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Accumulated Proton-Donating Ability of Solvent Molecules in Proton Transfer

Sun-Young Park and Du-Jeon Jang*

School of Chemistry, Seoul National University, NS60, Seoul 151-742, Korea

Received September 4, 2009; E-mail: djjang@snu.ac.kr

Abstract: Solvent-inventory experiments on the excited-state proton transfer of a 7-hydroxyquinoline molecule complexed cyclically with two alcohol molecules in the host medium of *n*-alkane have been carried out with various combinations of alcohols having different proton-donating abilities. Alcohol molecules participating in the hydrogen-bonded chain of the cyclic complex accelerate proton transfer in a concerted fashion by accumulating their proton-donating abilities. The rate-determining deprotonation of the alcohol molecule hydrogen-bonded directly to the imino group of 7-hydroxyquinoline is stimulated by the push-ahead effect of the next alcohol molecule in the hydrogen-bonded chain. Our results provide a clue at the level of molecules on the fundamental mechanistic elucidation of proton transport occurring through a proton wire consisting of diverse amino acids.

Introduction

Proton transfer is among the most common reactions in chemical and biological phenomena.[1−14] Biological proton transport generally takes place over long range through a hydrogen (H)-bonded network or chain of polar amino acids and water molecules in a protein.[7−11] There are many proteins that have H-bonded networks to serve the function of long-distance proton transport: alcohol dehydrogenase, bacteriorhodopsin, carbonic anhydrase, and cytochrome *c* oxidase.[6−13] In particular, bacteriorhodopsin is an example of a light-driven proton pump that is capable of moving protons across a cell membrane against the concentration gradient.[9,10] Thus, it is fundamentally and practically important to understand the details of such long-range proton-transfer processes. However, it is extremely difficult to dissect proton-transfer processes along a proton wire consisting of various amino acids due to the structural complexity, as well as massiveness, of proteins.[9−11,14,15] Thus, a simple model system is desirable to understand the molecular mechanism of long-range proton relay occurring in biological systems. To reduce the complexity of a biological system in a systematic way, we have employed a simplified model system of a 7-hydroxyquinoline (7HQ) molecule complexed cyclically with two different alcohol molecules having dissimilar proton-donating abilities.

Amphoteric aromatic molecules are especially interesting to study proton transfer because they can be experimental models for biological proton-relay systems.[7,17−21] In this regard, 7HQ, which has both a photoacidic enolic group and a photobasic imino group, has been extensively explored.[16,19,21−25] However, the two prototropic groups of 7HQ are too far from each other to donate or accept a proton directly. Thus, protic solvent molecules are indispensable for the excited-state proton transfer (ESPT) of 7HQ.[16,22−25] Solvent-mediated proton transfer occurs with three possible cases:[5] proton transfer from an acid to a solvent molecule with subsequent proton scavenging by a base (protolysis), direct proton relay from an acid to a base, and proton acceptance of a base from a solvent molecule with subsequent proton donation of an acid to the anionic solvent molecule (sovolysis) (Figure 1). Proton transfer via a H-bonded water chain tends to occur through protolysis,[21,22] whereas that via a H-bonded alcohol chain does so through solvolysis.[16,23]

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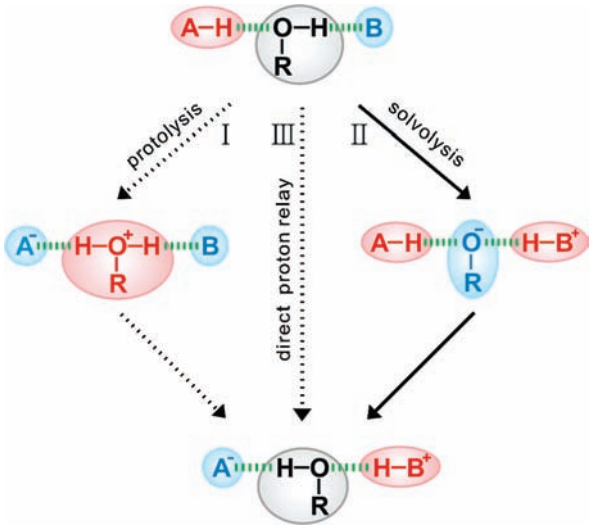

Figure 1. Double proton relay from an acid (AH) to a base (B) via a H-bonded alcohol molecule (ROH) occurring with three possible cases (I, II, or III). In case I (protolysis), an alcohol molecule is converted into a cation by binding with a proton dissociated from an acid, whereas, in case II (solvolysis), which is most plausible to occur, an alcohol molecule is turned into an anion by donating a proton to a base first. Case III (direct proton relay) is very hard to take place. Each arrow refers to a single barrier process.

