# Anomalously Slow Proton Transport of a Water Molecule

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Supporting Information

**ABSTRACT:** Unusually low proton-transporting ability of a water molecule has been observed in the excited-state proton transfer (ESPT) of a 7-azaindole (7AI) molecule complexed cyclically with a water molecule in diethyl ether and dipropyl ether. In contrast with ultrafast (<1 ps) proton diffusion along a systematically structured hydrogen-bond network in an aqueous solution, the proton transport of a water monomer has been observed to be extremely slow ( $\sim$ 1 ns) because it is hard for a monomeric water molecule alone to accept or donate a proton. Thus, polar ether molecules surrounding a cyclic



hydrogen-bonded 1:1 7AI—water complex (Nc) play a crucial role in the ESPT of Nc. The proton acceptance of a water molecule from the acidic amino group of 7AI via tunneling to form a hydronium ion, which is the rate-determining step, initiates ESPT, and the subsequent rapid proton donation of the hydronium ion to the basic imino group of 7AI takes place barrierlessly to complete ESPT without accumulating any intermediate. Due to the anomalously weak proton-transporting ability of a water monomer, the elaborate reorganization of the hydrogen-bond bridge in Nc to form an optimized precursor configuration is required for proton tunneling.

## **1. INTRODUCTION**

Water, which is the prime agent in most biological phenomena and chemical processes, has often been the subject of many experimental and theoretical studies.<sup>1–10</sup> The characteristic physical and chemical properties of water, such as the high boiling point, the strong surface tension, and the high vaporization enthalpy, originate primarily from systematically well-structured hydrogen (H)-bond networks.<sup>11</sup> In an aqueous solution, H bonds break and form continuously,<sup>12</sup> and their breaking and forming dynamics is coupled closely to proton mobility in water.<sup>13–15</sup> Because H bonds play a pivotal role in a great number of chemical and biological processes such as acid—base reactions and proton pumps through membrane—protein channels,<sup>3,16–18</sup> many researchers have tried to elucidate the structural change mechanism of H-bond networks at the molecular level.<sup>19,20</sup> Since the famous concept of fast proton transfer via structural diffusion in water was proposed by Grotthuss in 1806,<sup>21</sup> subsequent explanations have refined the concept by invoking thermal hopping, proton tunneling, or solvation effects.<sup>3,20–25</sup> Computer simulations have shown that interconversion between an Eigen cation  $(H_3O^+ \cdot (H_2O)_3)$ , whose hydronium core is H-bonded to three H<sub>2</sub>O molecules, and a Zundel cation  $(H^+ \cdot (H_2O)_2)$ , where a proton fluctuates between two water molecules, leads to fast proton migration in water.<sup>26–28</sup> Recently, we have reported the excited-state proton transfer (ESPT) of 7-hydroxyquinoline (7HQ) along a H-bonded water dimer in diethyl ether (DEE) and dipropyl ether (DPE); the sequential Grotthuss-type proton-transport mechanism of water via interconversion between two hydration complexes, an an Eigen cation and a Zundel cation, has been experimentally demonstrated.<sup>7,8</sup>

Thus, the anomalously high mobility of a proton in water is attributed to fast interconversion between the Eigen and the Zundel cations through well-organized H-bond chains. Then, one would be concerned about whether a water molecule alone can transport a proton facilely in the absence of H-bond networks. In this regard, to understand the proton-transport mechanism of a water monomer at the molecular level, we have employed a model system of a 7-azaindole (7AI) molecule complexed cyclically with a water molecule and investigated the ESPT of the cyclic 1:1 7AI—water complex.

Proton transfer plays a decisive role in a wide variety of chemical and biological processes relevant to vital phenomena, <sup>1,6,17,18,29</sup> and amphoteric aromatic molecules such as 7AI and hydroxyquinolines have been the subject of growing interest to researchers who study proton-relay dynamics.<sup>7–10,30–51</sup> In particular, 7AI, which is an analogue of nucleobases such as adenine and guanine, has been explored intensively because it is a novel optical probe to investigate the structure of proteins and the dynamics of enzymatic catalyses in biological systems.<sup>36–51</sup> On one hand, because a 7AI dimer is structurally similar to a DNA base pair, experimental and theoretical mechanistic studies on the proton transfer of the 7AI dimer have received considerable attention.<sup>36–39</sup> On the other hand, the normal species (N) of monomeric 7AI can undergo ESPT with assistance of protic solvents, such as water and alcohols, to produce the tautomeric species (T), so that

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Scheme 1. ESPT Mechanism of a Cyclically H-Bonded 1:1 7AI–Water Complex in Ethers



solvated cluster species of 7AI, that is, 7AI complexed with protic solvents via H-bonding, have also attracted a lot of interest.<sup>40–51</sup> Thus, during the last several decades, the ESPT dynamics of 7AI catalyzed by the H-bonded counterpart of a protic solvent, as well as the proton-switching mechanism of 7AI dimers, has been investigated extensively. In particular, the mechanism of the solvent-catalyzed ESPT of 7AI in water and alcohols has been widely discussed as a two-step model;<sup>40-47</sup> the first step is solvent reorganization to form a cyclically H-bonded 7AI-solvent complex, and the second step is intrinsic proton transfer. In bulk water or alcohols, because the solvent reorganization is the ratedetermining step of ESPT, the intrinsic proton transfer is hard to be observed directly.<sup>43–45</sup> However, in aprotic media such as *n*-alkanes and ethers, a 7AI molecule associates with a water molecule to form a cyclic complex already in the ground state, and thus, the intrinsic ESPT of the cyclic complex can be explored directly without being interfered with by solvent reorganization.<sup>40</sup>

Here, we report the ESPT of cyclically H-bonded 1:1 7AI-water complexes (Nc) in diethyl and dipropyl ethers (Scheme 1). The rate-determining step of the ESPT of Nc is the proton acceptance of a water molecule from the pyrrolic amino group via tunneling to form a hydronium ion, and the subsequent barrierless proton donation of the transiently formed hydronium ion to the pyridinic imino group completes the ESPT without accumulating any intermediate. As a result, we have found that the ESPT of 7AI along a water monomer is immensely slowed down compared with the ESPT of 7HQ along a water dimer.<sup>7,8</sup> Whereas a water dimer can transport a proton rapidly through interconversion between an Eigen cation and a Zundel cation, a water monomer alone can barely do. Due to such extraordinarily reduced proton-transporting ability of a water molecule without having a H-bond network, it is hard for a water monomer alone to accept a proton from the acidic amino group of 7AI at the rate-determining step of the ESPT of Nc. Nevertheless, Nc can undergo ESPT in ethers via transiently forming a charged intermediate species, that is, a deprotonated 7AI anion H-bonded to a hydronium ion, because polar ether molecules surrounding Nc can stabilize the charged intermediate species.

