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Long-Range Proton Relay Shows an Inverse Linear Free Energy Relationship Depending on the pK_a of the Hydrogen-Bonded Wire

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ABSTRACT: The long-range proton transfer dependence on the pK_a of hydroxyl molecules in hydrogen (H)-bonded wires was investigated using quantum mechanical calculations. The triple proton transfer takes place in an asynchronous and concerted fashion between carboxylic and imidazole groups linked by two H-bonded chain molecules. Four hydroxyl molecules with different acidities, water, 2-fluoromethanol, 2,2,2-trifluoromethanol, and phenol, were used to construct sixteen H-bonded wires. The proton transfer rate increased with the acidity of the chain molecules. The rate was found to be more dependent on the particular chain molecule with relatively small structural changes in the wire, which can act as a solvent, rather than molecules with larger O-H bond cleavage in the TS. An inverse

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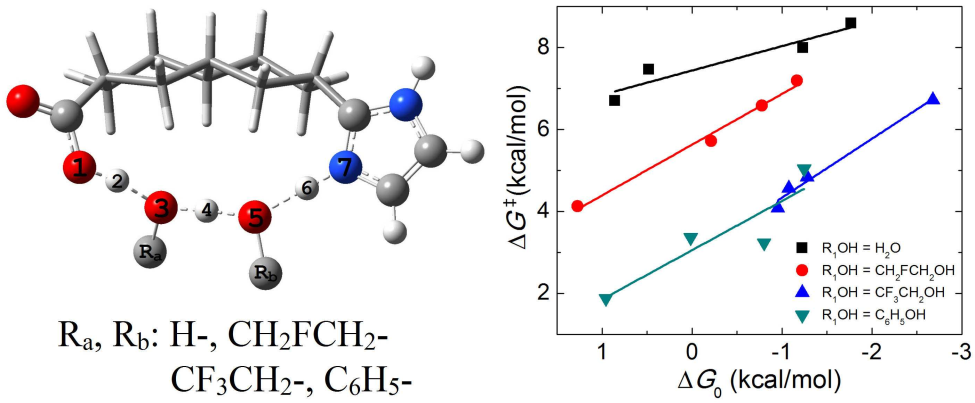
linear free energy relationship was recognized for the first time in the multiple proton transfer with a change in hydroxyl molecules. The activation and reaction free energies decreased and increased, respectively, with respect to the acidity of the chain molecules. This inverse LFER can be explained by the pK_a slide rule, in which the pK_a dependence of H-bond strength in a wire has an opposite trend for chain molecules that donate and accept a H-bond. Therefore, the pK_a of wire molecules can have different roles, which leads to the very unusual relationship between the activation and reaction free energies.

TOC GRAPHICS



R_a, R_b: H-, CH_2FCH_2-
CF_3CH_2-, C_6H_5-

KEYWORDS. Long-range proton transfer, Grotthuss mechanism, inverse linear free energy relationship, hydrogen-bonded wire, pK_a slide rule.

Introduction

Proton transfer plays an important role in many chemical and biological processes.[1-3] In a protic solvent or in a confined environment such as a proton channel or an enzyme active site, proton transfer can take place over long distances through hydrogen (H)-bonded networks, and some polar amino acid residues and/or solvent molecules mediate this proton transfer.[4-6] Therefore, long-range proton transport must be influenced by the properties of

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mediating solvent molecules and/or amino acid residues in a protein. Recently Riccardi *et al.*[7] suggested that long-range proton transfers in solutions and within enzymes can exhibit very different molecular details depending on the pK_a values of participating groups and electrostatic interactions with the environment. Mohammed *et al.*[8, 9] measured proton transfer through water bridges and suggested that proton transfer occurs by a sequential Grotthuss-type hopping mechanism through the H-bond network of the solvent.

Solvent structures near mediating water molecules must play an important role in the dynamics of direct proton relay. It has recently been shown that when the end groups have acidic or basic pK_a values, proton transfer take place through protolytic or solvolytic pathways with H_3O^+ or OH^- character in the TS, respectively; therefore, the rate constant becomes larger when the mediating water has H-bond accepting or donating solvent molecules, respectively.[10] The dynamics of direct multiple proton relay will be much more complicated when non-identical hydroxyl molecules are components of a single H-bonded chain, as is found in many biological systems. Kwon *et al.*[11] found that the rate constants of double proton transfer in 7-azaindole-alcohol complexes were dependent on the acidity of mediating alcohol molecules in the H-bonded wire. Recently, a triple proton transfer process through an H-bonded wire has been investigated with 7-hydroxyquinoline (7HQ) complexes and two different alcohol molecules in a non-polar solution.[12, 13] Very interestingly, the observed rate was relatively fast when a less acidic alcohol, rather than a more acidic one, was directly H-bonded to the base (imino-group) in the mixed 7HQ-R_aOH-R_bOH ($R_a \neq R_b$) complex to start the proton transfer reaction. This observation was explained based on a hypothesis that proton transfer from R_bOH to the base is promoted by a more acidic R_aOH from the back along the asynchronous solvolytic pathway leading to accumulation of proton-donating abilities.[14] The proton transfer of R_bOH was stimulated by the so-called

