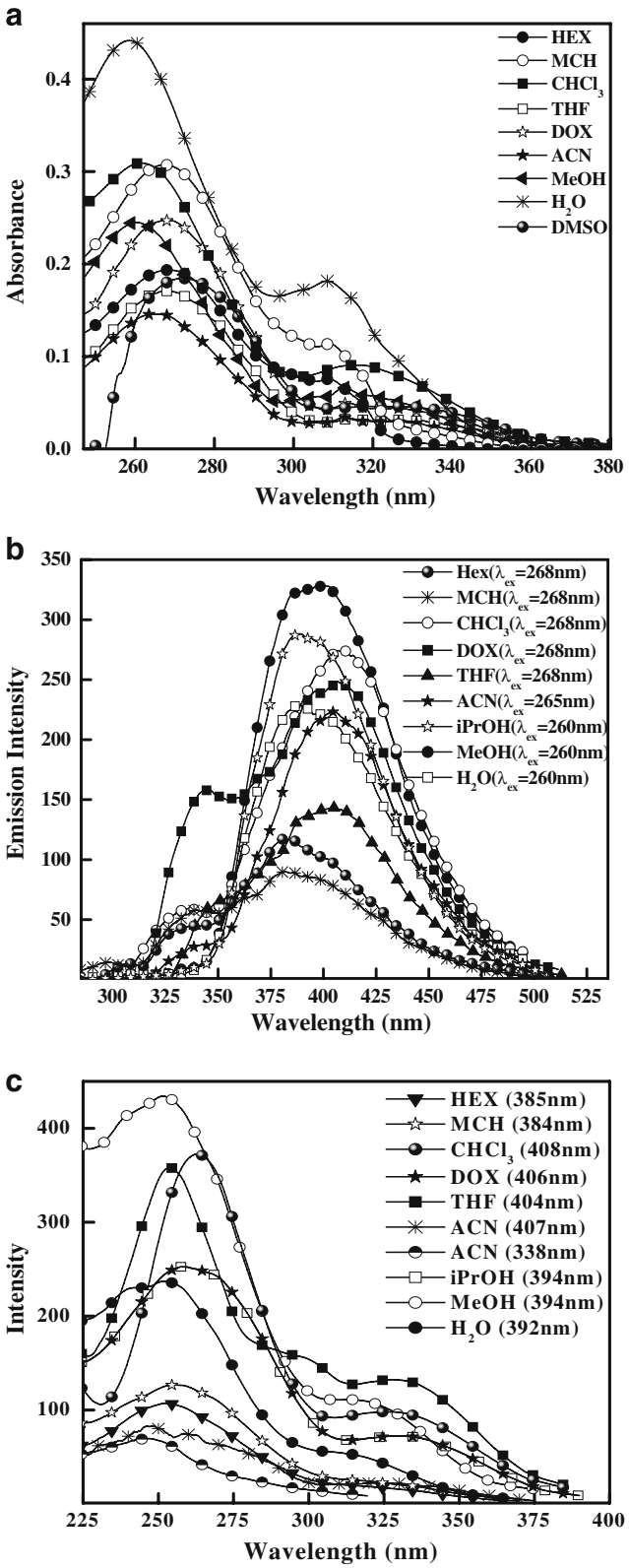

Fig. 1 **a** Absorption spectra of FP2HP in different solvents at room temperature, **b** Fluorescence emission spectra of FP2HP in solvents of differing polarity at room temperature. **c** Fluorescence excitation spectra of FP2HP at different emission maxima

slowly until pH 11 was achieved. Toluene was added to the alkaline mixture and the resulting mixture was refluxed for 1.5 h. After cooling to room temperature the separated aqueous layer was extracted with toluene. The combined organic extracts were washed with water and dried Na_2SO_4 and toluene was evaporated in vacuum. The solid residue was recrystallized from the mixture of dichloromethane and n-heptane to yield yellow crystals of 3-dimethylamino-2-(4-fluorophenyl)-proplactim. To a solution of sodium methoxide in methanol cyanoacetamide, the above product was added. The mixture was stirred at room temperature for 1.5 h and then refluxed for 10 h. During this time, a yellow solid precipitate was formed. The reaction mixture was diluted with water and acidified with 10% HCl. The yellow solid was filtered off, washed with water, ethanol and diethyl ether and then with n-hexane. This afforded 2-hydroxy-5-(4-fluorophenyl)-nicotinonitrile as a yellow solid. This product was added to a mixture of acetic acid and conc. HCl and refluxed for 18 h, diluted with water and cooled under stirring. The solid was filtered off, washed with water and then 50% ethanol. This afforded 2-hydroxy-5-(4-fluorophenyl)-nicotinic acid as a light gray solid. A mixture of the above product and freshly distilled quinoline was stirred and heated to 215°C for 14 h under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and n-heptane were added. The solid was filtered off and washed with n-heptane and then recrystallized from a mixture of dichloromethane and n-heptane to get pure 5-(4-fluorophenyl)-2-hydroxypyridine.

