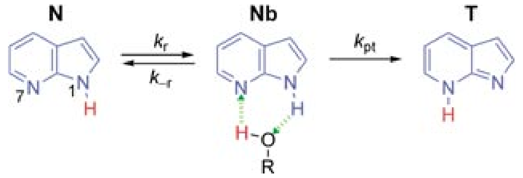
Proton Transfer

Asymmetric Double Proton Transfer of Excited 1:1 7-Azaindole/Alcohol Complexes with Anomalously Large and Temperature-Independent Kinetic Isotope Effects**

*Oh-Hoon Kwon, Young-Shin Lee, Han Jung Park, Yongho Kim, and Du-Jeon Jang**

Proton transfer has been attracting considerable attention because it plays a key role in a wide variety of biological and chemical processes.[1–4] Since the discovery of the double-helix structure of DNA by Watson and Crick in 1953, it has been suggested that the tautomerization of DNA base pairs causes inappropriate pairing of bases to result in point mutations. Photo-induced proton transfers are often considered to be useful for understanding the causes of mutagenesis in DNA replication. Thus, proton transfers in the dimers of 7-azaindole (7AI), structurally similar to H-bonded DNA base pairs, have been studied extensively.[5] 7AI is a chromophoric moiety of 7-azatryptophan, a novel in situ optical probe for the structures and dynamics of proteins.[6] Metal–7AI complexes are reported to have potential applications in electroluminescent devices.[7] A number of researchers have shed light on the excited-state double proton transfer (ESDPT) of 7AI, catalyzed by the H-bonded counterpart of a protic solvent molecule or a 7AI molecule in a dimer.[4–6,8–13]

The mechanism of solvent involvement in the excited-state tautomerization of 7AI in water and alcohols has attracted considerable attention.[4,6,9–12] In particular, the two-step model described in Scheme 1 has been discussed widely.[9–11] The first step is solvent reorganization (k_r) about the normal (**N**) 7AI molecule to form a cyclic H-bonded 1:1 7AI/solvent complex (**Nb**), and the second step is intrinsic proton transfer (k_{pt}) relayed by the complexed protic solvent molecule to give the tautomer (**T**). Intrinsic proton transfer is often presumed to be very fast and governed by tunneling.[9c,10] In one limit, solvent reorganization is the rate-limiting step such that the observed rate constant becomes k_r. In the opposite limit when equilibrium (k_r/k_{-r}) between solvent reorganization and solvent randomization (k_{-r}) is rapid relative to k_{pt}, the observed rate constant is independent of solvent dynamics and is expressed as $(k_r/k_{-r})k_{pt}$.[10] In water and alcohols 7AI has been proposed to undergo ESDPT following the latter scenario.[9–11] Although 7AI/water complexes formed in aprotic solvents have been suggested to undergo ESDPT as well,[13a] the intrinsic proton-transfer dynamics of **Nb** has been rarely studied experimentally and is not well understood.[12]



Scheme 1. The widely discussed ESDPT mechanism of 7AI in alcohols (ROH) and water. In this study **Nb** is directly photo-generated from the ground state.

Since the unusual catalytic activity of 2-pyridinone in epimerization reactions was found in 1952 by Swain and Brown,[14] concerted and stepwise motions of protons have been long-standing subjects. Schowen[4] reviewed this issue to assert that double proton transfer obeys Jencks's principle: if an intermediate along a stepwise route has a very high-energy structure, a transition state with a lower energy can exist for a concerted reaction to occur. The tautomerization of photoexcited 7AI dimers is reported to take place in a stepwise manner in which the zwitterionic intermediate is stabilized by charge delocalization in aromatic rings.[5b,c] On the other hand, the ESDPT of 7AI in neat water and alcohols was proposed to proceed in a concerted manner.[16] However, because the ESDPT rates of 7AI in neat protic solvents were revealed later to rely on thermodynamic solvation properties,[9–11] the harmony and the dissonance of proton motions in **Nb** deserve revisiting. In this paper, we present the dynamics and the nature of ESDPT initiated by the direct excitation of cyclically H-bonded 1:1 7AI/alcohol complexes at the ground state.