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"push-ahead effect" of the R_aOH in the H-bonded chain, and the strength of this effect increased with the gap between the proton-donating abilities of the two alcohols.[14]

The acidity of mediating alcohols would obviously affect the rates of direct long-range proton relay. However, the role of mediating molecules in direct proton relay has rarely been studied either experimentally or theoretically, and the accumulative role of chain molecules is not yet fully understood. If the so-called "push-ahead effect" of mediating alcohols plays an important role in direct multiple proton relay, it would not be limited to the excited-state 7HQ complex. We, therefore, developed a theoretical model to investigate the role of mediating hydroxyl molecules, in which carboxylic and imidazole moieties at the ends of *trans*-decalin were linked by an H-bonded chain made up of two hydroxyl molecules, as depicted in Figure 1.

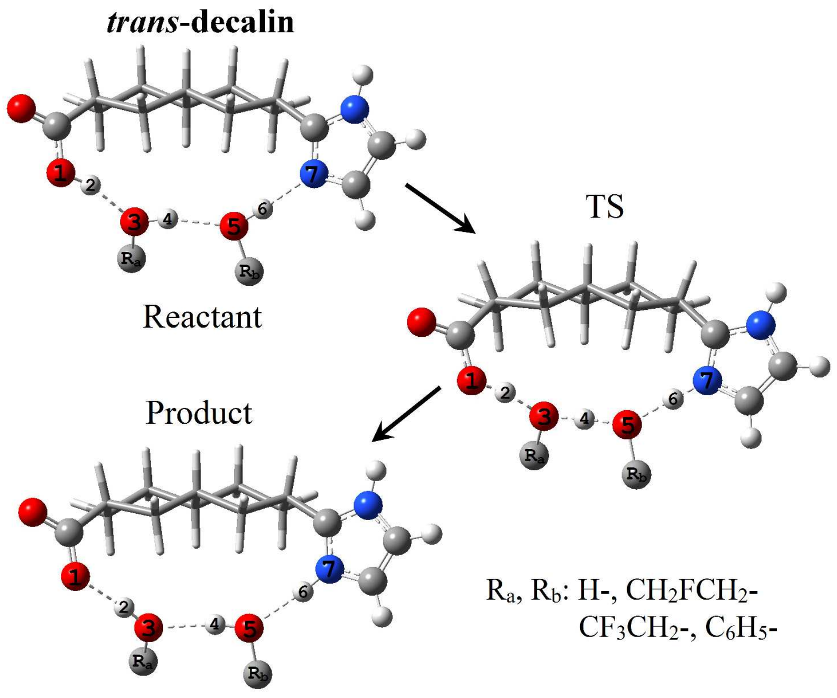

Figure 1. The multiple proton transfer process via an H-bonded chain made up of two different alcohols.

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Carboxylic and imidazole groups are biologically important molecules, which are moderately acidic and basic, respectively, in aqueous solution. Therefore, this model could be used to mimic the long-range proton relay in biological systems. The distance between carboxylic group (donor) and imidazole (acceptor) in this model was about 7.5 Å, which was sufficient for two hydroxyl molecules to form a H-bonded chain. Among four hydroxyl molecules with different acidities (water, 2-fluoromethanol, 2,2,2-trifluoromethanol, and phenol), different pairs were selected as H-bonded chain components in this study.

Computational Methods

The structures at all stationary points (reactant, product, and TS) were fully optimized in aqueous solution at the M06-2X[15] level using the *Gaussian 09* program.[16] The MIDIX[17] basis set was used for the *trans*-decalin skeleton, and the 6-31+G(d,p) basis set was used for all other structures. Solvent effects were calculated using the Solvation Model D (SMD).[18] Each minimum and TS was confirmed to have zero and one imaginary frequency, respectively, and free energies were calculated using the frequencies in solution.

The pK_a value of the generic acid HA was calculated from the following equation:

$$pK_a = \Delta G^0(aq)/2.303RT$$

where $\Delta G^0(aq)$ is the free energy of dissociation of HA as determined by the thermochemical cycle below[19] (with $n = 3$).

$$\begin{tikzcd}
HA\bullet nH_2O_{(g)} \arrow[r, "\Delta G^\circ(g)"] \arrow[d, "\Delta G^\circ_S(HA\bullet nH_2O)"] & H^+_{(g)} \arrow[d, "\Delta G^\circ_S(H^+)"] & + & A^-\bullet nH_2O_{(g)} \arrow[d, "\Delta G^\circ_S(A^-\bullet nH_2O)"] \\
HA\bullet nH_2O_{(aq)} \arrow[r, "\Delta G^\circ(aq)"] & H^+_{(aq)} & + & A^-\bullet nH_2O_{(aq)}
\end{tikzcd}$$

From the thermochemical cycle, $\Delta G^0(aq)$ can be calculated as

$$\Delta G^0(aq) = G^0(H^+, aq) + G^0(A^-\cdot nH_2O, aq) - G^0(HA\cdot nH_2O, aq)$$

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$$= \Delta G^0(\mathrm{g}) + \Delta\Delta G_S^{\ 0}$$

where $\Delta\Delta G_S^{\ 0} = \Delta G_S^{\ 0}(\mathrm{H}^+) + \Delta G_S^{\ 0}(\mathrm{A}^-\cdot n\mathrm{H_2O}) - \Delta G_S^{\ 0}(\mathrm{HA}\cdot n\mathrm{H_2O})$.