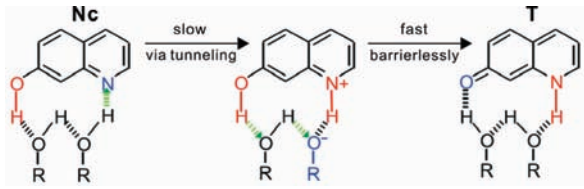

Figure 2. Triple proton relay in the excited-state tautomerization of 7HQ occurring via two H-bonded alcohol molecules in an asymmetrically concerted fashion. While the rate-determining step is the deprotonation of the alcohol molecule adjacent to the imino group, subsequent proton transfer from the enolic group to the transient alkoxide moiety is completed rapidly without accumulating the intermediate. Each arrow refers to a single barrier process.

On one hand, in a bulk alcoholic solvent, solvent reorganization to form a H-bonded complex of a 7HQ molecule with two alcohol molecules takes place prior to ESPT.[25] Because the solvent reorganization is the rate-determining step, it is hard to observe intrinsic ESPT directly in a bulk alcohol. On the other hand, in a nonpolar aprotic medium, a 7HQ molecule forms a cyclic complex with two alcohol molecules (Nc) at the ground state, so that ESPT can take place along a H-bonded alcohol chain directly without going through solvent reorganization.[16,23] It has been reported that the triple proton transfer of 7HQ along a H-bonded alcohol chain takes place through solvolysis in an asymmetrically concerted fashion and that its rate-determining step is the proton acceptance of the imino group of 7HQ from the adjacent alcohol molecule in Nc (Figure 2) because the rate constant of ESPT is influenced by the acidity, rather than the basicity, of the alcohol molecule.[16] However, the dynamics of proton relay along a heterogeneously H-bonded chain consisting of different solvent molecules has not been explored for any molecular systems yet. The dynamics is considered to be very important because the long-range proton transfer of biological systems often occurs through a proton wire made of H-bonded various amino acids.[15,17,26] Thus, we have employed a heterogeneously H-bonded chain as a simple model of the proton wire by combining two different alcohols.

Here we report solvent-inventory experiments, as altered proton-inventory experiments,[16] on the ESPT of a 7HQ molecule complexed cyclically with two alcohol molecules having different proton-donating abilities. Our results show that two alcohol molecules participating in the H-bonded chain of the cyclic complex accelerate proton transfer in a concerted fashion by accumulating their proton-donating abilities. The rate-determining deprotonation of the alcohol molecule H-bonded directly to the imino group of 7HQ is stimulated by the push-ahead effect of the next alcohol molecule in the H-bonded chain. The results can shed light at the level of molecules on the fundamental mechanistic elucidation of proton transport occurring through a proton wire consisting of diverse amino acids.

Experimental Section

While 7HQ (99%) was used as purchased from Acros, alcohols (anhydrous, ≥99.5%) and *n*-alkanes (anhydrous, ≥99%), purchased from Sigma-Aldrich, were distilled once and stored over molecular sieves of 4 Å prior to use. Alcohol molecules of Nc were varied for solvent-inventory experiments by dissolving 7HQ in *n*-alkanes containing two different alcohols. In a *n*-alkane, while the concentration of 7HQ was 10 μM, the total concentration of two alcohols was kept at 30 mM. Absorption spectra were measured with a UV/vis spectrophotometer (Scinco, S3100). Fluorescence 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). Fluorescence kinetic profiles, excited with third-harmonic pulses (355 nm) of a mode-locked Nd:YAG laser of 25 ps (Quantel, YG501), were detected using a streak camera of 10 ps (Hamamatsu, C2830) attached to a CCD detector (Princeton Instruments, RTE128H). Emission wavelengths were selected by combining band-pass filters and cutoff filters. Fluorescence kinetic constants were extracted by fitting kinetic profiles to computer-simulated exponential curves convoluted with instrument response functions. All the measurements were carried out at room temperature.