The solvents methylcyclohexane (MCH), cyclohexane (CH), tetrahydrofuran (THF), 1,4-dioxane (DOX), carbon tetrachloride (CCl_4), acetonitrile (ACN), dimethylsulfoxide (DMSO), isopropanol (Iso-prop), 1-butanol (BuOH) and methanol (MeOH) were purchased from Spectrochem and the purity of solvents have been checked in the wavelength range used. Triple distilled water was used for the preparation of aqueous solutions.

The absorption and emission spectra of FP2HP have been taken by Hitachi UV-Vis (Model U-3501) spectrophotometer and Perkin Elmer (Model LS-50B) fluorimeter, respectively. Temperature variation fluorescence spectra have been measured by keeping the emission cell compartment at a chosen temperature using variable temperature chiller. In all measurements, the sample concentration has been maintained within the range 10^{-5}–10^{-6} mol/dm^3.

Fluorescence lifetime measurement has been done by Time Correlated Single Photon Counting (TCSPC) technique using nanoLED-07 (IBH UK) [28]. The light source used in the TCSPC set up is a nano LED of wavelength 295 nm.

All calculations have been performed with the Gaussian 03 package [29]. All possible ground state conformers of FP2HP have been optimized at Hartree Fock (HF) and Density Functional Theory (DFT) level using B3LYP functional and 6–31G** basis set. The optimization of the FP2HP in different solvents has been carried out using Polarized Continuum Model (PCM) at Hartree Fock (HF) level [30, 31]. The ground state potential energy surfaces along the proton transfer coordinate have been done using relaxed scan [30, 31]. The excited state behaviors of FP2HP are obtained in the light of Time Dependent Density Functional Theory (TDDFT).

Results and discussions

Absorption spectra

Figure 1a depicts the absorption spectra of FP2HP in different solvents at room temperature. The FP2HP molecule exhibits two absorption bands irrespective of the nature of the solvent such as H-bonding ability and polarity. Comparing with the absorption spectra of 2-hydroxypyridine having similar absorption bands at ~227–230 nm and at ~297–

Table 1 Spectroscopic parameters measured by absorption and fluorescence spectra of FP2HP molecule at room temperature

Solvents	λ_{Abs} (nm)	λ_{Em} (nm)	ϕ_f (FP2HP- form) ($\times 10^2$)	ϕ_f (FP2PY- form) ($\times 10^2$) (λ_{ex}=265 nm)	ϕ_f (FP2PY- form) ($\times 10^2$) (λ_{ex}=310 nm)
CYC	268, 312	335, 387	0.104	3.649	0.90
MCH	268, 312	335, 387	0.207	5.516	1.50
THF	269, 325	352, 403	0.054	2.814	2.23
DOX	268, 325	346, 405	1.432	9.317	3.23
ACN	266, 325	338, 407	0.244	10.924	2.47
DMSO	273, 330	342, 403	0.035	4.121	4.61
BuOH	265, 322	395	–	23.477	6.20
iPrOH	262, 320	392	–	22.745	6.12
MeOH	260, 318	396	–	16.785	4.44
H_2O	259, 310	394	–	33.309	9.25

305 nm, the higher energy band of FP2HP at ~260 nm and the lower energy band at ~315 nm are ascribed to the absorption band of the lactim and lactam form of FP2HP, respectively. In the ground state, structurally aromatic lactim form may predominate over the lactam form due to higher stability. Later on by theoretical calculation we have found that the relative stability of two forms depends on the nature of the solvent. However, the red sided absorption band with low intensity of the lactam form may be due to less S_0–S_1 energy gap and low oscillator strength than the lactim form. The position of the bands are solvent dependent, but the effect of solvents on the lactam form is more prominent than that of lactim one. From Table 1 it is clear that the low energy absorption band is red shifted with polarity of the aprotic solvents. From now onwards the lactim form is ascribed as FP2HP and the lactam form as 5-(4-fluorophenyl)-2-pyridone (FP2PY). The position of lactim form is blue shifted with increasing H-bond forming ability of solvents due to intermolecular H-bonding interaction with the protic solvents. But the spectral characteristics of the lactam form indicate stabilizing dipolar interaction between the solvent dipole and the solute. However, it is important to note that the absorption spectra of FP2PY undergoes a detectable red shift on going from nonpolar solvent, e.g. CYC, MCH to polar protic solvents e.g. MeOH, but is again blue shifted from methanol to water. Such solvatochromic dependency of the absorption spectra of the presently investigated ESIPT probe seems to bear considerable consistency with the spectroscopic behavior of another closely related molecular system, 2,6-diaminopyridine, recently reported [32], and thus further substantiates the solvent effect on the spectroscopic properties of FP2HP.