# 2. EXPERIMENTAL SECTION

**2.1. Materials.** While 7AI ( $\geq$ 99%) was used as purchased from Sigma-Aldrich, DEE (anhydrous,  $\geq$ 99.7%) and DPE (anhydrous,  $\geq$ 99%), purchased from Sigma-Aldrich, were stored over molecular sieves of 4 Å for 24 h prior to use to remove even a trace amount of humidity. Water ( $\geq$ 18 M $\Omega$  cm) distilled triply with a Milli-Q system (Millipore) was used. The protic <sup>1</sup>H (H) atoms of both 7AI and water were exchanged with <sup>2</sup>H (D) atoms by dissolving 7AI in DEE or DPE containing D<sub>2</sub>O (isotropic purity  $\geq$  99.9%, received from Sigma-Aldrich) for the



Figure 1. Maximum-normalized absorption spectra of 7AI in DEE (top) and DPE (bottom) having  $H_2O$  concentrations indicated inside.

measurements of kinetic isotope effects. In every sample, the concentration of 7AI was kept at 50  $\mu$ M, which is low enough to prevent the formation of dimers or oligomers of 7AI; that is, practically all of the 7AI molecules exist as monomers.

2.2. Measurements. Absorption spectra were measured with a UV/vis spectrophotometer (Scinco, S3100). Emission spectra were obtained using a home-built fluorometer consisting of a Xe lamp of 75 W (Acton Research, XS432) with a monochromator of 0.15 m (Acton Research, Spectrapro150) and a photomultiplier tube (Acton Research, PD438) attached to a monochromator of 0.30 m (Acton Research, Spectrapro300). To obtain timeresolved fluorescence kinetic profiles, a mode-locked Nd:YAG laser (Quantel, Pizzicato) with the pulse duration of 25 ps was employed for excitation, and a streak camera of 10 ps (Hamamatsu, C2830) attached to a CCD detector (Princeton Instruments, RTE128H) was used for detection. Samples were excited with 288 nm pulses generated from a Raman shifter, filled with CH<sub>4</sub> gas of 15 atm and pumped by the fourth-harmonic pulses of 266 nm from the laser. Emission wavelengths were selected by combining band-pass and cutoff filters. Fluorescence kinetic constants were extracted by fitting kinetic profiles to computersimulated exponential curves convoluted with instrument response functions. The sample temperature was controlled using a refrigerated bath circulator (Jeio Tech, RC-10V). Unless specified otherwise, all of the static and kinetic measurements were carried out at room temperature.

## 3. RESULTS AND DISCUSSION

**3.1. Steady-State Absorption and Emission Spectra.** Figure 1 shows the absorption spectra of 7AI in DEE and DPE with a variation of water content; the lowest absorption band of N in both DEE and DPE, having the band maximum at 288 nm, shifts to the red and grows at 310 nm as the concentration of water increases. The spectral changes of the N-absorption band imply



**Figure 2.** (a) Emission spectra, with excitation at 288 nm, of 7AI in DEE (top) and DPE (bottom) having H<sub>2</sub>O concentrations indicated inside. (Insets) Magnified emission spectra to show tautomeric fluorescence. (b) Plots of [water]<sup>-1</sup> versus  $(F - F_0)^{-1}$  in DEE (left) and DPE (right), where *F* is the fluorescence intensity at 530 nm. The best-fitted lines yield 10.6 M<sup>-1</sup> with H<sub>2</sub>O and 5.5 M<sup>-1</sup> with D<sub>2</sub>O for the formation constants ( $K_{\rm Nc}$ ) of a 1:1 7AI–water complex in DEE, and they yield 14.3 M<sup>-1</sup> with H<sub>2</sub>O and 13.7 M<sup>-1</sup> with D<sub>2</sub>O for  $K_{\rm Nc}$  in DPE.

that 7AI molecules associate with water molecules via H bonding to produce 7AI-water complexes in both ethers. In the ground state, the stable structure of 7AI-alcohol complexes in *n*-alkanes has been reported to have a cyclically H-bonded 1:1 geometry.<sup>40</sup> Similarly, a 7AI molecule is supposed to form a H-bonded cyclic complex of Nc with a water molecule in aprotic media of ethers (see below), as shown in Scheme 1. On the basis of the fact that the absorption band of T has not been observed even at a high concentration of water ( $\geq 200$  mM), we infer that Nc does not undergo proton transfer in the ground state. However, the emission spectra of Figure 2a show that the proton transfer of N\* through a water monomer takes place to produce T\*; only one emission band from N\* appears at 345 nm in pure ethers, while a new additional band from T\* grows at around 515 nm with the addition of water. This indicates that the excited-state tautomerization of 7AI in DEE and DPE is operative in the presence of water.

With the concentration increment of water dissolved in ethers, the N\* emission band shifts to the red (Figure S1 in the Supporting Information), and the intensity of T\* fluorescence increases gradually (Figure 2a); the band maximum of N\* fluorescence shifts from 345 nm in neat DEE to 351 nm in DEE containing 200 mM water, while it shifts from 343 nm in neat DPE to 347 nm in DPE having 200 mM of water (Figure S1 in the Supporting Information). This suggests that 7AI monomers are converted into Nc, which can undergo ESPT to generate T\*, as the concentration of water increases. An isoemissive point at around 470 nm is observed in both DEE and DPE (the insets of Figure 2a), implying that only two emitting species, that is, N\* and T\*, exist. Thus, we infer that no reaction intermediate accumulates during the ESPT process of N\* along a water molecule to yield T\*, although an intermediate state may form transiently (see below). On the other hand, we have figured out that the intensity of T\* fluorescence is much weaker in 7AI-water complexes than that in 7AI-alcohol complexes.<sup>40</sup> This suggests that the proton-transporting solvent, such as water or an alcohol-mediating ESPT, plays an important role in determining the ESPT dynamics of 7AI and that the proton-transporting ability of water is quite different from that of an alcohol (see below). Chapman and Maroncelli have reported that T\* fluorescence is not observable in neat water because the nonradiative relaxation of T\* is even much faster than the formation of T\* via ESPT of Nc\*.43 However, for the ESPT of monohydrated 7AI, T\* fluorescence has been observed, although its intensity is very weak.<sup>46</sup> These imply that the proton-accepting and proton-donating behaviors of a monomeric water molecule are quite different from those of bulk water having methodically wellorganized H-bond networks.