Figure 1 shows that the lowest absorption band of 7AI in *n*-heptane shifts to the red and grows at 310 nm with an increase in the concentration of methanol. The spectral changes imply that 7AI molecules associate with methanol molecules by H-bonding to produce complexes in the nonpolar solvent.[13] The linear Benesi–Hildebrandt plot of the

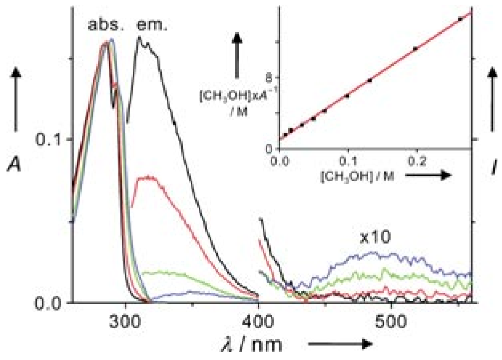


Figure 1. Absorption and emission ($\lambda_{exc} = 288$ nm) spectra of 7AI (1.6×10^{-5} M) in *n*-heptane having methanol concentrations of 0 (black), 8.2 (red), 33 (green), and 260 mM (blue). Inset: the Benesi–Hildebrandt plot ($\lambda_{abs} = 310$ nm) yields 50 M^{-1} for the association constant of 7AI with methanol to form **Nb** at 19 °C.

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inset in Figure 1 indicates that 7AI and methanol molecules form 1:1 complexes in *n*-heptane with an association constant (K_a) of 50 M^{-1}.[5a] Compared with the K_a values of 7AI dimers ($2.2\times10^3\,\text{M}^{-1}$) and 1:1 7AI/acetic acid complexes ($1.8\times10^4\,\text{M}^{-1}$) in nonpolar media,[13b] the K_a of 7AI/methanol complexes is quite small, implying that the hydrogen bonds of the complexes at the ground state are not strong owing to the relatively weaker H-bonding ability of methanol. The structures of ground-state H-bonded complexes with single methanol molecules in nonpolar solvents have been simulated to predict that **Nb** is a cyclic 1:1 complex having reasonably loose hydrogen bonds, especially between the pyridinic nitrogen of 7AI and the protic hydrogen of methanol (N···H–O).[9c,11]

Only the UV emission at 315 nm from **N** monomers appears in the absence of methanol. However, with methanol addition, the UV fluorescence shifts to 350 nm and decreases with the concomitantly growing fluorescence at 500 nm from **T**.[5a,13] Thus, we attribute the UV emission at 350 nm to H-bonded 1:1 complexes. The excitation spectrum of 7AI in *n*-heptane with 260-mM methanol, monitored at 500 nm, is spectrally identical with its lowest absorption band, indicating that both fluorescence bands at 350 and 500 nm originate from the same ground-state species. Therefore, we can infer that excited-state **T** molecules are generated by means of ESDPT from the 1:1 complexes of **Nb**.

The fluorescence at 350 nm of 7AI in *n*-heptane with 67-mM methanol[17] shows a biexponential decay profile composed of 88 (76 %) and 450 ps (24 %), while the fluorescence at 550 nm rises within 88 ps and decays in 1560 ps (Figure 2).

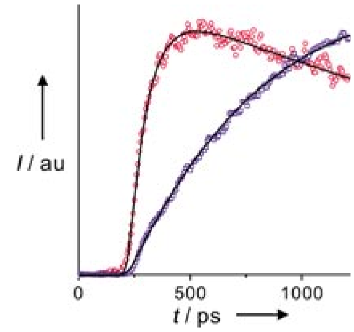


Figure 2. Fluorescence kinetic profiles of 7AI (1.6×10^{-5} M) in *n*-heptane with CH_3O^1H (red circles) and CH_3O^2H (blue squares) of 67 mM. Samples were excited at 288 nm and kinetic profiles were measured with instrumental response functions (IRF) of 25 ps at 550 nm. The lines fitting the circles and the squares were simulated with the rise time of 88 ps followed by the decay time of 1560 ps and the rise time of 1280 ps followed by the decay time of 1900 ps, respectively.