Results and Discussion

Absorption spectra of the normal species (N) of 7HQ in *n*-heptane shift to the red and lose their vibronic structures with the concentration increase of alcohols (Figure S1 of the Supporting Information), showing that 7HQ molecules associate with alcohol molecules via H-bonds, as reported in nonpolar aprotic media.[23,27] The association constant (K) can be deduced from the linear relationship between $[ROH]^{-2}$ and A^{-1} (see the Supporting Information for details), implying that a 7HQ molecule and two alcohol molecules form a 7HQ·$(ROH)_2$ complex. K decreases with the complexity of the alcohol but increases with the proton-donating ability (α) of the alcohol (Table S1 of the Supporting Information), indicating that the magnitude of α plays an important role in the formation of H-bonded complexes. The most stable ground-state structure of 7HQ·$(ROH)_2$ is reported to have the cyclic geometry of Nc.[24] The H-bond involving the imino group is calculated to be 0.2 Å longer than that involving the enolic group in Nc.[24] Thus, the H-bond strength of ROH···N is relatively low to determine

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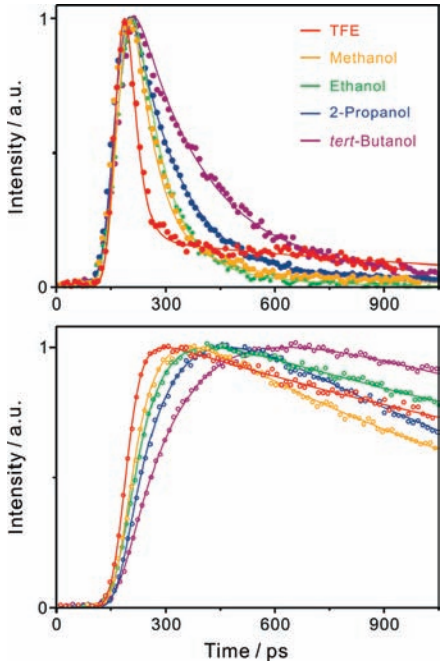

Figure 3. Alcohol-dependent fluorescence kinetic profiles of 10 μM 7HQ in *n*-heptane having 30 mM of indicated diverse alcohols. Samples were excited at 355 nm and monitored at 420 nm for the decay kinetics of the normal species (top) and at 550 nm for the rise kinetics of the tautomeric species (bottom). Solid lines are the best-fitted curves to extract fluorescence kinetic constants, and TFE refers to 2,2,2-trifluoroethanol.

the formation of Nc. On the other hand, the absorption band of the tautomeric species (T) of 7HQ, presumably at 410 nm,[21] was not observed in any explored alcohols, signifying that T does not exist in the ground state. However, the excitation of Nc at 345 nm gives rise to prominent T* fluorescence at 530 nm as well as N* fluorescence at 370 nm (Figure S2 of the Supporting Information), suggesting that the ESPT of 7HQ is operative in *n*-heptane in the presence of an alcohol. Figure S2 shows that N* fluorescence decreases with the α value of an alcohol, inferring that the strength of α plays an important role in the formation of T* via ESPT (see the Supporting Information for details).

After excitation of Nc at 355 nm, fluorescence kinetic profiles of N* and T* in *n*-heptane were obtained at 420 and at 550 nm, respectively, with variation of alcohols having different α values (Figure 3). N* fluorescence shows biexponential decay, while T* fluorescence does single rise and single decay (Table S2 of the Supporting Information). T* fluorescence rises concomitantly with the fast-decay component of N* fluorescence for every alcohol, implying that the ESPT of Nc occurs to form T* without accumulating any intermediates. Considering relative errors, we take the fast-decay time of N* rather than the rise time of T* for the further consideration of the ESPT time (k_{pt}^{-1}) of Nc. The slow-decay component of N* fluorescence is attributed to the relaxation of excited noncyclic 7HQ·$(ROH)_2$ or 7HQ·(ROH). k_{pt} does not vary with the concentration of an alcohol although the fractional initial amplitudes of the two decay components of N* fluorescence do, indicating that the collision-induced formation of Nc does not occur to conduct ESPT within the lifetime of N*. The ESPT time of Nc tends to decrease with the α value of the alcohol. This agrees well with the previous report[16] that the ESPT of 7HQ along a H-bonded alcohol chain occurs in an asymmetrically concerted fashion with a rate-determining step, which is the proton acceptance of