The standard-state free energy of solvation maybe written as $\Delta G_S^{\ 0}(\mathrm{X}) = \Delta G_S^{\ *}(\mathrm{X}) + \Delta G_C^{\ 0}$, where $\Delta G_S^{\ *}(\mathrm{X})$ corresponds to the solvation free energy in a process in which the concentration of solute X is the same in the gas phase and in a dilute liquid, and $\Delta G_C^{\ 0}$ is the free energy required to bring the concentration to their standard-state values. The standard states of a 1 atm ideal gas and a 1 M ideal solution are approximately 1.89 kcal/mol. In this work, we used the value of $G^0(\mathrm{H}^+, \mathrm{aq})$ is –6.28 kcal/mol, which comes from the Sackur-Tetrode equation,[20, 21] and the value of $\Delta G_S^{\ 0}(\mathrm{H}^+)$ is –264.0 kcal/mol,[22] which corresponds to $\Delta G_S^{\ *}(\mathrm{H}^+)$ is –265.9 kcal/mol. All structures of protonated hydroxyl molecules were fully optimized in the gas phase and in solution at the M06-2X/6-311++G(2df,2pd) level.

Results and Discussion

Hydroxyl solvent-mediated long-range proton transfer can occur via three pathways:[9, 23] proton transfer from an acid to solvent followed by proton scavenging by a base (sequential protolysis), water hydrolysis by base with subsequent neutralization of the acid by hydroxide anion (sequential solvolysis), and direct proton relay from an acid to a base (Scheme 1). When the end groups have large acidic or basic pK_a values compared to water, sequential protolysis or solvolysis mechanisms are more favorable, respectively. When the end groups have moderate acidic or basic pK_a values, direct multiple proton relay can take place through concerted but asynchronous protolytic or solvolytic pathways (Scheme 1), respectively, which can be used as models of the intrinsic classical Grotthuss[24] or "proton-hole" transfer[25] mechanism, respectively. In this study, $\mathrm{R_aOH}$ and $\mathrm{R_bOH}$ denote hydroxyl molecules bound to carboxylic and imidazole groups, respectively.

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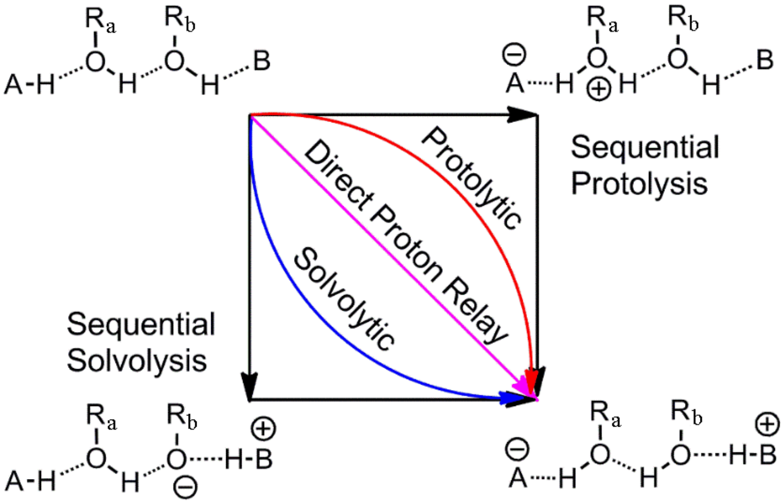

Scheme 1. Possible mechanisms of long-range proton transfer.

While no H_3O^+ or OH^- ions are generated as intermediates in the pathways, the transition state (TS) can have H_3O^+ or OH^- character. In the protolytic TS of the direct proton relay (Scheme 1), R_aOH has cationic character by accepting a proton partly dissociated from an acid while R_bOH hardly changes. However, in the solvolytic TS, R_bOH has anionic character by donating a proton partly to the base while R_aOH hardly changes. We denote *precedent* alcohols as those that accept or donate proton early and have cationic or anionic character in the TS of the protolytic or solvolytic direct proton relay, respectively, and *succedent* alcohols as those that form an H-bond to the *precedent* alcohols without a significant structural change. The *succedent* alcohols can also be considered a solvent in the first solvation shell that stabilizes the solute by forming an H-bond.

The pK_a values of the four hydroxyl molecules along with carboxylic group (which is approximate as pK_a of acetic acid) and ImH^+ are listed in Table 1. From these four molecules, sixteen different H-bonded chains could be derived. Structures of reactants, products, and TSs for the triple proton transfer were fully optimized at the M06-2X/6-31+G(d,p)/MIDIX level in aqueous solution.