The rise time is identical with the fast-decay time at 350 nm, indicating that k_{pt} is (88 ps)$^{-1}$.[18] Quite intriguing is that the k_{pt} of 1:1 complexes isolated in the nonpolar solvent is not as large as the expected values of $\geq$ (5 ps)$^{-1}$.[9c,10] The slow-decay time at 350 nm is assigned to the fluorescence lifetime of noncomplexed 7AI.[17]

The ESDPT process of **Nb** occurs by the concerted relay of the two hydrogens through a single transition state or by the stepwise transfer of the two protons by forming a charged cationic or anionic intermediate. Proton-inventory experiments for the rates of ESDPT by varying the deuteration degree of protic hydrogen atoms in 1:1 7AI/alcohol complexes can give a clue to this issue.[16] We consider that four possibly different cyclic complexes of $^1H\cdots N_7N_1{-}^1H$, $^1H\cdots N_7N_1{-}^2H$, $^2H\cdots N_7N_1{-}^1H$, and $^2H\cdots N_7N_1{-}^2H$ in isotopically mixed systems have the intrinsic rate constants of $k_{pt}(^1H^1H)$, $k_{pt}(^1H^2H)$, $k_{pt}(^2H^1H)$, and $k_{pt}(^2H^2H)$, respectively. If $X_D =$ [protic ^{2}H]/([protic ^{1}H] + [protic ^{2}H]), then we can deduce Equations (1) and (2).

$$d[^1H\cdots N_7]/dt = -\{(1-X_D)k_{pt}(^1H^1H) + X_D k_{pt}(^1H^2H)\}[^1H\cdots N_7] \tag{1}$$

$$d[^2H\cdots N_7]/dt = -\{(1-X_D)k_{pt}(^2H^1H) + X_D k_{pt}(^2H^2H)\}[^2H\cdots N_7] \tag{2}$$

Because the isotope exchange of hydrogen is much slower than ESDPT, we expect that the fluorescence of **T** changes with time following Equation (3).

$$\mathbf{T}(t) = \{1-A_1\exp(-k_f\,t)-A_2\exp(-k_s\,t)\}\exp(-t/\tau_d) \tag{3}$$

While the composition of protic-hydrogen isotopes gives the ratio of A_1/A_2, the fitted parameters of k_f and k_s consist of rate constants as described by Equations (4) and (5), respectively.

$$k_f = k_{pt}(^1H^1H) + \{k_{pt}(^1H^2H)-k_{pt}(^1H^1H)\}X_D \tag{4}$$

$$k_s = k_{pt}(^2H^1H) + \{k_{pt}(^2H^2H)-k_{pt}(^2H^1H)\}X_D \tag{5}$$

Finally, $k_{pt}(^1H^1H)$, $k_{pt}(^1H^2H)$, $k_{pt}(^2H^1H)$, and $k_{pt}(^2H^2H)$ can be extracted from the plots of k_f and k_s with variation of X_D to be (93 ps)$^{-1}$, (196 ps)$^{-1}$, (700 ps)$^{-1}$, and (1200 ps)$^{-1}$, respectively (Figure 3). To assert the concerted mechanism of ESDPT, it is necessary to show that $k_{pt}(^1H^2H) = k_{pt}(^2H^1H)$ and that $\{k_{pt}(^1H^2H)\}^2 = k_{pt}(^1H^1H)\,k_{pt}(^2H^2H)$.[4,16] However, our data suggest that two hydrogens move in succession. We also infer that one of the two steps, presumably the first step, is rate-limiting, as suggested from the kinetically insignificant formation of cationic or anionic intermediate species (vide infra).

In a nonpolar medium 1:1 7AI/methanol complexes are theoretically shown to possess weakly H-bonded structures, the substantial fraction of which have the H-bond length of N···H–O longer than the nominal H-bond length of 2.5 Å.[9c,11] However, 1:1 7AI/acetic acid complexes undergo very facile ESDPT through short and strong hydrogen bonds.[13c] Thus, we have also obtained k_{pt} and kinetic isotope effect (KIE) values with diverse alcohols having different values of Kamlet–Taft acidity (α) and basicity (β).[19,20] The magnitudes of α and β provide explicit measures for the respective donating and the accepting abilities of the hydrogen bonds. It is evident from Table 1 that k_{pt} tends to decrease, whereas KIE tends to increase with an increase in α. Even for the complexes with alcohols having $\beta = 0$, ESDPT is very facile and the rate increases profoundly with an increase in α. Thus, the acidity of an alcohol is inferred to control the energetics of