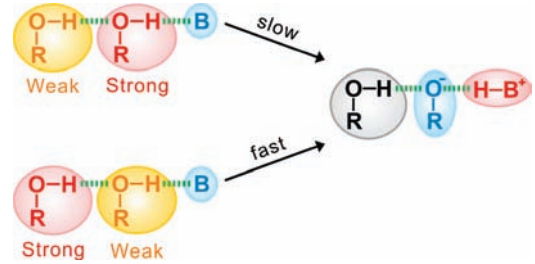

Figure 4. Schematic diagram, where each arrow refers to a single barrier process, showing that the rate of proton transfer from an alcohol molecule to a base depends on the sequence of two different alcohol molecules. When W, rather than S, is H-bonded to the base directly to initiate the reaction, the rate is relatively fast. This suggests that proton transfer from W to the base is pushed by S from the backside along the proton-transfer pathway, resulting in the accumulation of proton-donating abilities of two alcohol molecules. When S is adjacent to the base, W hardly stimulates the deprotonation of S because S alone is acidic enough to donate a proton to the base.

the imino group from a directly H-bonded alcohol molecule via tunneling, because the rate constant of ESPT is affected by the acidity, rather than the basicity of the alcohol. Otherwise, *tert*-butanol, which has the largest proton-accepting ability among all the employed alcohols, should give the shortest ESPT time of Nc.

Considering that long-range proton relay in biological systems often takes place through a proton wire made of H-bonded diverse amino acids,[15,17,26] we have employed H-bonded mixed-alcohol chains having different alcohol molecules as a simple model of the proton wire (Figure 4) and investigated the ESPT dynamics of 7HQ along the mixed-alcohol chain. Figure 4 shows two possible cases in which two different alcohol molecules are sequentially H-bonded to a base: one is that the relatively strong-acidic alcohol (S) is H-bonded to the base directly, and the other case is that the relatively weak-acidic alcohol (W) is. It would be an issue whether the reactions of these two cases occur at the same rate. If two cases have different rate constants, then it would attract considerable attention to find out which case has the larger rate constant. To tell the conclusion first, these two cases have different rate constants, and the latter case has the larger rate constant because the rate-determining proton donation of W to the imino group is stimulated by the push-ahead effect of S. This suggests that the proton-donating abilities of alcohol molecules are accumulated to accelerate proton transfer. To find the answer to this question, we have carried out solvent-inventory experiments, as altered proton-inventory experiments,[16,20,22,28] for the ESPT rate of Nc by varying the mole fractions of two alcohols systematically. k_{pt} decreases with the increase of X_W, which is [W]/([S] + [W]) (Figure 5).

In proton-inventory experiments,[16] all of three protic hydrogen atoms that participated in the ESPT have been considered because any of them can be either ^{1}H (H) or ^{2}H (D). However, in solvent-inventory experiments, the proton of the enolic group of 7HQ remains the same without considering which alcohol molecules are H-bonded to the 7HQ molecule although three protic hydrogen atoms undergo transfer along a H-bonded chain. While protic hydrogen atoms (H or D) are varied in proton-inventory experiments, alcohol molecules (S or W) as solvent molecules are exchanged in solvent-inventory experiments. Thus, only two protic protons belonging to the alcohol molecules

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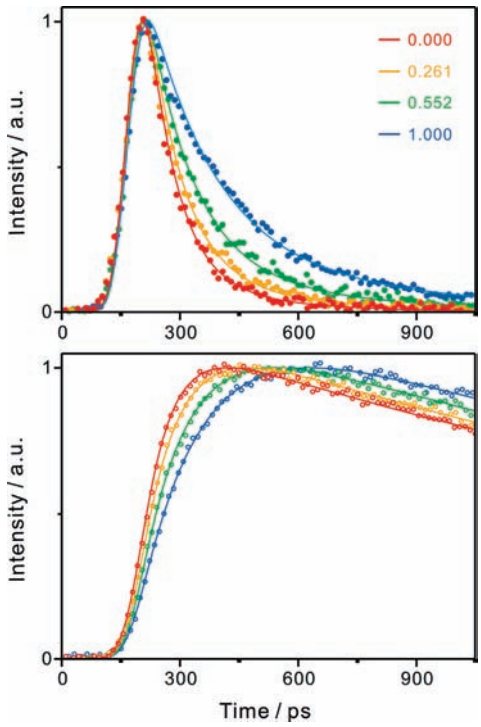