We have deduced the formation constant of Nc  $(K_{\rm Nc})$  by monitoring T<sup>\*</sup> fluorescence;  $K_{\rm Nc}$  can be estimated by eq 1.<sup>52</sup>

$$\frac{1}{C} = \frac{c}{F - F_0} - K_{\rm Nc} \tag{1}$$

where F and  $F_0$  denote fluorescence intensity at 530 nm measured at the molar water concentrations of *C* and 0, respectively, and *c* is a proportionality constant. A linear relationship between 1/C and  $1/(F - F_0)$  confirms that a 7AI molecule associates with a water molecule to form a cyclic 1:1 complex (Figure 2b) and that the fluorescence of proton-translocated T\* originates entirely from Nc<sup>\*</sup>. While  $K_{\rm Nc}$  values are found to be 11.3 and 5.5 M<sup>-2</sup> in H<sub>2</sub>O- and D<sub>2</sub>O-added DEE, respectively, they are 14.3 and 13.7  $M^{-1}$  in H<sub>2</sub>O- and D<sub>2</sub>O-added DPE, respectively. We have found out that the observed  $K_{\rm Nc}$  values in ethers are much smaller than the previously reported formation constant of a 1:1 7AI-methanol complex in *n*-heptane (50  $M^{-1}$ ).<sup>40</sup> This implies that H bonds between a 7AI molecule and a water molecule are weaker than those between a 7AI molecule and a methanol molecule, and we attribute this to the polar solvent effect of ethers; DEE ( $\varepsilon$  = 4.27 cP at 20 °C) and DPE ( $\varepsilon$  = 3.38 cP at 20 °C) are much more polar than *n*-heptane ( $\varepsilon = 1.92$  cP at 20 °C). Moreover, while an alcohol molecule can form H bonds with a 7AI molecule only, a water molecule can form an additional H bond with an ether molecule besides H bonds with a 7AI molecule.

**3.2. Time-Resolved Fluorescence Kinetic Profiles.** The fluorescence kinetic profiles of 7AI in DEE and DPE containing 50 mM of water have been obtained with variation of protic hydrogen isotopes as well as monitoring of wavelengths (Figure 3). Although the kinetic profiles of N\* fluorescence monitored at 380 nm show single-exponential decay, those of T\* fluorescence monitored at 550 nm have single-exponential rise and decay. If N\* fluorescence showed double-exponential decay and its fast decay time matched with the rise time of T\* fluorescence, we could undoubtedly regard the fast decay time as the ESPT time of



**Figure 3.** Fluorescence kinetic profiles of 7AI in DEE (top) and DPE (bottom) having  $H_2O$  (open) and  $D_2O$  (closed). The concentration of water was kept at 50 mM in every sample, which was excited at 288 nm and monitored at 380 nm (blue) for N\* fluorescence and at 550 nm (red) for T\* fluorescence. Solid lines are the best-fitted curves to extract time constants given in Table 1.

Nc and the slow decay time as the relaxation time of excited 7AI monomers or noncyclic 7AI—water complexes that cannot undergo proton transfer. However, on the basis of the fact that Figure 2a shows only two emission bands of N\* and T\* with an isoemissive point at around 470 nm and that the rise of T\* fluorescence at 550 nm has only one component, we consider that the ESPT of Nc to produce T\* takes place in a concerted fashion, rather than in a stepwise fashion, without accumulating any intermediate species and that the rise time of T\* fluorescence corresponds to the ESPT time of Nc (see below).

In aprotic media of DEE and DPE, a 7AI molecule and a water molecule forms a cyclically H-bonded complex, that is, Nc, already in the ground state because of the low solubility of water in ethers. Thus, the intrinsic ESPT of 7AI along a water monomer in ethers can be observed directly without being interfered by slow solvation such as solvent reorganization to form Nc. While the absorption spectra of 7AI in water-added DEE do not show tautomeric absorption (Figure 1), its emission spectra show  $T^*$ fluorescence at around 515 nm (Figure 2). This suggests that only the ESPT of Nc\* produces T\*, although Nc has already formed in the ground state. Moreover, no intermediate species has been observed in the emission spectra (Figure 2), and all of the observed rise times of T\* fluorescence in both ethers are invariant regardless of changes in water content (Table 1). In these regards, we attribute the observed rise time of T\* fluorescence at 550 nm to the ESPT of Nc\*. The ESPT time in H<sub>2</sub>O-added DEE has been observed to be as long as 1050 ps, which is close to the relaxation time of excited 7AI monomers in DEE without having water (2600 ps) (Table 1). Accordingly, the ESPT time of Nc and the relaxation time of excited 7AI monomers or noncyclic 7AI-water complexes are too similar to be experimentally distinguishable;

Table 1.	Fluorescence	Time	Constants	of	7AI	in	Water-
Added E	thers						

medium <sup>a</sup>	[water]/mM	$isotope^b$	$\lambda_{\rm em}{}^c/{\rm nm}$	rise time/ps	decay time/ps
DEE	0	Н	380	d	2600
	20	Н	380		1880
			550	1050	1860
		D	380		2320
			550	1900	2020
	50	Н	380		1250
			550	1050	1380
		D	380		2140
			550	1900	1950
DPE	0	Н	380		2970
	20	Н	380		2070
			550	1170	3350
		D	380		2850
			550	2380	3300
	50	Н	380		1480
			550	1170	1880
		D	380		2670
			550	2380	3500
7		6 8 8 8	- 1		1

<sup>*a*</sup> The dielectric constants of DEE and DPE are 4.27 and 3.38, respectively, at 20 °C. <sup>61</sup> <sup>*b*</sup> H and D are protic <sup>1</sup>H and <sup>2</sup>H atoms, respectively. <sup>*c*</sup> Wavelength of monitored fluorescence. <sup>*d*</sup> Instant.

two decay times of N\* fluorescence might be observed individually if they were largely different. For this reason, N\* fluorescence monitored at 380 nm gives only one observable decay time where the ESPT time of Nc and the relaxation time of excited monomers or noncyclic complexes are convoluted. Hence, we take the rise time of T\* as the ESPT time of Nc; the ESPT times in DEE are 1050 ps with H and 1900 ps with D, while those in DPE are 1170 ps with H and 2380 ps with D (Table 1).