Emission and excitation spectra

It is well known that in case of 2HP, the energy difference between the two tautomers is sufficiently small and hence both the forms exist in non-polar solvents. But the energy barrier for PT reaction in the ground as well as in the excited electronic states is large [33]. On excitation at any of the absorption band of 2HP either at ~230 nm or ~300 nm, single emission at ~350–370 nm has been observed that was assigned as the local emission of 2PY form. In case of FP2HP, on 260 nm excitation, the molecule shows two emission bands: one at ~338 nm and another at ~407 nm (Fig. 1b) and it shows only one emission at ~407 nm on 315 nm excitation. Though the PT barrier in the ground state is quite high but this barrier for PT reaction from lactim to lactam, i.e. FP2HP to FP2PY, decreases in the $\pi\pi^*$ excited singlet state due to large exothermicity. Single emission band at ~395 nm is observed in case of polar protic solvents. Here PT reaction is more feasible due

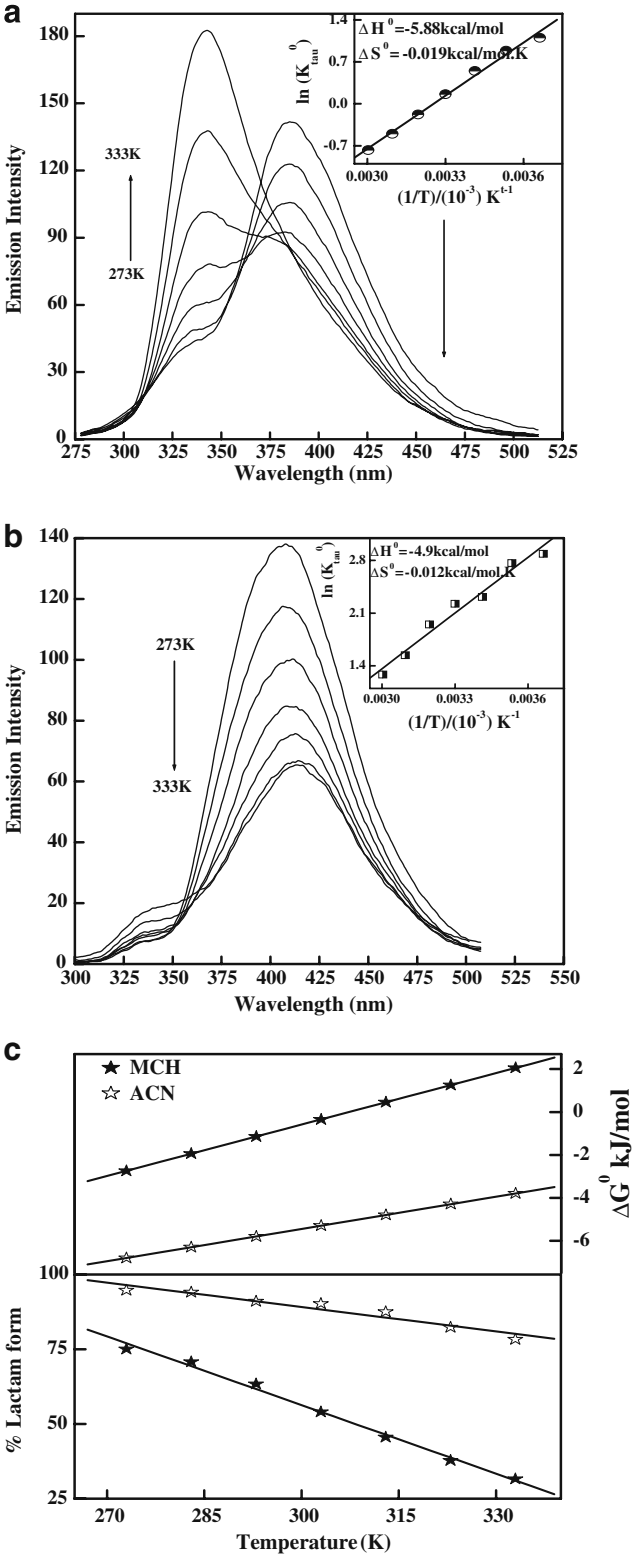

Fig. 2 Fluorescence emission spectra (λ_{ext}=260 nm) of FP2HP as a function of temperature in (**a**) MCH and (**b**) ACN solvent, (inset; Plot of $\ln K_{tau}^0$ vs 1/T). **c** Plot of ΔG^0 and % of Lactam form vs temperature for FP2HP in MCH and ACN solvent

Table 2 Experimental tautomeric equilibrium constants (K_{tau}^0) and standard free energy change (ΔG^0) (kcal/mol) of FP2HP at different temperatures obtained from Fig. 2a,b and Eqs. 1, 2, 3 and 4