Figure 5. Alcohol composition-dependent fluorescence kinetic profiles of 10 μM 7HQ in *n*-heptane having 30 mM total concentrations of ethanol and *tert*-butanol. Samples were excited at 355 nm and monitored at 420 nm for the decay kinetics of the normal species (top) and at 550 nm for the rise kinetics of the tautomeric species (bottom). The mole fractions of *tert*-butanol out of the two alcohols (X_W) are indicated inside, and solid lines are the best-fitted curves to extract time constants.

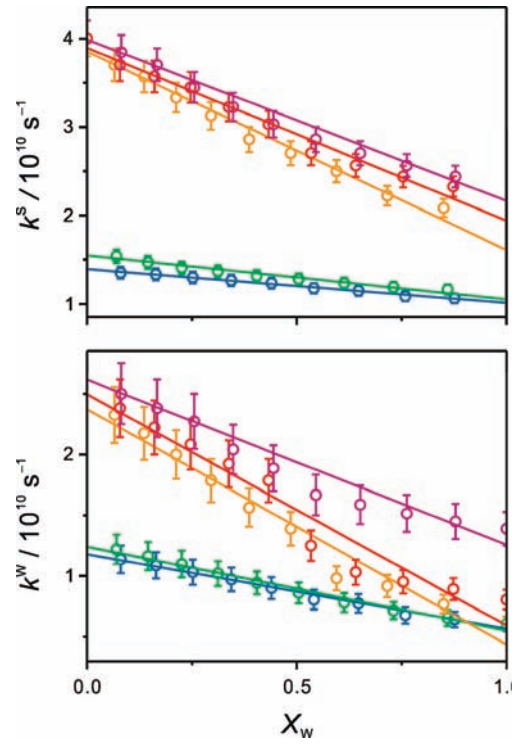

Figure 6. Plots of k^S (top) and k^W (bottom) with variation of X_W for 7HQ of 10 μM in *n*-heptane having 30 mM of the total concentration of two alcohols. Solid lines are the best linear fittings to obtain k^{SS}, k^{WS}, k^{SW}, and k^{WW} in five individual combinations: TFE and ethanol (purple), TFE and 2-propanol (red), TFE and *tert*-butanol (yellow), methanol and *tert*-butanol (green), and ethanol and *tert*-butanol (blue). Standard deviations are 5% for k^S and 10% for k^W. The plots of k^W in three combinations involving TFE deviate from the fittings to some extent because TFE is much more acidic than the other employed alcohols.

of Nc should be considered in the solvent-inventory experiments because the enolic proton belonging to 7HQ is not varied. Accordingly, Nc can have four different types of alcohol exchange: SS, WS, SW, and WW, where two successive characters denote two alcohol molecules H-bonded to the acidic enol of 7HQ in turn (Figures 2 and 4). We have employed five combinations of two different alcohols having dissimilar α values: TFE and ethanol (**1**), TFE and 2-propanol (**2**), TFE and *tert*-butanol (**3**), methanol and *tert*-butanol (**4**), and ethanol and *tert*-butanol (**5**). The k_{pt} values of the above four types of Nc* are denoted as k^{SS}, k^{WS}, k^{SW}, and k^{WW}, respectively. Because $X_S = 1 - X_W$, we can deduce eqs 1 and 2 in accordance with the alcohol H-bonded to the imino group of 7HQ because the protonation of the imino group is the rate-determining step of ESPT.