The ESPT of 7HQ along a water dimer in DEE has been reported to take place through interconversion between Eigen and Zundel cations on a time scale of 38 ps,<sup>7,8</sup> which is much faster than the ESPT of 7HQ along a methanol dimer in nheptane (62 ps).<sup>34</sup> Because of the unique properties of water where each molecule can have as many as four H bonds, protons can be hydrated stably and transferred rapidly through densely wellordered H-bond chains in water. The ESPT pathway of 7HQ along a water dimer is known to be opposite to that of 7HQ along an alcohol dimer due to different properties of water and an alcohol, which are primary solvents in proton transport;<sup>7,8,34</sup> a water molecule initiates ESPT by accepting a proton from 7HQ, whereas an alcohol molecule does so by donating a proton to 7HQ. Similarly, although the proton donation of an alcohol molecule to the pyridinic imino group of 7AI occurs as the first step in the ESPT of a 1:1 7AI-alcohol complex,<sup>40</sup> we consider that in the ESPT of Nc, that is, a 1:1 7AI-water complex, the proton acceptance of a water molecule from the pyrrolic amino group of 7AI takes place first (see below). However, the ESPT time of 7AI along a water monomer in ethers is 30 times longer than that of 7HQ along a water dimer in ethers<sup>7,8</sup> and 10 times longer than that of 7AI along an alcohol monomer in *n*-heptane.<sup>40</sup> In an aqueous solution, proton diffusion occurs very fast via interconversion between Eigen and Zundel cations through systematically well-structured H-bond networks; this is well-known as the proton-hopping mechanism.<sup>20</sup> However, a water monomer

in the absence of a H-bond network hardly accepts or donates a proton because of its extremely weak proton-transporting ability. Table S1 in the Supporting Information designates that for water, the proton-donating and the proton-accepting abilities of a monomer ( $\alpha_m$  and  $\beta_m$ ) are enormously smaller than the respective ones of bulk ( $\alpha$  and  $\beta$ ). As is well known, the unusual physical features of water, for example, the high boiling point and the strong surface tension, originate chiefly from methodically wellorganized huge H-bond networks. Thus, we infer that the dynamics of water-involved reactions depends largely on the presence and the size of a H-bond network. On the other hand, the observed anomalously slow ESPT time also proves that a 7AI molecule associates with a water molecule to form a 1:1 complex; if a 7AI molecule associated with two water molecules to form a 1:2 complex, the ESPT dynamics would be observed to be similar to the ESPT dynamics of a 1:2 7HQ-water complex showing a very fast ESPT time of 38 ps, as reported earlier.<sup>7,8</sup> Gas-phase ultrafast pump-probe studies have revealed that the ESPT of 7AI clustered with more than two water molecules takes place within several picoseconds.50

The  $\alpha_m$  value of water is very similar to the  $\alpha_m$  value of an alcohol, whereas the  $\beta_{
m m}$  value of water is much smaller than the  $\beta_{\mathrm{m}}$  value of any alcohol (Table S1 in the Supporting Information). For the ESPT of a 1:1 7AI-alcohol complex,<sup>40</sup> the rate constant of ESPT (  $k_{\rm pt})$  tends to increase with  $\alpha_{\rm m}$  of the alcohol because the rate-determining step is proton transfer from the alcohol molecule to 7AI; however, the value of  $k_{pt}$  for the ESPT of Nc does not follow this tendency (Figure S2 in the Supporting Information). For this reason, we have proposed that in contrast with the ESPT of the 7AI-alcohol complex, the ESPT of a 1:1 7AI-water complex is initiated by proton transfer from the pyrrolic amino group of 7AI to the water molecule and that the proton acceptance of the water molecule, having very weak  $\beta_{\rm m}$ , to form a hydronium ion is the rate-determining step. Besides, the aprotic polar media of DEE and DPE can solvate protons (or hydronium ions) effectively by their electronegative oxygen atoms. Considering the preferential solvation of cations by ethers and the well-known simplest continuum theory of ionic solvation, that is, the Born model<sup>55</sup> where the solvation free energy depends linearly on the reciprocal of the radius of a spherical ion, we infer that the excess solvation free energy will be larger with a delocalized anion over a deprotonated 7AI moiety and a localized cation on the hydronium ion than that in the opposite case, that is, the formation of a protonated-7AI cation and a hydroxyl ion. Sakota and Sekiya have suggested that because 7AI becomes acidic in the first excited singlet state, the  $\pi - \pi^*$  excitation of 7AI makes the N-H bond of the pyrrole ring break easily.<sup>56</sup> Furthermore, a theoretical study on the ESPT of a 1:1 7AI-water complex has recently reported that in the transition state, the proton of the pyrrolic amino group of 7AI is located close to the water molecule in Nc while the proton H-bonded to the pyridinic imino group of 7AI still belongs to the water molecule;<sup>48</sup> thus, it is very plausible that a hydronium ion, rather than a hydroxyl ion, forms transiently during ESPT (see below). Therefore, we suggest that the ESPT of a 1:1 7AI-water complex is initiated by the proton acceptance of a water molecule from the pyrrolic amino group of 7AI to form a hydronium ion and a deprotonated-7AI anion transiently, as shown in Scheme 1, and that the observed rise time of T\* fluorescence becomes the ESPT time of Nc. On the other hand, while the rise time of T\* fluorescence is as long as 1050 ps in DEE, its decay time is just 1380 ps (Table 1); although the observed T\* decay time is a typical one,<sup>40</sup> it is very close to the T\*



**Figure 4.** Logarithmic values of the rate constants of the T\* fluorescence rise, that is, the ESPT rate constants of Nc ( $k_{pt}$ ), versus water concentrations in DEE (open) and DPE (closed) with variation of protic hydrogen isotopes (circles for H and squares for D).

rise time that is unusually long. Correspondingly, the intensity of  $T^*$  fluorescence at 515 nm is very weak (Figure 2a). Thus, we consider that the anomalously weak proton-transporting ability of a water monomer in the absence of a H-bond network brings about the extraordinarily slow ESPT of Nc to yield very weak  $T^*$  emission despite the ordinary decay time of  $T^*$  fluorescence.