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Table 1. pK_a values of acid, base, alcohols, and Löwdin partial charges of the hydroxyl groups

	CH_3CO_2H	ImH^+	H_2O	CH_2FCH_2OH	CF_3CH_2OH	C_6H_5OH
pK_a	4.75 [26]	6.95 [26]	15.74	14.42 [27]	12.37 [28]	9.89 [26]
O charge			–0.63	–0.54	–0.49	–0.43

Only one asynchronous and concerted solvolytic TS was found without any intermediate for these reactions. In the reactant, the H-bond distances between R_bOH and imidazole (O_5–$H_6\cdots N_7$) were 1.85, 1.75, 1.66, and 1.64 Å for water, 2-fluoromethanol, 2,2,2-trifluoromethanol, and phenol, respectively. Note that for a given R_bOH, four H-bonded chains could be constructed because four hydroxyl molecules were used for R_aOH; therefore, each distance listed above is an average value of these four H-bonded chains. As the H-bond length becomes shorter, the H-bond energy becomes larger. This is true in general for a single H-bond. However, because it is not easy to estimate the energy of a specific H-bond in a relay chain, it is necessary to investigate whether the general relation between H-bond length and energy works equally well in the H-bonded relay chain. We used the natural bond order (NBO) analysis of H-bond,[29-31] where the charge transfer interaction between the lone pair electron of oxygen (or nitrogen) and anti-bonding orbital of O–H bond is an important component of the H-bond, which therefore can be used to estimate the strength of H-bond; the larger the charge transfer interaction, the stronger the H-bond becomes. A good correlation was found between the charge transfer energies of each H-bond in the H-bonded chain and its lengths (Table S1 and Figure S1), which suggests that in general the H-bond becomes stronger as its length becomes smaller in the H-bonded wire.

The H-bond energies with phenol and water would be the largest and smallest, respectively. These trends are in good agreement with the pK_a slide rule, in which the strength of the A–H···B bond increases with decreasing value of $\Delta pK_a = pK_a(A–H) −$

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$pK_a(B^+–H)$.[32] In the product, the H-bond distances of $N_7–H_6\cdots O_5$ were 1.90, 1.92, 1.99, and 2.08 Å for water, 2-fluoromethanol, 2,2,2-trifluoromethanol, and phenol, respectively. The H-bonds of ImH^+ with water and phenol were the strongest and weakest, respectively. To apply the pK_a slide rule in this case, we need the pK_a values of the protonated hydroxyl molecules. The pK_a value of H_3O^+ is −1.74 in water;[33] however, there are no experimental data for the other molecules. We calculated the pK_a values at the M06-2X/6-311++G(2df,2pd) level based on the thermodynamic cycle described previously,[19] which were –0.81, –2.70, –5.59, and –8.32, respectively, for H_3O^+, $CH_2FCH_2OH_2^+$, $CF_3CH_2OH_2^+$, and $C_6H_5OH_2^+$. These results indicate that the H-bond strength of the product also satisfies the pK_a slide rule. The Löwdin partial charges[34] of OH groups are also listed in Table 1. The strength of the H-bond depends on the magnitude of the partial charge. An alcohol with a large negative charge on oxygen can act as a good H-bond acceptor. Therefore, among the four tested molecules, H_2O and C_6H_5OH were the best and worst H-bond acceptors, respectively.

The distance between the O_1 and N_7 atoms (donor–acceptor distance) decreased from 7.20 Å in the reactant to 6.75 Å at the TS and was restored to its original value in the product. The two end groups move closer with a minimum distance at the TS, a phenomenon that has also been observed in previous studies.[35, 36] Several distances of selected bonds at the TS with two identical molecules in the chain are listed in Table 2. The $O_1–H_2$ and $N_7–H_6$ distances were quite small (averaging approximately 1.05 Å) whereas the $O_3–H_2$ and $O_5–H_6$ distances were quite long (averaging approximately 1.55 Å). Additionally, the H_4 proton was closer to the O_3 atom than the O_5 atom; the $O_3–H_4$ and $O_5–H_4$ distances were approximately 1.17 Å and 1.24 Å, respectively. These results indicate that, in the TS, R_bOH has a larger structural change than R_aOH and an R_bO^--like moiety with a partial negative charge was generated. This structure would be the typical TS for the solvolytic proton relay mechanism (Scheme 1). This result is in agreement with experimental data that the direct triple proton transfer in 7-

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HQ along an H-bonded alcohol chain proceeds via a solvolytic pathway in an asymmetrically concerted fashion.[13]

Table 2. Löwdin partial charges of the R_bO^--like moiety of the TS and distances of selected bonds at TSs with a H-bonded chain consisting of two identical alcohols.