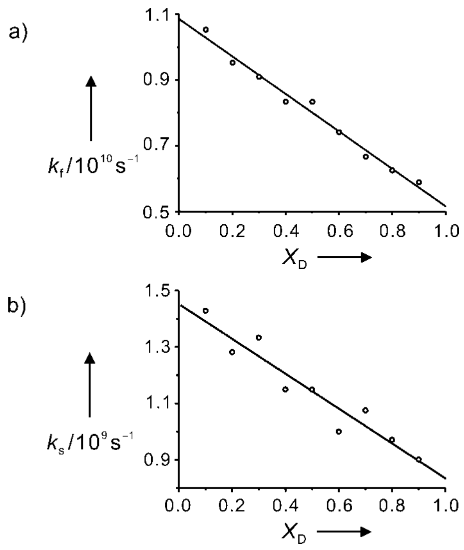


Figure 3. Plots of a) k_f and b) k_s with variation of X_D for 7AI (1.6×10^{-5} M) in *n*-heptane with 67 mM of methanol consisting of CH_3O^1H and CH_3O^2H, where k_f and k_s are the fast and the slow components of k_{pt}, respectively, and X_D is [protic ^{2}H]/([protic ^{1}H] + [protic ^{2}H]). The obtained values of $k_{pt}(^1H^1H)$, $k_{pt}(^1H^2H)$, $k_{pt}(^2H^1H)$, and $k_{pt}(^2H^2H)$ are $(93\text{ ps})^{-1}$, $(196\text{ ps})^{-1}$, $(700\text{ ps})^{-1}$, and $(1200\text{ ps})^{-1}$, respectively.

Table 1: Alcohol-dependent variation of k_{pt} and KIE.[a]

Alcohol	α	β	k_{pt} [ps^{-1}]	KIE
1,1,1,2,2,2-hexafluoroisopropyl alcohol	1.96	0	$\geq 6^{-1}$	[b]
2,2,2-trifluoroethanol	1.51	0	62^{-1}	5.8
methanol	0.93	0.62	88^{-1}	14.5
ethanol	0.83	0.77	95^{-1}	15.3
2-propanol	0.76	0.95	108^{-1}	17.6
tert-butanol	0.68	1.01	114^{-1}	20.2

[a] Alcohol concentrations and experimental conditions are described in Figure 2, and the values of α and β are taken from ref. [19]. The α and β values measured from bulk alcohols are given here because those from monomeric alcohols, showing similar trends, are not available for all the alcohols employed.[20] The average deviations of k_{pt} and KIE are ±5% and ±10%, respectively. [b] Not measurable due to our limited IRF.

ESDPT. The less acidic alcohol makes ESDPT less exoergic, that is, energetically more symmetric, reducing the overall rate but enhancing the relative contribution of tunneling in the reaction. This suggests that the H-bond donating ability of alcohol in the coordinate of N···H–O plays the key role for the dynamics of ESDPT. Keeping in mind that the decay time of **Nb** and the rise time of **T** coincide and that k_{pt} is dependent on the acidity of alcohol, we propose that the tautomerization of 7AI is initially triggered by the transfer of a proton from the alcohol molecule to the pyridinic nitrogen (N7) of 7AI, forming a cationic 7AI intermediate species, and completed by rapid proton transfer from the pyrrolic nitrogen (N1) of the intermediate to the transient alkoxide moiety. The intermediate complexes are unstable enough to be kinetically insignificant because both the alkoxide moiety and the 7AI cation are energetically unfavorable. Note that our results are consistent with the suggestion that cyclic H-bonded 1:2 7-hydroxyquinoline/alcohol complexes undergo excited-state tautomerization in a stepwise manner.[21] Thus, we infer that the observed kinetic results of ESDPT originate mainly from single-proton transfer in the O–H···N7 of **Nb**.