At low concentrations of water ( $\leq$  80 mM), the ESPT time of Nc is invariant regardless of water content dissolved in ethers (Table 1 and Figure 4), implying that the collision-induced formation of Nc does not occur within the lifetime of Nc\*. In other words, Nc only, already existing in the ground state, undergoes proton transfer upon excitation. However, the ESPT time of Nc varies with the media of ethers, which are secondary solvents surrounding Nc; in particular, an ether molecule forms a H bond with the water monomer of Nc (Scheme 1). We attribute the different ESPT times of Nc in DEE and DPE to the dissimilar dielectric constants of two ethers.<sup>8</sup> In a polar reaction such as proton or electron transfer, if the reactant and the product have different polarities, the reaction rate is generally sensitive to medium polarity.<sup>8,36,53</sup> In this regard, during the ESPT process of Nc, the polar media of ethers are expected to lower the energy of an ionic intermediate state that is formed transiently but not observed (see below). Of note is that the solvation of an intermediate species by a solvent medium is completed typically in 1 ps. The ionic intermediate state can be stabilized better in the more polar medium of DEE ( $\varepsilon$  = 4.27 at 20 °C) than that in the less polar medium of DPE ( $\varepsilon$  = 3.38 at 20 °C), and thus, the more polar DEE helps Nc\* undergo proton transfer relatively more readily via forming charged intermediate species transiently; the ESPT of Nc has been observed to occur faster in DPE than in DEE on that account. Both the acidity, correlated with  $\alpha$ , and the basicity, correlated with  $\beta$ , of the two secondary solvents, that is, DEE and DPE, are supposed to affect the ESPT rate of Nc as well as the stabilization of the charged intermediate species. However, because two ethers have zero acidity and almost the same basicity, we consider that the dissimilar ESPT times in two ethers come mainly from the polarity difference between two secondary solvents. Thus, in the ESPT of Nc, the polar character of the secondary solvent (ether) molecule, which is H-bonded to the primary solvent (water) molecule, enhances the proton-accepting ability of a monomeric water molecule at the rate-determining step that is proton transfer from 7AI to water. On the other hand, the exchange of all of the protic H atoms with D atoms has revealed that the

kinetic isotope effect (KIE), calculated as  $k_{pt}(H)/k_{pt}(D)$ , of the ESPT of Nc is 1.8 in DEE and 2.0 in DPE (Table 1 and Table S1 in the Supporting Information). Generally, in the condensed phase, vibrationally assisted quantum tunneling by heavy-atom motions helps ESPT to occur facilely, and KIE tends to decrease with the increment of medium viscosity.<sup>34,40</sup> However, the KIE in the ESPT of Nc is observed to be slightly larger in DPE than that in DEE, although the viscosity of DPE ( $\eta$  = 0.396 cP) is larger than that of DEE ( $\eta$  = 0.224 cP). Accordingly, it can be inferred that medium polarity plays a more important role than medium viscosity does in the ESPT of 7AI along a monomeric water molecule. Moreover, the value of KIE in the ESPT of Nc is even much smaller than that in the ESPT of a 1:1 7AI-alcohol complex (Table S1 in the Supporting Information).<sup>40</sup> Thus, we consider that although the ESPT of Nc occurs via tunneling, there is something more important than tunneling in the ESPT process because of the immensely weak proton-accepting ability of a water molecule; that is configurational optimization for efficient proton tunneling by the reorganization of the H-bond bridge in Nc prior to intrinsic ESPT (see below).

The value of  $k_{pt}$  for the ESPT of Nc in water-added ethers is independent of water content up to 80 mM, but then, it increases with the concentration of water (Figure 4 and Table S2 in the Supporting Information). At a low concentration of water  $(\leq 80 \text{ mM})$ , the water molecule of Nc has a negligible chance to be H-bonded to another water molecule, so that it is H-bonded to an ether molecule to remain as a water monomer. However, at a high water concentration (>80 mM), the water molecule of Nc can be H-bonded to another water molecule to form a dimeric water chain. In other words, whereas the secondary solvent molecule, which is H-bonded to the water molecule of Nc, is always an ether molecule at a low concentration of water, it could be a water molecule at a high concentration of water. We need to note that the 7AI-water complex having a dimeric water chain at a high concentration of water still has the cyclic 1:1 geometry, that is, Nc, rather than the 1:2 geometry (see below) and that the complex is still surrounded by ether molecules. Thus, an extra water molecule H-bonded to the water molecule of Nc does not transport a proton directly in the ESPT of Nc but helps the water molecule of Nc accept a proton facilely. Of note is that an ether molecule can form a H bond with a proton or a hydronium ion but cannot relay a proton on its own. After a proton is transferred from the acidic amino group of 7AI to the water molecule of Nc, it cannot be diffused away via the dimeric water chain because Nc is isolated in an aprotic medium of DEE or DPE. Accordingly, the proton hydrated in the dimeric water chain has no choice but to move to the basic group of 7AI.