ROH	R_bO^- charge	Bond Distance					
		O_1–H_2	H_2–O_3	O_3–H_4	H_4–O_5	O_5–H_6	H_6–N_7
H_2O	–0.54	1.08	1.39	1.17	1.24	1.49	1.11
CH_2FCH_2OH	–0.59	1.06	1.44	1.17	1.24	1.51	1.09
CF_3CH_2OH	–0.63	1.02	1.56	1.17	1.25	1.64	1.06
C_6H_5OH	–0.68	1.00	1.69	1.19	1.22	1.81	1.04

Large negative partial charges were predicted for the R_bO^--like moiety in the TS of the direct triple proton relay (Table 2), which confirms the asynchronous solvolytic mechanism. In this solvolytic pathway, R_bOH and R_aOH can be denoted *precedent* and *succedent* hydroxyl molecules, respectively, because the former donates proton early and becomes an R_bO^--like moiety and the latter seems to stabilize the R_bO^--like moiety by forming a strong H-bond in the highly asynchronous TS.

The property of the TS can be visualized with a correlation plot of H-bond distances. In A–H···B complexes, the r_{AH} and r_{BH} distances correlate with each other; the r_{AH} and r_{BH} values satisfy the Pauling equation under the assumption that the sum of bond orders is conserved during the H-transfer reaction. Limbach *et al.*[37, 38] have suggested that both proton transfer and hydrogen-bonding coordinates could be combined into the same correlation and defined the natural hydrogen bond coordinates $q_1 = (r_{AH} - r_{BH})/2$ and $q_2 = r_{AH} + r_{BH}$ to represent the correlation between r_{AH} and r_{BH} for A–H···B reactions. For a linear H-bond, q_1 and q_2 represent the dislocation of H from the H-bond center and the distance between the two heavy atoms, respectively. These coordinates can be used to study the characteristics of

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the TS, such as earliness or lateness, bond order, and asynchronicity. A negative or positive q_1 value represents an early or late TS, respectively, and a small or large q_2 value represents a tight or loose TS, respectively. Additionally, at the TS of the direct multiple proton relay, the q_1 values of each hydrogen in flight would be very similar or different in the synchronous or asynchronous mechanisms, respectively.

The correlation between O_1–H_2 and O_3–H_2 distances (H_2 transfer), O_3–H_4 and O_5–H_4 distances (H_4 transfer), and O_5–H_6 and N_7–H_6 distances (H_6 transfer) in the TS are depicted in Figure 2. For simplicity, the q_2 and q_1 values of the H transfer are denoted as “the H correlation points”.

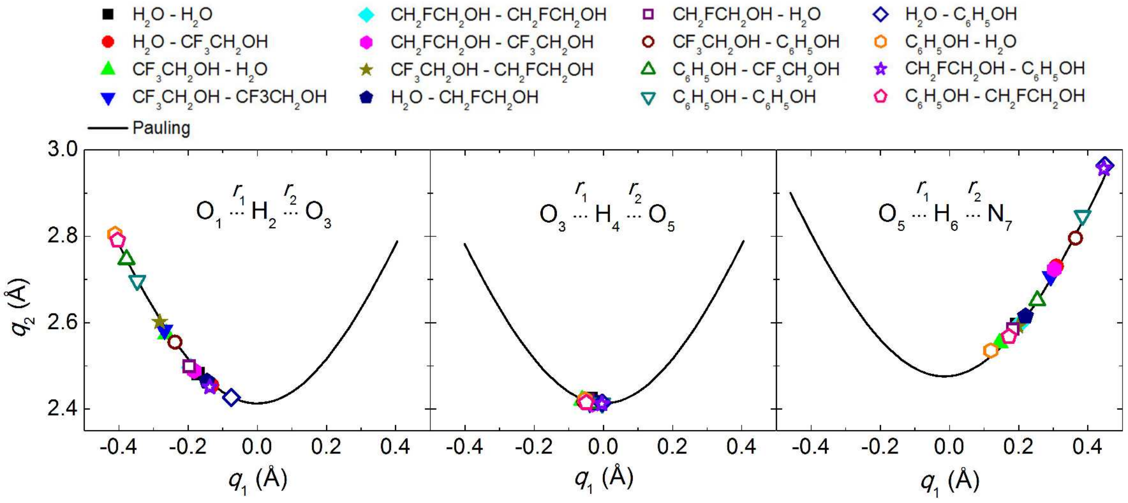

Figure 2. Correlation for the H-bond distances of TS, $q_2 = r_1 + r_2$ vs. $q_1 = ½ (r_1 - r_2)$. The solid lines designate the correlation that satisfies the conservation of bond order, where parameters for Pauling equations were from the literature.[38]

All correlation points of the TS were at or near the solid lines satisfying the Pauling equation of bond order,[37, 38] which implies the bond order is conserved during the multiple proton relay. When phenol is used for R_aOH, the H_2 correlation points appeared in the upper-left side of the correlation plot along the solid line, and when phenol is used for R_bOH, the H_6

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points appeared in the upper-right side of the plot. In general, all H_2 and H_6 points appeared in the upper-left side and the upper-right side, respectively, and the H_4 points appeared in the middle of the correlation plot, which indicates that H_2 and H_6 are closer to O_1 and N_7, respectively, while H_4 is centered between O_3 and O_4. These results indicate that the multiple proton relay takes place by a highly asynchronous pathway and a $[R_aO\text{–}H\text{–}OR_2]^-$-like moiety would be generated as part of the TS.