Temp (K)	MCH solvent			ACN solvent		
	K_{tau}^0	ΔG^0 (using Eq. 2)	ΔG^0 (using Eq. 4)	K_{tau}^0	ΔG^0 (using Eq. 2)	ΔG^0 (using Eq. 4)
273	3.012	−0.598	−0.655	17.938	−1.566	−1.626
283	2.425	−0.498	−0.464	15.868	−1.555	−1.506
293	1.731	−0.320	−0.273	10.120	−1.348	−1.386
303	1.176	−0.098	−0.082	9.243	−1.339	−1.266
313	0.837	0.111	0.109	7.022	−1.212	−1.146
323	0.607	0.320	0.300	4.668	−0.989	−1.027
333	0.462	0.511	0.491	3.607	−0.849	−0.907

to lowering of exothermicity as well as lowering of barrier energy in an environment capable of making intermolecular hydrogen bonding with solvent molecules. Excitation spectra for 338 nm emission band show that this emission is originated from the species absorbing at 260 nm (Fig. 1c). So we have assigned this band (~338 nm) to LE of the FP2HP form. The excitation spectra monitored at 407 nm originates two bands that are quite similar to that of the absorption spectra of the molecule. Therefore, red shifted band arises not only from the LE emission of the lactam form, but from the lactim form due to ESIPT reaction.

The data presented in Table 1 reveals that the emission band maxima position of FP2HP shows some solvent dependency in the form that the emission maxima is comparatively red shifted with increasing solvent polarity. Such an effect, in analogy to literature, may be interpreted to be the result of charge migration from the hydroxyl oxygen to the heterocyclic ring part of the molecule upon photoexcitation [30–32, 34]. This, in turn, will decrease the charge density of the hydroxyl oxygen and hence its proton donor ability [30–32, 34]. However, in comparison to the recent report on 2,6-diaminopyridine [32], the observed solvatochromic effect in our case is not so large, and seems not surprising since an amino functional moiety can function as a better charge donor than a hydroxyl group. It is, indeed, noteworthy that the absorption and fluorescence solvatochromic shifts of FP2HP are somewhat greater than the model compound 2-hydroxypyridine. This might be an indication towards the presence of intramolecular hydrogen bond and excited state intramolecular proton transfer in FP2HP [32]. The occurrence of ESIPT in FP2HP has, however, been elaborately discussed in the upcoming sections.

Fluorescence quantum yield

The fluorescence quantum yield of FP2HP and FP2PY forms in solvents of different polarities are measured

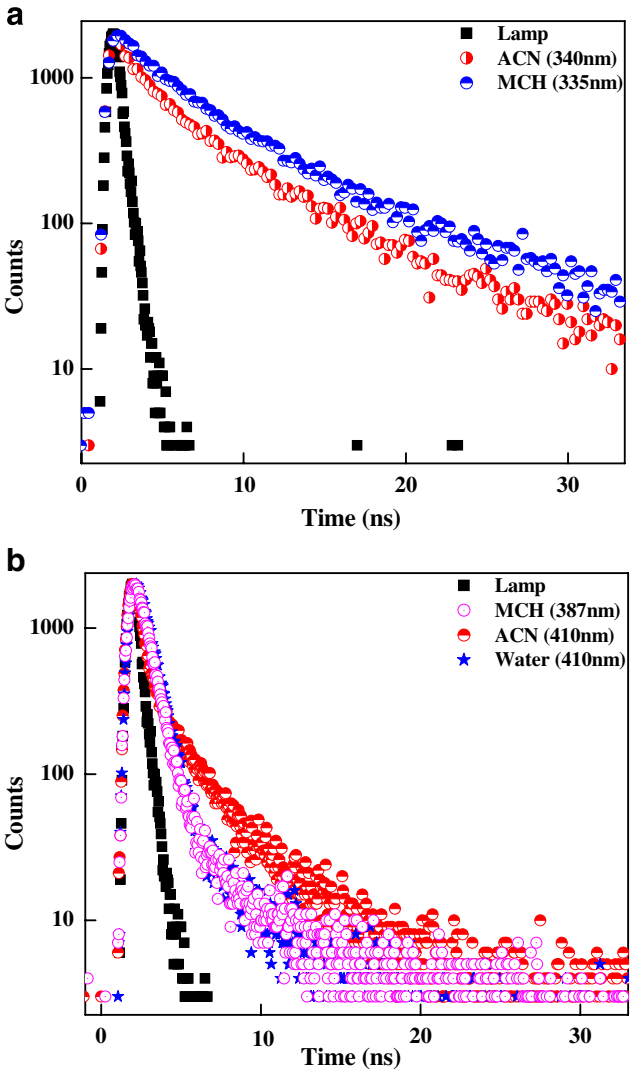

Fig. 3 **a** Fluorescence decay profiles of lactim tautomer of FP2HP in MCH (λ_{mon}=335 nm) and in ACN ($\lambda_{mon.}$=340 nm), **b** Fluorescence decay plots of lactam tautomer of FP2HP in MCH ($\lambda_{mon.}$=387 nm), ACN ($\lambda_{mon.}$=410 nm) and H_2O ($\lambda_{mon.}$=410 nm)

relative to Tryptophan (ϕ_R=0.13) in Tris-HCl buffer and β-napthol (ϕ_R=0.23) in MCH as the secondary standard, respectively (Table 1) [35]. The quantum yield values are calculated using the following equation,

$$\Phi_S = \Phi_R . \frac{A_S . OD_R . n_S^2}{A_R . OD_S . n_R^2}$$

Where, ϕ_S and ϕ_R are the quantum yields, A_S and A_R are the integrated fluorescence areas, OD_S and OD_R are the absorbance values and n_S and n_R are the refractive indices for sample and reference molecule, respectively.