With the increasing number of water molecules H-bonded to the water molecule of Nc, the value of  $k_{\rm pt}$  would become larger because the water molecule of Nc can accept a proton from 7AI easily with assistance of the H-bonded water molecules; the water molecule of Nc does not exist as a monomer anymore, so that the proton-accepting ability of the water molecule of Nc increases. Nevertheless, even with 200 mM water, the ESPT time of Nc is as long as 900 ps (Table S2 in the Supporting Information), implying that the cyclic 1:1 geometry of 7AI—water complexes is still preserved even in the presence of excess water molecules. If a 7AI molecule formed a cyclic 1:2 complex with two water molecules, ultrafast proton transport through interconversion between Eigen and Zundel cations would take place, and thus, the ESPT time of a 1:2 7AI—water complex would be similar to the reported ESPT time of a 1:2 7HQ—water complex (38 ps in DEE).<sup>7</sup> It is noteworthy that the reported ESPT time of a 1:1 7AI-alcohol complex is close to that of a 1:2 7HQ-alcohol complex.<sup>34,40</sup> The ESPT of 7AI clustered with more than two water molecules has been reported to occur within several picoseconds.<sup>50</sup> We consider that the  $k_{pt}$  value of Nc increases with the increasing concentration of water over 80 mM because the number of 7AIwater complexes having a dimeric water chain increases. On the other hand, when deuterated water  $(D_2O)$  was added to an ether, the  $k_{\rm pt}$  value of Nc remained the same regardless of D<sub>2</sub>O content up to the highest concentration in this work. This suggests that the D<sub>2</sub>O molecule of Nc has a negligible chance to be D-bonded to another D<sub>2</sub>O molecule even at the high D<sub>2</sub>O concentration of 200 mM because D-bonding ability is generally much weaker than H-bonding ability. Recall that the  $K_{\rm Nc}$  value of a 1:1 7AI-H<sub>2</sub>O complex is almost two times larger than the value of a 1:1  $7AI-D_2O$  complex in DEE (Figure 2b). Similarly, the association of a 7AI-D<sub>2</sub>O complex with another D<sub>2</sub>O molecule is considered to be substantially weaker than the association of a  $7AI-H_2O$  complex with another  $H_2O$  molecule. Thus, the concentration of 7AI-D<sub>2</sub>O complexes having a dimeric D<sub>2</sub>O chain is too low to increase the  $k_{pt}$  value of Nc noticeably at the D<sub>2</sub>O concentration of  $\leq 200$  mM.

3.3. Proton Inventory Experiments. On the basis of the result that the excitation of Nc at 288 nm gives rise to only two emission bands at 345 nm for N\* fluorescence and at 515 nm for T\* fluorescence with an isoemissive point at around 470 nm (Figure 2a), we have suggested that the ESPT of Nc takes place concertedly without accumulating any intermediate. In the concerted process of ESPT, then it would be an issue whether two hydrogen atoms participating in the ESPT of Nc move synchronously. Proton inventory experiments for the  $k_{pt}$  of Nc with a variation of deuteration degrees of protic hydrogen atoms system-atically can give a clue to this issue.<sup>36,40,57–59</sup> Nc can have four different types of isotopic exchange,  $H_{-1}N_{7}N\cdots H$  (HH),  $H_{1N} \xrightarrow{7}{N} \cdots D$  (HD),  $D_{1N} \xrightarrow{7}{N} \cdots H$  (DH), and  $D_{1N}$  $_7$ N···D (DD), where the two successive hydrogen atoms in parentheses denote protic hydrogen atoms bound covalently to the nitrogen atom of the pyrrole ring and H-bonded to the nitrogen atom of the pyridine ring in turn (Scheme 1). The ESPT rate constants of those four types of Nc are denoted as  $k^{\text{HH}}$ ,  $k^{\text{HD}}$ ,  $k^{\text{DH}}$ , and  $k^{DD}$ , respectively. Because the rate-determining step is proton transfer from the pyrrolic amino group  $(_1N-H)$  to the water molecule of Nc, we can deduce eqs 2 and 3 for  $k_{pt}$  according to the protic hydrogen isotope of the pyrrolic amino group.

$$d[H^*]/dt = -(X_H k^{HH} + X_D k^{HD})[H^*]$$
(2)

$$d[D^*]/dt = -(X_H k^{DH} + X_D k^{DD})[D^*]$$
(3)

where \* denotes either H or D,  $X_{\rm H}$  is  $[{\rm H}]/([{\rm H}] + [{\rm D}])$ , and  $X_{\rm D}$  is  $1 - X_{\rm H}$ . Figure S3 in the Supporting Information shows that  $k_{\rm pt}$  decreases with the increase of  $X_{\rm D}$ . In an isolated system such as a 7AI–water complex in an ether, the collision-induced formation of Nc is too slow to take place; that is, the exchange of any protic hydrogen isotope in Nc does not occur within the lifetime of Nc\*. The rise component of T\* fluorescence giving  $k_{\rm pt}$  can be further decomposed into two rise components of  $k^{\rm H}$  and  $k^{\rm D}$  as eq 4.

$$-\exp(-k_{\rm pt}t) = -\{X_{\rm H} \exp(-k^{\rm H}t) + X_{\rm D} \exp(-k^{\rm D}t)\}$$
(4)

Then, experimentally observed parameters of  $k^{H}$  and  $k^{D}$  consist of the above-described four different  $k_{pt}$  values according to eqs



**Figure 5.** Plots of  $k^{\rm H}$  (circles) and  $k^{\rm D}$  (squares) with variation of  $X_{\rm D}$  for Nc in DEE (opens) and DPE (closed). The total concentration of water was kept at 50 mM in every sample. Solid lines are the best linear fittings to obtain  $k^{\rm HH}$ ,  $k^{\rm HD}$ ,  $k^{\rm DH}$ , and  $k^{\rm DD}$  as  $(1060 \text{ ps})^{-1}$ ,  $(1230 \text{ ps})^{-1}$ ,  $(1660 \text{ ps})^{-1}$ , and  $(1930 \text{ ps})^{-1}$ , respectively, in DEE and as  $(1180 \text{ ps})^{-1}$ ,  $(1550 \text{ ps})^{-1}$ ,  $(1980 \text{ ps})^{-1}$ , and  $(2460 \text{ ps})^{-1}$ , respectively, in DPE.

5 and 6, respectively.

$$k^{\rm H} = k^{\rm HH} + (k^{\rm HD} - k^{\rm HH})X_{\rm D}$$
(5)

$$k^{\rm D} = k^{\rm DH} + (k^{\rm DD} - k^{\rm DH})X_{\rm D}$$
 (6)