The kinetic isotope effect (KIE) of k_{pt}, $k_{pt}(^1H^1H)/k_{pt}(^2H^2H)$, for a 1:1 7AI/methanol complex is observed to be as great as 14.5 at 19 °C (Figure 2). The large KIE and the small k_{pt} of ESDPT imply the existence of an appreciably high barrier and the importance of tunneling through hydrogen bonds. The Arrhenius plots of k_{pt} in Figure 4 clearly show that not only k_{pt} but also KIE is independent of temperature within our experimental errors. This suggests that tunneling is operative certainly in the ESDPT of 7AI.[22,23] These types of temperature-independent Arrhenius plots have been reported in the enzymatic proton transfer of lipoxygenase.[24] Temperature-independent KIEs have also been observed in the proton transfers of thermophilic alcohol dehydrogenase[25] and solid-state porphyrin at low temperature.[26] Temperature-independent and large KIEs in enzymes have been explained with a model employing vibrationally enhanced proton tunneling[27] originally suggested by Dogonadze et al.[28,29] When the tunneling contribution is large, the ratio of the Arrhenius preexponential factors, $A(^1H)/A(^2H)$, is much less than unity in general. However, if tunneling becomes large enough to be equally effective for both ^{1}H and ^{2}H, then the ratio becomes much greater than unity. We have found $A(^1H)/A(^2H)$ to be 37 from Figure 4, which suggests that the ESDPT of 7AI/methanol complexes takes place with extensive tunneling contribution (vide infra).

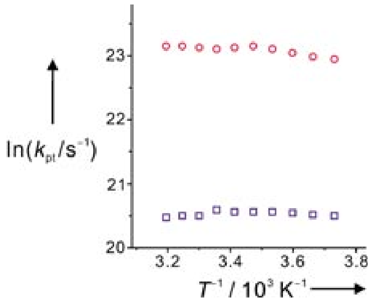


Figure 4. Arrhenius plots for the k_{pt} of 7AI (1.6×10^{-5} M) in *n*-heptane having CH_3O^1H (circles) and CH_3O^2H (squares) of 67 mM.

The intrinsic double proton transfer, which is governed mostly by tunneling, requires optimized angles and proper H-bond lengths in addition to a cyclic H-bonded structure. The formation of such a precursor configuration for tunneling from the 1:1 7AI/alcohol complex of **Nb** is not sensitive to isotope effects and consists mostly of heavy-atom motions with a little reorganization energy. The precursor-configuration optimization and the intrinsic tunneling are in two orthogonal reaction coordinates of the potential hypersurface, and solvent fluctuations play a crucial role in the formation of such a pretunneling configuration. In the regime that only the motions of hydrogen including tunneling limit the rate, KIE is predicted to be neither dependent on solvent viscosity nor equal to unity. Alternatively, when heavy-atom reorganization assists quantum tunneling, KIE depends on viscosity. The heavy-atom reorganization that is required to reach the optimal pretunneling configuration becomes slow as viscosity increases. Thus, the tunneling contribution is reduced and KIE tends to be small with increased viscosity.[30] Table 2 shows that both k_{pt} and KIE tend to decrease as solvent viscosity increases. These trends suggest that the rate of the overall proton-transfer reaction is affected by the configuration-optimization rate of **Nb** more at higher viscosity. If the motions of hydrogen limit the rate, KIE increases in general as k_{pt} becomes smaller. However, our results are opposite to this, supporting the idea that solvent fluctuations assist tunneling in the ESDPT of **Nb**.

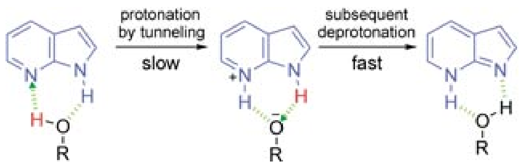
Table 2: Viscosity-dependent variation of k_{pt} and KIE.[a]

Solvent	Viscosity [cP]	k_{pt} [ps^{-1}]	KIE
n-heptane	0.41	88^{-1}	14.5
n-decane	0.92	93^{-1}	13.7
n-dodecane	1.45	97^{-1}	12.5

[a] Methanol concentrations and experimental conditions are described in Figure 2, and viscosity values measured at 20°C are taken from ref. [31].