As shown in Table 1, it is clear that lactim form undergoes excited state PT reaction indicated by the large value of quantum yield of lactam form than lactim form. Comparing the quantum yield of FP2PY form for different excitation, it is clear that for 260 nm excitation, the corresponding value is higher than that for 315 nm excitation. For the former one, lactim form tautomerises to lactam through intramolecular proton transfer mechanism and the corresponding value gives the total of lactam form as well as tautomerized lactam form. On the other hand, 315 nm excitation gives only the emission of the lactam form, so this quantum yield value corresponds only to lactam form of FP2HP. This comparison clearly indicates lactim-lactam tautomerism in the excited state.

Effect of temperature

The effect of temperature variations on the spectral properties of FP2HP in non-polar and polar aprotic solvents are presented in Fig. 2a and b. In both the cases of MCH and ACN solvent with increase of temperature the emission intensity of FP2HP form increases with concomitant decrease of the intensity of FP2PY form. However, the increase in intensity for FP2HP form and the decrease in intensity of FP2PY form are more pronounced in non-polar solvent MCH than polar aprotic ACN solvent. This indicates that temperature influences the position of FP2HP-FP2PY equilibrium. As shown in Fig. 2c, the percentage of lactam form decreases rapidly in MCH than ACN solvent with increase of temperature. Temperature is essentially a measure of overall kinetic energy. Kinetic energy as well as its components of vibrational and rotational energy also increases with increase of temperature. So the atoms comprising the FP2HP molecule oscillate and rotate much faster, hence the intramolecular hydrogen bond O-H...N is weakened thereby reducing the possibility of intramolecular proton transfer. The temperature dependent lactim → lactam reaction is characterized by tautomeric equilibrium constant (K_{tau}^0) which can be calculated using the relation given below;

$$K_{tau}^{\ 0} = \frac{I_{Lactam}}{I_{Lactim}} \quad (1)$$

Where I_{Lactam} and I_{Lactim} represent the emission intensity of lactam (FP2PY form) and lactim (FP2HP form) form, respectively. As seen in Table 2, K_{tau}^0 value decreases with increasing temperature thereby favoring the lactim formation.

The standard free energy ΔG^0 is related to K_{tau}^0 as,

$$\Delta G^0 = -RT \ln(K_{tau}^{\ 0}) \quad (2)$$

The standard enthalpy (ΔH^0) and entropy (ΔS^0) can be computed as

$$\ln(K_{tau}^{\ 0}) = -\frac{\Delta H^0}{RT} + \frac{\Delta S^0}{R} \quad (3)$$

So from the plot of $\ln(K_{tau}^0)$ vs 1/T as shown in inset of Fig. 2a and b, ΔH^0 and ΔS^0 can be determined for the lactim-lactam equilibrium. The ΔG^0 value thus can be recalculated for different temperature using the value of ΔH^0 and ΔS^0 using the following equation

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \quad (4)$$

As shown in Table 2, this recalculated ΔG^0 value is generally the same as it is calculated using Eq. 2. The feasibility of lactim formation is established from the plot of ΔG^0 vs T depicted in Fig. 2c where ΔG^0 value increases with increase of temperature.

Fluorescence lifetime

Fluorescence decay profiles for FP2HP have been measured in different solvents (Fig. 3, Table 3). FP2HP molecule undergoes biexponential decay due to the presence of lactim-lactam tautomers. The average fluorescence lifetime of FP2HP monitored at ~340 nm in MCH and ACN are

Table 3 Fluorescence lifetime data of FP2HP in non-polar, polar aprotic and polar protic solvents at room temperature

Solvents	λ_{mon} (nm)	A_1	τ_1 (ns)	A_2	τ_2 (ns)	$\tau_{avg.}$ (ns)	χ^2
MCH	335	0.537	2.71	0.463	7.85	5.09	1.01
MCH	387	0.976	0.74	0.024	4.56	0.83	1.20
ACN	340	0.569	1.58	0.431	6.34	3.63	1.04
ACN	410	0.850	0.45	0.150	2.80	0.80	1.06
H_2O	410	0.960	0.76	0.039	2.81	0.84	1.02

5.09 ns and 3.63 ns, respectively, while that for FP2PY are 0.83 ns, 0.80 ns and 0.84 ns in MCH, ACN and water, respectively. From the lifetime data analysis, it is clear that decay of proton transferred excited state, i.e. decay of FP2PY is faster than the FP2HP tautomer. On the other hand, decay time of FP2PY form is not so much affected on the nature of the solvents. Unfortunately a direct comparison of the lifetime of FP2HP with 2HP was prohibited due to extremely fast decay of 2HP falling beyond the measuring limit of the instrument.