$$d[*S]/dt = -\{(1 - X_W)k^{SS} + X_W k^{WS}\}[*S] \quad (1)$$

$$d[*W]/dt = -\{(1 - X_W)k^{SW} + X_W k^{WW}\}[*W] \quad (2)$$

where $*$ denotes either S or W. Because the association constants of Nc vary considerably with alcohols (Table S1), we have calibrated X_S and X_W considering different *K* values with S and W.[28,30−32] When $X_W = 0.5$, the calibrated value becomes 0.445 for combination **1**, 0.433 for combination **2**, 0.386 for combination **3**, 0.405 for combination **4**, and 0.440 for combination **5**. The fast decay component ($\tau_{fast} = k_{pt}^{-1}$) of Nc* can be further decomposed into two decay components of k^S and k^W as

$$\exp(-k_{pt}t) = X_S \exp(-k^S t) + X_W \exp(-k^W t) \quad (3)$$

where k^S and k^W consist of the four different k_{pt} values according to

$$k^S = k^{SS} + (k^{WS} - k^{SS})X_W \quad (4)$$

$$k^W = k^{SW} + (k^{WW} - k^{SW})X_W \quad (5)$$

The linear correlations of k^S and k^W with calibrated X_W (Figure 6) yield k^{SS}, k^{WS}, k^{SW}, and k^{WW}, given in Table 1, in five combinations. If ESPT occurs in a concerted fashion, then, according to the rule of the geometric mean, $k^{WS} = k^{SW} = (k^{SS}k^{WW})^{1/2}$ should hold.[20,28−32] However, our results show that $k^{WS} \neq k^{SW} \neq (k^{SS}k^{WW})^{1/2}$ in all of the five combinations, suggesting that two protons move in succession. In other words, the ESPT reaction of 7HQ along a mixed-alcohol chain occurs concertedly and yet asymmetrically.[16]

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Table 1. Rate Constants Extracted from Solvent-Inventory Experiments with Various Combinations of Alcohols

medium[a]	alcohol combination[b]	$(k^{SS})^{-1}$/ps	$(k^{WS})^{-1}$/ps	$(k^{SW})^{-1}$/ps	$(k^{WW})^{-1}$/ps	k^{SW}/k^{WS}
n-heptane	TFE and EtOH (**1**)	25	46	38	80	1.21
	TFE and PrOH (**2**)	26	51	40	169	1.28
	TFE and BuOH (**3**)	26	61	42	230	1.45
	MeOH and BuOH (**4**)	65	94	80	181	1.18
	EtOH and BuOH (**5**)	72	99	85	176	1.16
n-decane	MeOH and BuOH (**4′**)	66	121	108	188	1.12
n-dodecane	MeOH and BuOH (**4″**)	68	131	118	196	1.11

[a] The viscosities of *n*-heptane, *n*-decane, and *n*-dodecane at 25 °C are 0.39, 0.84, and 1.38 cP, respectively.[33,34] [b] Symbols for alcohols are TFE for 2,2,2-trifluoroethanol, MeOH for methanol, EtOH for ethanol, PrOH for 2-propanol, and BuOH for *tert*-butanol.

As results of the proton-inventory experiments of the 7HQ·(ethanol)$_2$ complex, it has been reported that the ESPT of the complex occurs via tunneling at the rate-determining step, which is the protonation of 7HQ by the deprotonation of the alcohol molecule H-bonded directly to the imino group of 7HQ, and that k^{HD} is smaller than k^{DH} due to tunneling.[16] Of note is that the ordering of three protic hydrogen atoms in the solvent-inventory experiments is opposite to that in the proton-inventory experiments and that the enolic proton of 7HQ should be excluded to compare solvent-inventory results with proton-inventory results. Thus, k^{DHH} ((250 ps)$^{-1}$) and k^{HDD} ((220 ps)$^{-1}$) in the proton-inventory experiments[16] can be reduced to k^{HD} and k^{DH}, respectively, and then, k^{HD} and k^{DH} can be compared with k^{SW} and k^{WS}. Considering the relative ESPT rates of Nc only to put it in an extreme way, we suggest that H and D correspond simply to S and W, respectively. Accordingly, at first thought, k^{SW} is supposed to be smaller than k^{WS} as reported.[16] However, on the contrary to the results of the proton-inventory experiments,[16] there is an exceptionally noticeable point in our results; that is, the k^{SW} value is significantly larger than the k^{WS} value in every combination (Table 1), as depicted in Figure 4. This disagrees with the fact that the rate constant increases with the α value of the alcohol molecule in Nc because the rate-determining step is the protonation of the imino group of 7HQ.[16] Even in the proton-inventory results of 7HQ·(ethanol)$_2$, k^{HD} is smaller than k^{DH}.[16] However, our results show that proton transfer along a H-bonded mixed-alcohol chain is facilitated when W, rather than S, initiates the protonation of 7HQ by donating a proton to the imino group. Then, we can infer that the proton transfer from W to 7HQ is pushed by S from the backside along the proton-transfer pathway of Nc*. This push-ahead effect leads to accumulate the proton-donating abilities of two alcohols in Nc*, resulting in the acceleration of ESPT in a concerted fashion. On the contrary, when S triggers the proton transfer, W hardly helps S to donate a proton to the imino group because S alone is acidic enough to initiate ESPT. Consequently, k^{SW} is larger than k^{WS} due to the cooperative proton-donating effect of S.[31]