Free energies of activation ($\Delta G^{\ddagger}$) and reaction (ΔG_0) for the triple proton relay through an H-bonded chain made up of different pairs of hydroxyl molecules are listed in Table 3.

Table 3. Activation and reaction free energies ($\Delta G^{\ddagger}$ and ΔG_0, respectively, kcal/mol) for the triple proton relay with different pairs of chain molecules.

Pair	Order [a]	$\Delta G^{\ddagger}$	ΔG_0	Pair	Order [a]	$\Delta G^{\ddagger}$	ΔG_0
H_2O and CF_3CH_2OH	S – S	4.57	−1.08	H_2O and CH_2FCH_2OH	S – S	6.58	−0.77
	S – W	6.72	−2.68		S – W	7.19	−1.17
	W – S	7.47	0.48		W – S	8.00	−1.23
	W – W	8.59	−1.77		W – W	8.59	−1.77
CH_2FCH_2OH and CF_3CH_2OH	S – S	4.57	−1.08	CF_3CH_2OH and C_6H_5OH	S – S	1.88	0.96
	S – W	4.84	−1.28		S – W	3.37	0.02
	W – S	5.72	−0.21		W – S	4.08	−0.95
	W – W	6.58	−0.77		W – W	4.57	−1.08
H_2O and C_6H_5OH	S – S	1.88	0.96	CH_2FCH_2OH and C_6H_5OH	S – S	1.88	0.96
	S – W	5.04	−1.24		S – W	3.23	−0.80
	W – S	6.70	0.86		W – S	4.13	1.27
	W – W	8.59	−1.77		W – W	6.58	−0.77

[a] S and W denote hydroxyl molecules with relatively strong and weak acidities, respectively.

When the same molecule was used for both R_aOH and R_bOH, the activation energies were 1.88, 4.57, 6.58, and 8.59 kcal/mol for C_6H_5OH, CF_3CH_2OH, CH_2FCH_2OH, and H_2O, respectively. The smaller the pK_a of the H-bonded chain molecule, the lower the activation energy. Similarly, when only one chain molecule is varied while the other remains

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unchanged, the smaller the pK_a of the molecule, the lower the activation energy (Table S2). This result probably occurs because the proton relay becomes easier as the O–H bonds of the chain become weaker. It is very interesting that the change in activation energy was larger when R_aOH rather than R_bOH was changed as depicted in Fig. S2 (the slope of $\Delta G^‡$ vs. pK_a is larger with the change of R_aOH).

The correlation between activation energy and pK_a of the H-bonded wire is plotted in Fig. 3. The acidity of the H-bonded wire is represented by $a \times \mathrm{p}K_{a_1} + (1-a) \times \mathrm{p}K_{a_2}$, where $0 \leq a \leq 1$, and $\mathrm{p}K_{a_1}$ and $\mathrm{p}K_{a_2}$ are acidity constants for R_aOH and R_bOH, respectively. The activation energy increased with the sum of the pK_a's of the H-bonded wire. A good correlation was found with $a = 0.62$, which indicates that R_aOH, the *succedent* alcohol, has a larger influence than R_bOH, the *precedent* one, on the activation energy. These results suggest that the acidity of the wire cumulatively increases proton transfer rates, but each molecule contributes differently to the rate. The solvent effect of the *succedent* alcohol (R_aOH) stabilizing the solute (*precedent* alcohol losing a proton) in the wire is more important in reducing the activation free energy than the acidity of the solute itself. All proton transfer reactions between acids and bases will give a Brönsted relation, $\log k_A = \alpha \log K_A$ + constants, which is a linear free energy relationship (LFER) that can be expressed as $\delta(\Delta G^‡) = \alpha\, \delta(\Delta G_0)$, where $\Delta G^‡$ is the free energy of activation and ΔG_0 is the standard free energy change for the proton transfer reaction. The α value is normally about 0.5 for a symmetric single proton transfer reaction, which suggests that the activation energy is changed by about half of the reaction energy resulting from the pK_a change of the acid (a *precedent* molecule in our case). However, with the same change in pK_a for the solvent molecule in the first solvation shell, the solvation energy for the solvolytic TS with a large anionic character can be larger than the activation energy resulting from the Brönsted relation.

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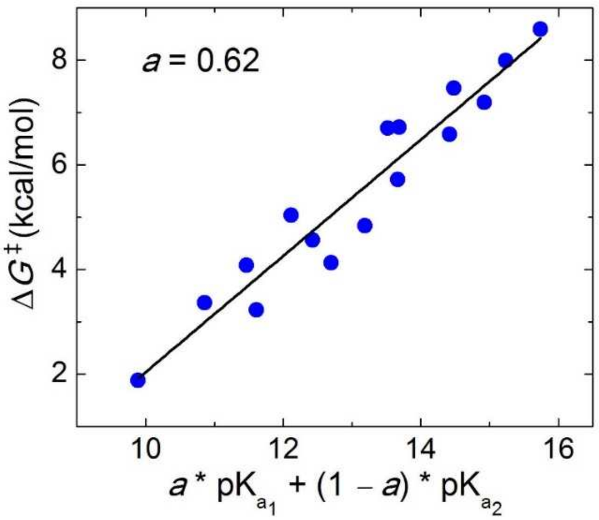

Figure 3. Correlation between activation energy and acidity of an H-bonded wire made up of two hydroxyl molecules.