Quantum chemical results

The global minimum structure of FP2HP has been obtained by ground state optimization of different low energy computed structures (Fig. 5) at Hartree Fock (HF) level and Density Functional Theory (DFT) level using B3LYP functional and 6–31G** basis set. Considering all possible structures of FP2HP, the lactim form (FP2HP) is most stable than any of the other forms in the gas phase. Intramolecular hydrogen bonded lactam form (FP2PY) is also more stable than open form. As the energy difference between the lactim and lactam form is sufficiently small (~0.267 kcal/mol at DFT level), these two forms may exist in the ground state. In the excited state the FP2PY form is stabilized by ~12.343 kcal/mol (DFT level) than FP2HP form as depicted in Fig. 4b. The optimized parameters for the lactim and lactam tautomers in the ground state at DFT level and HF level are presented in Table 4. Calculation predicts possible hydrogen bond between the two electronegative centers in both the lactim and lactam form. The DFT calculations using B3LYP functional at 6–31G** basis set were performed with the variation of torsional angle in order to calculate the strength of intramolecular hydrogen bonding estimated by the difference in energy between the closed conformer (FP2HP-from) and the open conformer. The calculated intramolecular hydrogen bond energy (E_{IMHB}) at DFT level for the closed conformer is determined to be 5.52 kcal/mol. Intramolecular strained four member hydrogen bonded ring may be cause of weak hydrogen bond energy. Interestingly the calculated dipole moment for the FP2HP is very low, but the corresponding dipole moment for the FP2PY is high (Table 4). Therefore, solvent polarity induced stabilization of the lactam form is expected to be high. That may be the cause of solvent polarity dependent variation of absorption band for the lactam form but not for the lactim form.

Theoretical study on the lactim-lactam tautomerism of FP2HP has been performed in a series of solvents with increasing dielectric constant (ε). We have adopted five solvents including CH (ε=2.015), CCl_4 (ε=2.228), THF (ε=7.58), ACN (ε=37.5) and DMSO (ε=46.7) and carried out PCM calculations at HF level using 6–31G** basis set to