As shown in Figure 2b, the value of  $K_{\rm Nc}$  varies considerably with protic hydrogen isotopes, so that we have calibrated  $X_{\rm H}$  and  $X_{\rm D}$  considering different  $K_{\rm Nc}$  values with H and D. When  $X_{\rm D}$  is 0.5, its calibrated value becomes 0.342 in DEE and 0.489 in DPE. The linear correlations of  $k^{\rm H}$  and  $k^{\rm D}$  with calibrated  $X_{\rm D}$ , shown in Figure 5, yield  $k^{\rm HH}$ ,  $k^{\rm HD}$ ,  $k^{\rm DH}$ , and  $k^{\rm DD}$  as  $(1060 \text{ ps})^{-1}$ ,  $(1230 \text{ ps})^{-1}$ ,  $(1660 \text{ ps})^{-1}$ , and  $(1930 \text{ ps})^{-1}$ , respectively, in DEE and  $(1180 \text{ ps})^{-1}$ ,  $(1550 \text{ ps})^{-1}$ ,  $(1980 \text{ ps})^{-1}$ , and  $(2460 \text{ ps})^{-1}$ , respectively. tively, in DPE. If the ESPT of Nc occurs concertedly and synchronously, the rule of the geometric mean that  $k^{\text{HD}} = k^{\text{DH}} = (k^{\text{HH}}k^{\text{DD}})^{1/2}$  should hold.<sup>40,57–59</sup> However, the rule is not valid in both DEE and DPE, indicating that two protons participating in the ESPT of Nc do not move at the same time but move in succession. Considering results described so far, thus, we conclude that the ESPT of 7AI via a water molecule occurs in an asymmetrically concerted fashion; two protons taking part in the ESPT of Nc move asynchronously, although ESPT occurs concertedly. Such asymmetric character usually appears in a concerted reaction when a single transition state is involved in the rate-determining step with forming an intermediate transiently but without accumulating the intermediate.<sup>7,8,34,40</sup>

A number of theoretical researchers have carried out calculations for the ESPT of 7AI-water or 7AI-alcohol complexes at various numbers of proton-transporting solvent (water or an alcohol) molecules.48,49 To explore the ESPT mechanism of 7AI in detail, they have studied how many solvent molecules are required to form the most stable cyclic complex, which species between a cationic intermediate and an anionic intermediate is preferred to form during ESPT, and which geometry the intermediate species has in the transition state. Recently, Duong and Kim have performed a detailed ab initio reaction dynamics study on the ESPT of a 1:1 7AI-water complex using variational transition-state theory calculations including multidimensional tunneling.<sup>48</sup> They have found that two protons participating in the H-bond bridge of the cyclic 1:1 7AI-water complex are transferred concertedly and yet asynchronously. The position of the variational transition state is very different from the conventional

Table 2. Comparison of Isotope-Dependent Rate ConstantsExtracted From Figure 5

medium	$k^{\rm HD}/k^{ m DH}$ (R1)	$k^{\rm HH}/k^{ m HD}$ (R2)	$k^{\rm HH}/k^{ m DH}$ (R3)	$k^{\rm HD}/k^{ m DD}$ (R4)	$k^{\rm DH}/k^{\rm DD}$ (R5)	
DEE	1.35	1.16	1.57	1.57	1.16	
DPE	1.28	1.31	1.68	1.59	1.24	

transition state, and vibrationally adiabatic energy surfaces in the first excited singlet state depend largely on isotopic substitutions, resulting in a large variational effect even at 0 K; the adiabatic surfaces are flat, and thus, the tunneling effect is not significantly large. Similarly, our results show that although the ESPT of Nc in ethers takes place in an asymmetrically concerted manner via tunneling, tunneling contribution to ESPT is not substantially large. In other words, there is something more important than tunneling in the ESPT of Nc because of the extremely small  $\beta_m$  value of a water molecule (see below).

To understand the ESPT mechanism of Nc at the molecular level and the medium polarity effect on the ESPT dynamics, we need to compare the ratios given in Table 2 thoroughly. First, we have figured out that  $k^{\text{HD}}/k^{\text{DH}}$  (R1) in DEE (1.35) is larger than R1 in DPE (1.28). As described above, if the ESPT of Nc took place concertedly and symmetrically, R1 should be unity. However, R1 is found to be significantly larger than unity in both DEE and DPE, so that the ESPT of Nc in ethers has been suggested to occur concertedly and yet asymmetrically. Thus, we can estimate the asymmetric degree of the ESPT reaction by considering how much the value of R1 deviates from unity. On the basis of the result that the value of R1 is larger in DEE than that in DPE, we suggest that the asymmetric character of ESPT is stronger in DEE than that in DPE. We attribute this to the larger dielectric constant of DEE (4.27 at 20 °C) than that of DPE (3.38 at 20 °C); the more polar DEE molecules lower the energy of the ionic intermediate state, which forms transiently during ESPT, as shown in Scheme 1, better than the less polar DPE molecules do. Second, we have found out that either one of  $k^{\text{HH}}/k^{\text{DD}}$  (R2) or  $k^{\text{DH}}/k^{\text{DD}}$  (R5) is significantly smaller than either one of  $k^{\text{HH}}/k^{\text{DD}}$  (R3) or  $k^{\text{HD}}/k^{\text{DD}}$  (R4) in both DEE and DPE, although R2 and R5 are very similar to each other and R3 and R4 are also close to each other. Those four ratios of R2-R5 represent kinetic single-isotope effects (KSIEs); R3 and R4 indicate the KSIEs of the hydrogen atom bound covalently to the nitrogen atom of the pyrrole ring, while R2 and R5 signify the KSIEs of the hydrogen atom H-bonded to the nitrogen atom of the pyridine ring. The result that R3 and R4 are larger than R2 and R5 designates that the ESPT rate is dependent mostly on the protic hydrogen isotope of the pyrrolic amino group regardless of the other hydrogen isotope H-bonded to the pyridinic nitrogen atom; that is, observed KIE values are correlated primarily with the first single-proton transfer from 7AI to the water monomer of Nc. In this regard, the observed KIE values of 1.8 and 2.0 in DEE and DPE, respectively, are not small for single-proton transfer, implying that the first single-proton transfer occurs via tunneling (see below). Eventually, these results support our suggestion that the double-proton transfer of Nc\* takes place in an asymmetrically concerted manner involving the rate-determining tunneling process; the first proton transfer occurs via tunneling through a barrier at the rate-determining step, and the second proton transfer takes place barrierlessly.