For two hydroxyl molecules in an H-bonded chain, S or W denote molecules with relatively stronger or weaker acidities, respectively, and the first and second letters represent R_aOH and R_bOH, respectively. The activation energies in this study were always smaller with S–W chains than with W–S chains, which implies that the direct multiple proton relay is always faster when the *succedent* hydroxyl molecule (R_aOH) is more acidic than the *precedent* hydroxyl molecule (R_bOH) rather than the alternative arrangement. Fig. 4 shows the correlation between the pK_a gap of the two hydroxyl molecules in the chain and the ratio of activation energies with S–W and W–S chains, $\Delta G^{\ddagger}$(W–S)/$\Delta G^{\ddagger}$(S–W). The $\Delta G^{\ddagger}$(W–S)/$\Delta G^{\ddagger}$(S–W) ratio is always larger than unity and increases with the pK_a gap. These results are consistent with the experimental rate constants for the excited-state triple proton transfer in mixed 7HQ-R_aOH- R_bOH ($R_1 \neq R_2$) complexes, which are larger when R_aOH is more acidic than R_bOH.[14] It was postulated that proton donation is pushed by another hydroxyl group from the backside along the proton-replay pathway, the so-called "push-ahead effect".[14, 39] This experimental observation, however, may be attributed to the fact that the *succedent* hydroxyl molecule in the wire has a larger influence on the activation energy. This

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stabilizing effect of R_aOH will eventually help proton donation by R_bOH to the acceptor; therefore, the so-called "push-ahead effect" seems to be operable.

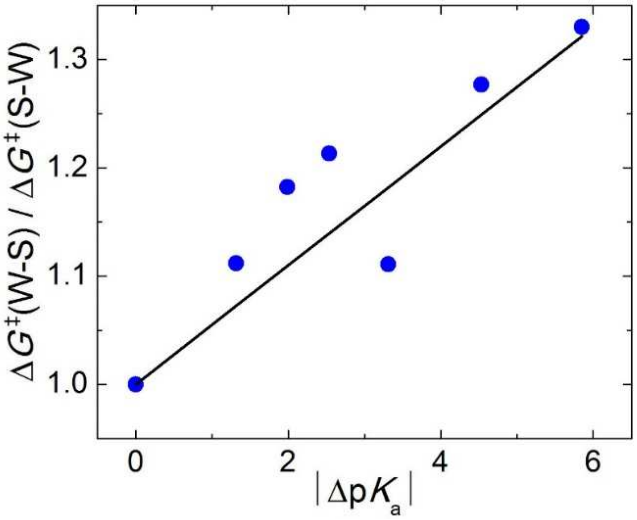

Figure 4. Correlation between the pK_a difference of two hydroxyl molecules in the wire and the ratio of activation energies, $\Delta G^{\ddagger}$(W–S)/$\Delta G^{\ddagger}$(S–W).

The activation energy of the long-range proton relay was monitored when only *precedent* hydroxyl molecule R_bOH was changed in the wire, and the relationship between the free energies of activation and reaction are depicted in Fig. 5A. It is very interesting that as the reaction free energy becomes smaller (more negative), the activation energy becomes larger (Fig. 5A), which indicates an inverse LFER. To the best of our knowledge, an inverse LFER has never been reported for any proton transfer reaction. Most LFERs for proton transfer reactions have been studied with structural variations in the proton donor or acceptor. In this study, hydroxyl molecules in the wire were not the final proton donor or acceptor in the multiple proton relay, but they participated in the proton transfer process and changed the energetics of the reaction. As described previously, acidic hydroxyl molecules in the wire reduced the free energy of activation. However, Fig 5B shows that an acidic R_bOH increased the reaction free energy because the H-bond between ImH^+ and R_bOH in the product

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becomes weaker as a more acidic molecule was used for R_bOH, due to the pK_a slide rule. The smaller the pK_a of R_bOH becomes (more acidic), the lower the activation energy and at the same time the higher the reaction free energy, which will give an inverse LFER. This study shows that the pK_a of the wire can have different roles in the activation energy and reaction free energy, which leads to the very unusual inverse LFER.