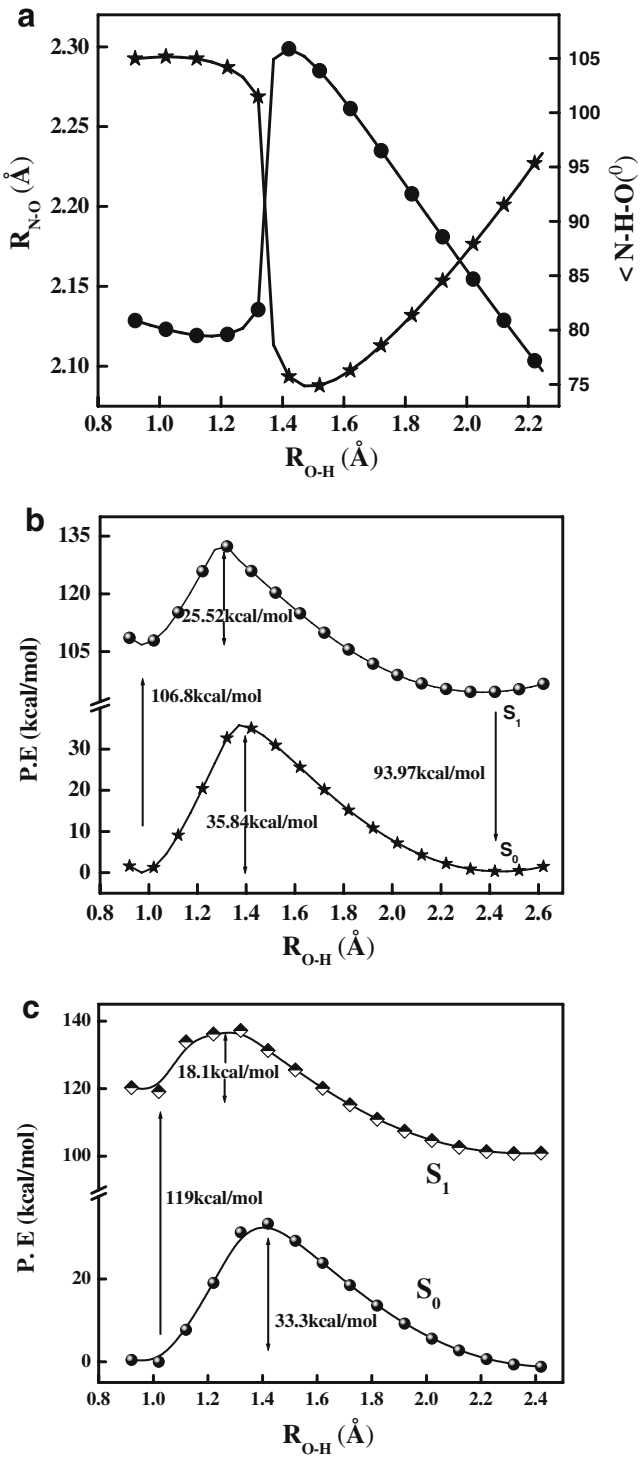

Fig. 4 **a** Variation of $O_d...N_a$ bond distance (-★-) and O_d-H_1-N_a bond angle (-●-) with R_{O-H} distance for FP2HP. Calculated potential energy E (kcal/mol) vs OH distance for the ground (S_0) as well as first excited singlet state (S_1) in the gas phase at DFT level using B3LYP functional and 6–31G** basis set (performing full geometry optimization at every step) for (**b**) FP2HP and (**c**) 2HP

Table 4 Structural parameters of FP2HP in the ground state at HF level using 6–31G** basis set and DFT level using B3LYP functional and 6–31G** basis set

Parameters	HF level		DFT level	
	FP2HP-form	FP2PY-form	FP2HP-form	FP2PY-form
O_d–H_1 (Å)	0.946	2.417	0.971	2.445
C_2 - O_d (Å)	1.334	1.203	1.352	1.226
C_2 - N_a (Å)	1.307	1.380	1.331	1.412
N_a - H_1 (Å)	2.258	0.996	2.245	1.013
O_d - N_a (Å)	2.263	2.247	2.293	2.289
∠ O_d – H_1 – Na (^{0})	78.245	68.237	80.467	69.126
μ (D)	0.605	3.022	0.505	2.828

obtain the geometries and its effect on lactim-lactam equilibrium. On going from gas phase to polar aprotic solvent with increasing dielectric constant of the medium, energy difference between the lactam and lactim tautomer increases favoring the lactam formation which is consistent with the larger dipole moment (μ) of the lactam tautomer than the lactim one as presented in Table 5. The calculated dipole moment in polar aprotic solvents is larger than that in the gas phase. It is noticeable that in polar aprotic solvent, the enhancement of dipole moment for the lactam tautomer is more than that of lactim tautomer. This increase in μ can be explained by the structural change of lactam and lactim form. As shown in Table 5, C_2-O_d bond length in lactam form is lengthened and C_2-N_a bond distance is contracted thereby increasing the dipole moment from gas to solvent with high ε value. The N_a...H_1 bond length for the lactim form is also increased from gas to DMSO by about 0.042 Å due to weakening of the intramolecular H-bond and favoring solute-solvent H-bonding. The O_d-H_1 bond distance and O_d-C_2-N_a bending angle of lactim tautomer are slightly increased (0.015 Å and 0.61^0) in polar solvents which enhances the solute dipole moment. These calculations clearly indicate how the solvent polarity affect the relative stability of two tautomers and the results correlate well with the experimental observation.

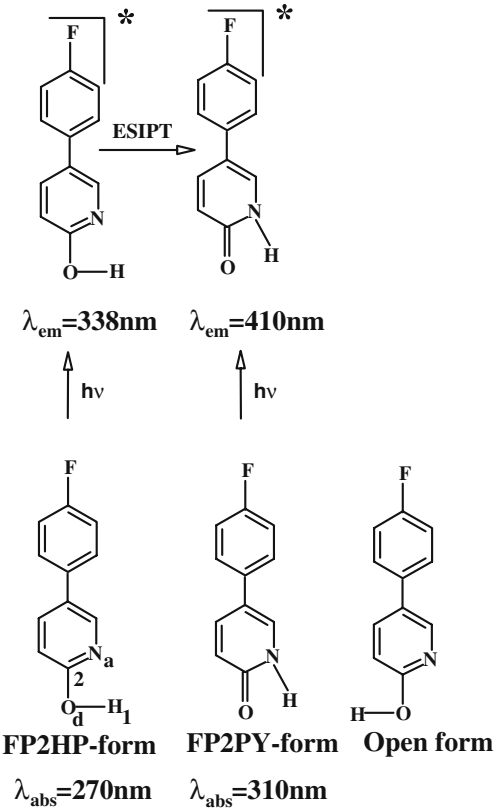

Fig. 5 Possible structures of FP2HP in the ground as well as excited state and their excitation and emission scheme

From the structural calculation (Table 4) it is found that both the lactim and lactam form may form four-member intramolecular hydrogen bonded ring at the proton translocation site. It is expected that the strained four member ring

Table 5 Optimized geometries of lactim (FP2HP) and lactam (FP2PY) tautomers in different solvents calculated at HF/6–31G** level using PCM model