Tunneling in our systems is conceptually identical to the vibrationally assisted tunneling suggested in enzymatic reactions.[25,27–29] The solvent fluctuations replace the low-frequency protein motions. Furthermore, the picture of the proton transfer in **Nb** is in line with that of 7AI dimers in which the heavy-atom motions of N···N coupled to N–H vibrations are crucial for tunneling.[5b,c] Also in accord with our picture is the acid–base reactions of 1-naphthol/ammonia clusters, which are strongly correlated to acid–base vibrational couplings assisted by solvent fluctuations.[32] It should be pointed out that proton transfer in the tautomerization of a 1:1 7AI/water complex has not been reported in the gas phase although it is observed in condensed phases.[13a,33,34] This discrepancy hints at the role of solvent fluctuations on the tautomerization of a 7AI monomer assisted by a protic guest molecule.

The ESDPT of a 1:1 7AI/alcohol complex in nonpolar *n*-alkanes occurs consecutively on a time scale of 100 ps with unusually large, temperature-independent, and viscosity-dependent KIEs near room temperature. The ESDPT is initially triggered by the proton transfer of the alcohol molecule to the pyridinic nitrogen of 7AI, forming a cationic 7AI intermediate species, and completed by rapid proton transfer from the pyrrolic nitrogen of the intermediate to the transient alkoxide moiety (Scheme 2). The H-bond between the pyridinic nitrogen atom of a 7AI molecule and the protic hydrogen atom of an alcohol molecule is suggested to play the central role for ESDPT. The intrinsic proton transfer of the complex is governed by single-proton tunneling from the alcohol molecule to the pyridinic nitrogen atom, although heavy-atom motions assist the complex to reach the optimized precursor configuration. The detailed dynamics of this process requires multidimensional reaction coordinates to be described properly and thus has great theoretical challenge.



Scheme 2. ESDPT mechanism of a 7AI molecule cyclically H-bonded to an alcohol molecule.

Experimental Section

7-Azaindole (≥ 99%) from Sigma-Aldrich, *n*-alkane (anhydrous), and alcohols were used as purchased. The protic hydrogen atoms of both 7AI and ROH of **Nb** were exchanged with ^2H atoms by dissolving 7AI in nonpolar solvents containing RO^2H (isotopic purity ≥ 99.5%) for the measurements of k_{pt} in proton-inventory experiments. Absorption and emission spectra were obtained by using a UV/Vis spectrometer (Scinco, S-3100) and a fluorimeter consisting of a 75-W Xe lamp (Acton Research, XS432) and two monochromators (Acton Research, Spectrapro), respectively. Fluorescence kinetic profiles, excited with Raman-shifted 288-nm pulses of a mode-locked Nd:YAG laser (Quantel, YG701), were detected using a 10-ps streak camera (Hamamatsu, C2830). Emission wavelengths were selected by combining band-pass filters and cut-off filters. Fluorescence kinetic constants were extracted by fitting profiles to computer-simulated exponential curves convoluted with IRF (fwhm: 25 ps). Sample temperature was controlled using a refrigerated bath circulator (Jeio Tech, RC-10V). Unless specified otherwise, all the measurements were carried out at a temperature of 19°C.

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[17] Of the 7AI molecules 93 % and 77 % are expected to form 1:1 complexes with methanol at methanol concentrations of 260 and 67 mM, respectively. To avoid the possible formation of polysolvated complexes, we have measured fluorescence kinetics at a concentration of 67 mM.[13a] The lifetime (450 ps) of noncomplexed 7AI in our system differs from reported values (~1.7 ns) of 7AI monomers in alcohol-free nonpolar solvents.[9a] However, the Benesi–Hildebrandt plot of **T** fluorescence shows good linearity, yielding $K_a = 45\,\text{M}^{-1}$. This eliminates the possibility of collision-induced ESDPT processes.

[18] The overall proton-transfer time of 7AI in neat methanol is obtained to be 130 ps, which is very close to the reported value of 124 ps.[9b]

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[22] We obtained k_{pt} and KIE values by monitoring the fluorescence rise at 550 nm, rather than the fluorescence decay at 350 nm, to avoid the fluorescence interference of noncomplexed 7AI at 350 nm.

[23] KIE values are reported to be 3.8 and 3.0 for the proton transfer of 7AI in neat water and methanol, respectively.[9,10]

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