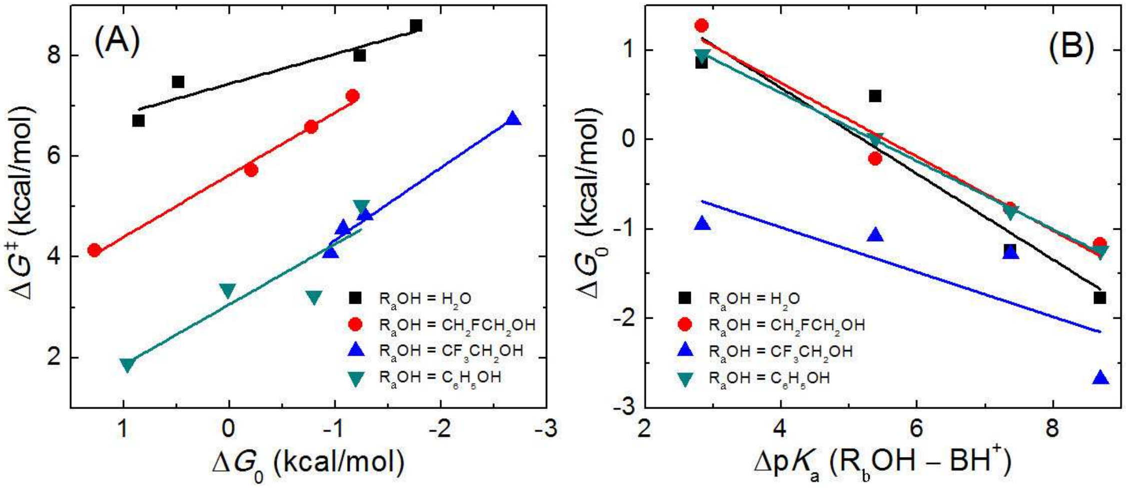

Figure 5. (A) LFERs for the direct proton relay with the change of R_bOH in the wire and (B) the free energy of reaction with respect to the pK_a difference between R_bOH and ImH^+.

In this study we investigated the role of pK_a of hydroxyl molecules on the multiple proton transfer through H-bonded wire in aqueous solution. Since the proton relay is very important in biological systems, it would be useful to consider our results in comparison with the proton relay in non-aqueous medium (protein) with a low dielectric constant. The concept of pK_a values breaks down in proteins and therefore the H-bond length may not be predicted by the pK_a values of both groups in water. This means that pK_a slide rule cannot be used to predict the H-bond energy and length in protein. It was shown that the proton transfer in the active site of protein is better modeled using the proton transfer in polar aprotic solvents and the polarity inside enzymes is induced mostly by polar side chains and bound water molecules,[40, 41] which can be mimicked as that of organic solvent with a dielectric constant of

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about 30. We calculated the activation and reaction free energies in a medium with the dielectric constant of 10, and the results are listed in Table S3 and Figure 6, which show a good inverse LFER too. This is probably because the relative acidity and basicity of our hydroxyl molecules are maintained in a nonpolar environment. This result suggests that, although the pK_a slide rule cannot be used to predict the proton transfer in protein, the general concept between acid-base property and the H-bond strength (and the free energy of activation) would work well to predict the proton relay through well-defined chain molecules.

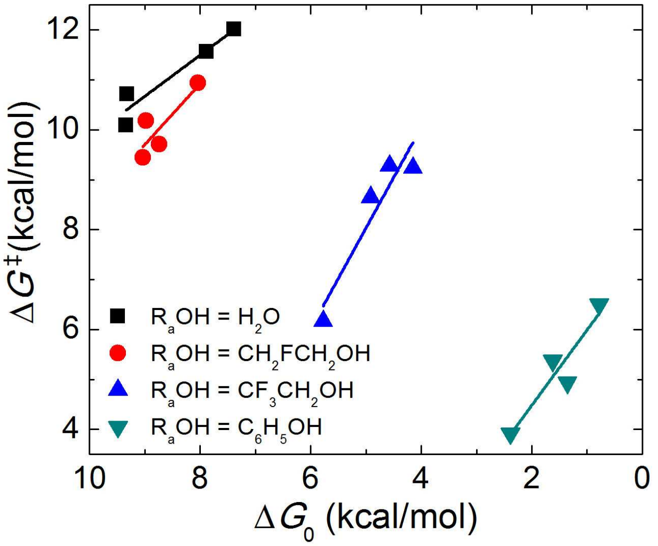

Figure 6. LFERs for the direct proton relay with the change of R_bOH in the wire in a medium with a dielectric constant of 10.

Conclusions

Direct triple proton relay was investigated with respect to the pK_a of H-bonded chain molecules. The multiple proton transfer in our model took place via a concerted and highly asynchronous solvolytic mechanism. We found that the hydroxyl molecules in the wire changed the activation energy of the multiple proton transfer. The lower the pK_a of the wire, the faster the rate of proton relay, and each molecule in the wire contributed differently to the

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rate. The activation free energy depended more on the pK_a of the *succedent* hydroxyl molecule in the wire, which acted as a solvent in the first solvation shell to stabilize the solute by forming a strong H-bond, than the pK_a of the *precedent* hydroxyl molecule, which loses a proton in the TS. An inverse LFER was found for the first time for the multiple proton transfer. The activation energy decreased with increasing reaction energy as the pK_a of the H-bonded wire was reduced. This inverse LFER can be explained by the pK_a slide rule; the pK_a dependence of H-bond strength has an opposite trend for hydroxyl molecules in the wire between reactant and product. The pK_a of the wire can have different roles in the activation and reaction free energies, which led to the very unusual relationship between them.

Footnote. Electronic supplementary information (ESI) available.

Notes

The authors declare no competing financial interests.

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