Parameters	Solvents					
	Gas (ε=1.0)	CH (ε=2.015)	CCl_4 (ε=2.228)	THF (ε=7.58)	ACN (ε=37.5)	DMSO (ε=46.7)
ΔE[a] (kcal/mol)	−1.898	−0.017	0.207	2.099	2.904	2.947
μ (FP2HP) (D)	0.605	0.7445	0.762	0.912	0.980	0.985
μ (FP2PY) (D)	3.022	3.517	3.577	4.098	4.330	4.352
C_2 - O_d (FP2PY) (Å)	1.203	1.209	1.210	1.217	1.221	1.221
C_2 - N_a (FP2PY) (Å)	1.380	1.375	1.374	1.368	1.366	1.366
N_a …H_1 (FP2HP) (Å)	2.258	2.275	2.276	2.292	2.299	2.300
O_d –H_1 (FP2HP) (Å)	0.946	0.951	0.952	0.958	0.961	0.961
∠O_d-C_2-N_a (FP2HP) (^{0})	117.983	118.220	118.251	118.480	118.586	118.596

[a] $\Delta E = (E_{FP2PY}-E_{FP2HP})$

may relax during the course of proton transfer process, i.e., proton transfer reaction is multi-dimensional in nature [36, 37]. Interestingly the plot of the variation of $O_d - H_1$ distances with $O_d...N_a$ distances and O_d-H_1-N_a angles shows a systematic change during proton transfer process (Fig. 4a). As the PT process proceeds, the $O_d...N_a$ distance decreases and attains a minima at 1.47 Å, then relaxes back to its lactam form. Simultaneously, O_d-H_1-N_a angle increases to a maximum at 1.42 Å with increase of R_{O-H} distance and then returns with the formation of lactam form. This clearly indicates that proton transfer process is multi-dimensional in nature [36, 37] and change in $O_d - H_1$ distance is coupled with two other structural parameters, i.e. $O_d...N_a$ distance and O_d-H_1-N_a angle. Figure 4b and c show the potential energy versus R_{O-H} distance for FP2HP and 2HP in the relaxed calculation where we have performed geometry optimization at each stage of OH bond length. In both cases the energy of S_0 and S_1 states increases with R_{O-H} distance and both the states exhibit double minima potential. In case of FP2HP, with respect to the global minimum lactim form the tautomerization reaction in the ground state has a barrier of 35.84 kcal/mol (Fig. 4b). It is worth to point out here that, in the gas phase, proton transfer process for transformation from 2HP to 2PY in the ground state does not proceed at room temperature and the calculated barrier height at the same level of theory is 33.3 kcal/mol (Fig. 4c). Comparing the calculated barrier of FP2HP with 2HP we can easily say that proton transfer in FP2HP does not occur in the ground state but both the forms exist because of their very small energy difference. In the first excited state, the energy barrier for $FP2HP^*$ to $FP2PY^*$ transformation along the proton transfer coordinate is 25.5 kcal/mol and this tautomerization reaction is inferred to be exothermic one. Very similar results are obtained in case of 2HP. The calculated barrier to the tautomerization of 2HP in the S_1 pathway is 18.1 kcal/mol and is lower than in the ground state. Therefore, intramolecular proton transfer may be expected in the excited state for both the molecules in the S_1 surface through the 4-member intramolecular H-bond. The calculated S_0–S_1 transition energy for the lactim and lactam form obtained from the PES (Fig. 4b and c) are found to be 106.80 kcal/mol and 93.97 kcal/mol, respectively, and are consistent with the observed absorption band for lactim and lactam forms at 268 nm (106.68 kcal/mol) and 312 nm (91.64 kcal/mol), respectively. The lower absorption intensity of the lactam from can be established from the calculated low oscillator strength for FP2PY form (f=0.0395) than FP2HP form (f=0.0597) (Fig. 5).

Summary

The photophysical behavior of 5-(4-fluorophenyl)-2-hydroxypyridine (FP2HP) has been studied by steady state and time resolved spectroscopy and quantum chemical calculations. The polarity and hydrogen bonding ability of the solvents have prominent influence on the stability of lactam form rather than the lactim form in the ground state and their subsequent spectral properties. Spectral signature predicts the evidence of PT reaction but not of PET reaction. Thermodynamics parameters such as K_{tau}^0, ΔG^0, ΔH^0 and ΔS^0 for keto-enol equilibrium obtained by temperature variation study support the weakening of four-member intramolecular H-bond with increase of temperature thereby favoring keto to enol formation.

Quantum chemical calculations at Hartree Fock and Density Functional Theory levels predict the existence of lactim and lactam tautomers due to comparable stability in the ground state. Calculations predict that with increasing polarity of the solvents, the equilibrium shifted towards lactam tautomer in the ground state and exhibiting more influential effect of the polarity of the solvent on the lactam tautomer. The potential energy curve shows the feasibility of proton transfer in the excited state leading to keto-lactim tautomerization due to lowering the barrier energy than in the ground state. The spectral properties obtained from experimental and theoretical studies of FP2HP are found to be very similar to that of its parent molecule 2-hydroxypyridine and the intramolecular H-bonding is weaker in FP2HP than 2-hydroxypyridine which may be the cause of higher PT barrier in FP2HP than 2-hydroxypyridine.

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