The strength of the push-ahead effect, the dependence of the ESPT rate on the accumulated proton-donating effect, can be estimated from the ratio of k^{SW}/k^{WS}. The ratios are noticeably larger than unity for all the explored combinations as given in Table 1, indicating that there are significant push-ahead effects. Furthermore, the ratio becomes larger with the increase of a gap between the α values of two alcohols in a combination, suggesting that the dependence of the ESPT rate on the accumulated proton-donating effect increases with the gap. However, considering that the ratio of k^{HD}/k^{DH} in the proton inventory experiment was 0.88,[16] which was substantially smaller than unity, we can infer that the push-ahead effect was not observed for the ESPT of 7HQ·(ethanol)$_2$. It is reported that proton transfer of the 7HQ·(ethanol)$_2$ complex along a H-bonded alcohol chain occurs via tunneling and that the ESPT of 7HQ·(ethanol)$_2$ has a large kinetic isotope effect of 15.0.[16] Therefore, the push-ahead effect is not observable in the ESPT of 7HQ·(ethanol)$_2$ because the tunneling effect, rather than the push-ahead effect, determines the rate in the proton-inventory experiments. On one hand, comparing three combinations of **3**, **4**, and **5** involving *tert*-butanol as W, we have found that the ratio of k^{SW}/k^{WS} increases with the α value of S. In particular, the ratio for combination **3** is much larger than the ratio for combination either **4** or **5** because TFE has an extremely large α value in comparison with other employed alcohols. In other words, when W initiates ESPT, the larger α value S has, the stronger the push-ahead effect is. On the other hand, comparing three combinations of **1**, **2**, and **3** involving TFE as S, we have found that k^{WS} increases on a large scale whereas k^{SW} enlarges very slightly with the increase of the α value of W. It can be inferred that although it is W that is H-bonded to the imino group directly, TFE of S, rather than W, plays the main role in the protonation of the imino group. This is attributed to the α value of TFE, much larger than the α values of the other explored alcohols.

Solvent-inventory experiments have been carried out in different *n*-alkanes as well, whose relative permittivities are very similar but whose viscosities are quite different. Table 1 indicates that the strength of the cooperative push-ahead effect decreases slightly with the viscosity increase of a host *n*-alkane medium. The ESPT of Nc occurs via tunneling and the heavy-atom reorganization, which is required to reach the optimal configuration having proper bond angles and short H-bond lengths for pretunneling, becomes slower with the increase of the medium viscosity.[16] Thus, the heavy-atom reorganization becomes more important in the overall rate of ESPT, resulting in the reduction of the cooperativity effect in a viscous medium. This work has addressed a question that is germane to the fundamental mechanism of the long-range proton transport occurring through a proton wire consisting of H-bonded diverse amino acids.

Conclusion

The excited-state proton transfer (ESPT) of 7-hydroxyquinoline (7HQ) along a H-bonded chain consisting of different alcohol molecules with dissimilar proton-donating abilities has been explored by carrying out solvent-inventory experiments with various combinations of alcohols. The two alcohol molecules of Nc (a cyclic complex of a 7HQ molecule with two alcohol molecules) accelerate proton transfer in a concerted fashion by accumulating their proton-donating abilities. When the relatively weak-acidic alcohol (W), rather than the relatively strong-acidic alcohol (S), of two different alcohol molecules initiates the protonation of 7HQ by donating a proton to the imino group, the proton transfer from W to 7HQ is pushed by S from the backside along the proton-transfer pathway of Nc*

to facilitate the ESPT of Nc. The strength of the push-ahead effect increases with a gap between the proton-donating abilities of two alcohols in a combination and decreases with the viscosity of a host *n*-alkane medium.

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Supporting Information Available: Absorption spectra, association constants, steady-state emission spectra, and fluorescence kinetic constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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