**3.4.** Arrhenius Plots. Figure 6 shows the Arrhenius plots of  $k_{pt}$  for the ESPT of Nc in water-added DEE, giving activation



**Figure 6.** Arrhenius plots for  $k_{\rm pt}$  of 7AI in DEE having 50 mM water. The best-fit lines reveal that while the activation energy ( $E_{\rm a}$ ) and the preexponential factor ( $A_{\rm f}$ ) with H as protic hydrogen atoms (open) are 0.96 kcal mol<sup>-1</sup> and 6.0 × 10<sup>9</sup> s<sup>-1</sup>, respectively,  $E_{\rm a}$  and  $A_{\rm f}$  with D (closed) are 1.06 kcal mol<sup>-1</sup> and 2.7 × 10<sup>9</sup> s<sup>-1</sup>, respectively.

energies  $(E_a)$  and preexponential factors  $(A_f)$ . Although the value of  $k_{pt}$  with H is significantly larger than the value with D, deduced  $E_{\rm a}$  values with H and D are very similar to each other and quite small. This implies that KIE, that is,  $k_{pt}(H)/k_{pt}(D)$ , is affected chiefly by the ratio of preexponential factors,  $A_{\rm f}({\rm H})/A_{\rm f}({\rm D})$ . Actually, the observed KIE value for the ESPT of Nc in DEE (1.8) is close to the  $A_{\rm f}({\rm H})/A_{\rm f}({\rm D})$  ratio (2.2). On the other hand, KIE is independent of temperature within our experimental errors, although  $k_{\rm pt}$  is dependent on temperature to some extent (Figure 6). These types of Arrhenius plots have been reported in solvent-mediated and enzymatic proton-transfer reactions.<sup>7,8,34,40,60</sup> In general, temperature-independent and large KIEs in enzymes have been explained with a model employing vibrationally enhanced proton tunneling. When the tunneling contribution to ESPT is large enough to be equally effective for both H and D, the ratio of  $A_{\rm f}({\rm H})/A_{\rm f}({\rm D})$  would become even much greater than unity. However, our observed KIE values for the ESPT of Nc (1.8 in DEE and 2.0 in DPE) are even much smaller than the values for the ESPT of 1:1 7AI-alcohol complexes in *n*-heptane.<sup>40</sup> Nonetheless, we consider that the KIE values are substantial for singleproton transfer, and thus, tunneling is operative through an appreciable barrier. Within the limit of the Born-Oppenheimer approximation, the potential energy hardly changes with isotope substitution, so that KIE originates mainly from changes of nuclear motions on the same potential energy surface.

Usually, configurational optimization in which solvent fluctuations play the main role is a prerequisite to proton tunneling, and solvent fluctuations decrease with the decrement of temperature due to the reduced solvent motions at low temperature. Accordingly, in the ESPT of Nc, the reorganization of the H-bond bridge with a little activation energy is required to form an optimized precursor configuration having proper H-bond distances and angles for pretunneling. As the temperature decreases, the  $k_{pt}$  value decreases somewhat because configurational optimization, which allows a proton to tunnel through the potential energy barrier, is retarded. Whereas intrinsic proton transfer via tunneling is isotopically sensitive, configurational optimization for pretunneling is isotopically insensitive; that is, configurational optimization is orthogonal to intrinsic proton transfer in the reaction coordinates of the potential hypersurface. Consequently, due to the extremely weak proton-transporting ability of a monomeric water molecule, more elaborate configurational optimization is required for proton tunneling, and thus, the tunneling contribution in the

ESPT of a 1:1 7AI-water complex is reduced, resulting in a small KIE.

### 4. CONCLUSIONS

The extraordinarily slow excited-state proton-transfer (ESPT) dynamics of 7-azaindole (7AI) along a water molecule has been investigated in aprotic polar media of diethyl ether (DEE) and dipropyl ether (DPE). The ESPT of a cyclically hydrogen (H)-bonded 1:1 7AI-water complex (Nc) in ethers occurs in an asymmetrically concerted fashion, rather than in a stepwise manner, via forming a charged intermediate species transiently with no accumulation of the intermediate. The ESPT of Nc is initiated by the proton acceptance of the water molecule from the pyrrolic amino group via tunneling to form a hydronium ion, which is the rate-determining step, and completed by the subsequent barrierless proton donation of the hydronium ion to the pyridinic imino group. Whereas proton diffusion in an aqueous solution having methodically well-organized H-bond networks has been known to take place swiftly through interconversion between Eigen and Zundel cations, proton transport by the water molecule of Nc has been observed to be extremely slow ( $\sim 1$  ns) because a water monomer has very weak proton-accepting ability in the absence of a H-bond network. The ESPT rate constant of Nc is larger in DEE than that in DPE because the more polar DEE molecules help the water monomer of Nc accept a proton relatively more facilely from 7AI at the rate-determining step by lowering the energy of ionic intermediates, that is, a deprotonated 7AI anion and a hydronium ion, which form transiently during ESPT. The asymmetric character of ESPT is stronger in DEE than that in DPE due to the larger dielectric constant of DEE. The ESPT rate is invariant regardless of water content dissolved in an ether up to 80 mM, but then, it increases with the water content. On one hand, at a low concentration of water ( $\leq$  80 mM), because the water molecule of Nc has a negligible chance to form a H bond with another water molecule, it is H-bonded to an ether molecule. However, at a high concentration of water (>80 mM), the water molecule of some Nc can be H-bonded to another water molecule to form a dimeric water chain, and thus, it can accept a proton readily from 7AI because of its enhanced proton-accepting ability. On the other hand, the ESPT rate is independent of deuterated water  $(D_2O)$  content up to the highest concentration of  $D_2O$  in this work (200 mM). This suggests that the association of a  $7AI-D_2O$ complex with another D<sub>2</sub>O molecule is much weaker than the association of a 7AI-H<sub>2</sub>O complex with another H<sub>2</sub>O molecule due to the lower hydrogen-bond ability of the D<sub>2</sub>O molecule. Small but significant kinetic isotope effects of ESPT have been observed, while the observed activation energy of the ESPT of Nc with H as a protic hydrogen isotope is similar to that with D. In conclusion, because of the anomalously weak proton-transporting ability of a water monomer without having a H-bond network, the elaborate reorganization of the H-bond bridge in Nc to form an optimized precursor configuration with proper H-bond distances and suitable bond angles is necessary for proton tunneling, resulting in anomalously slow proton transport of a water molecule.

# ASSOCIATED CONTENT

**Supporting Information.** Proton-accepting and protondonating abilities, fluorescence time constants, steady-state emission spectra,  $k_{pt}$  versus  $\alpha_m$  of proton-transporting solvents, and isotope-composition-dependent fluorescence kinetic profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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