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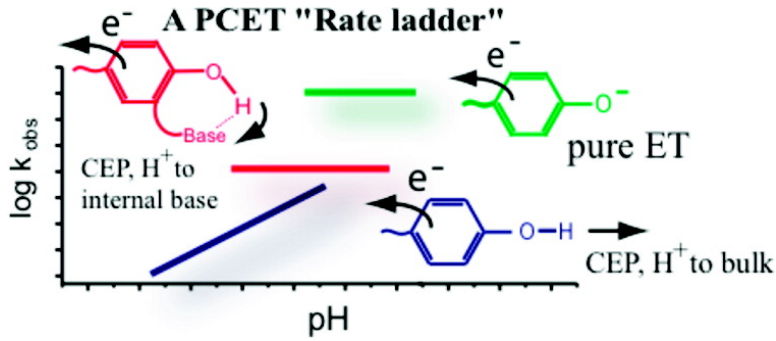

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The Rate Ladder of Proton-Coupled Tyrosine Oxidation in Water: A Systematic Dependence on Hydrogen Bonds and Protonation State

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Proton-coupled electron transfer (PCET) is currently much debated as it is an elementary reaction step involved in, for example, radical enzymes and solar fuel production schemes.[1] One example is the electron transfer (ET) from Y_Z, in photosystem II (PSII), where the phenolic proton simultaneously transfers to a nearby histidine via a hydrogen bond (H-bond). It is an example of bidirectional PCET where the electron and proton are transferred in different directions. Our previous studies on tyrosine (Y) oxidation in water solution, with Y attached to $Ru(bpy)_3^{2+}$ (**RuY**, Chart 1), showed unexpectedly a rate-dependence on pH that could not be explained by simple first-order dependencies on [OH^-] or buffer species.[2a,b] Instead we showed that the mechanism of PCET in **RuY** at pH < 10 is concerted (CEP) when Y is deprotonated directly to water. Recent studies on bimolecular oxidation of phenols with internal H-bonding bases showed instead a pH-independent rate of CEP when the internal base is the primary proton acceptor.[2c] Mechanistic studies on H-bonded phenols have also been made by others, using electrochemical and/or transient methods.[3,4] These are, however, for heterogeneous oxidation and/or in nonaqueous solvents. In the current paper we present direct measurements of the intramolecular PCET rate in aqueous solution, in two new tyrosine-based phenols with an internal carboxylate base linked to $Ru(bpy)_3^{2+}$: a salicylic acid derivate, **Ru-SA**, and a 2-hydroxyphenylacetic acid derivate, **Ru-PA** (Chart 1). We report systematically different rates and pH-dependencies depending on the H-bond situation (Figure 1).

The synthesis of the salicylic acid derived 2,2′-bipyridyl ligand in **Ru-SA** started with a Duff monoformylation of known 4-Me-2,2′-bpy-4-CONH-L-tyrosine ethyl ester,[5] which was subsequently oxidized to the carboxylic acid. The required acetic acid functionalized ligand in **Ru-PA** was obtained by one carbon homologation of a similar salicylic acid derived 2,2′-bipyridyl ligand using the Wolff rearrangement of the corresponding diazoketone (see Supporting Information (SI) for synthetic details). The final complexes have been fully characterized by NMR spectroscopy, mass spectrometry, and elemental analyses. Laser flash-quench techniques, with methyl viologen or $[Co(NH_3)_5Cl]^{2+}$ as electron acceptor, were used to generate [Ru^{III}] from the ^{3}[Ru^{II}]* MLCT excited state. The rate of the subsequent oxidation of Y by [Ru^{III}] was followed by transient absorption at 450 nm as a signature of [Ru^{II}] recovery accompanied with a 410 nm signature for Y• (see SI for experimental details).

The Rate Ladder. The pH dependence of the Y oxidation rate (k_{obs}) in the three Ru-complexes (Figure 1, left panel) illustrates a "rate ladder", as previously predicted,[6] where each step represents a different mechanistic regime depending on the Y protonation state and H-bonding situation; the rate is small for CEP to bulk water, higher with internal H-bonds, and even higher for a deprotonated Y. Note that the rates of these different steps span more than 5 orders of magnitude, illustrating the large effects of proton-coupling on ET reactions. For **RuY** with proton release directly to water, a weak pH-dependence was observed at pH < 10, with a slope of

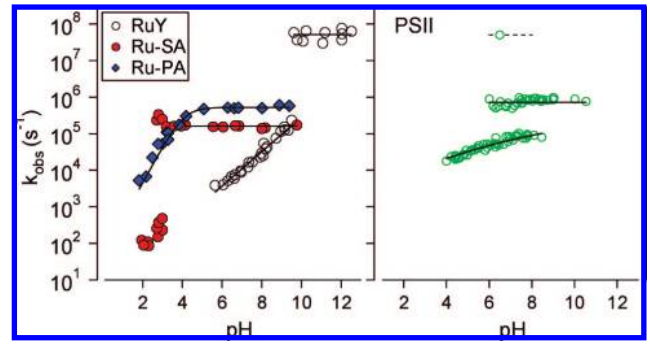
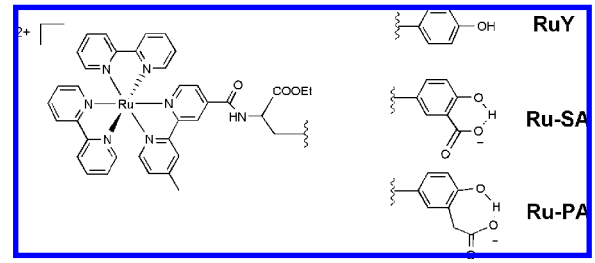


Figure 1 (Left) The "rate ladder" represented by the rate constant of Y oxidation in **RuY**, **Ru-SA**, and **Ru-PA** vs pH (see Supporting Information for conditions and results with different buffers). The **Ru-PA** data (blue) are fitted to eq 1. The **RuY** (ref 2a, b) and **Ru-SA** data at pH < 10 are fitted to straight lines with slopes of 0.5 and 0, respectively. (Right) Rate of constant of Y_z in Mn-depleted PSII vs pH (from ref 14) and intact PSII (dashed line, ref 7).

Chart 1. Structures of the Complexes Studied in This Paper



0.5 on a log−log scale. This pH-dependence was not induced by the buffer at the range of buffer concentrations employed[2a,b] (Figure S1). Although the mechanistic details are not fully understood this was earlier found to phenomenologically follow the Marcus equation for ET, assuming that the driving force follows the pH dependent Y potential: $E^{o\prime}(Y\bullet/Y) = E^{o}(Y\bullet/Y^-) + 0.059 \times \log(1 + 10^{pK_a(Y)\text{-}pH})$ (*V*).[2a] At pH > 10 **RuY** is mainly in the tyrosinate form and the oxidation is a pure, pH-independent ET, which has relatively small reorganization energy (0.9 eV).[2a] For **Ru-SA** and **Ru-PA**, instead, k_{obs} is pH-independent within 4 < pH < 10. For these complexes H-bonding is possible in their phenol (OH)/carboxylate ($-COO^-$) forms, that is, at 3 < pH < 14 for **Ru-SA** and 4 < pH < 11 for **Ru-PA** (Table 1). The pH-independent rate constant is therefore attributed to a PCET with carboxylate being the primary proton acceptor (see k_{HB} in Scheme 1).

PCET Mechanisms. PCET reactions may be sequential, with either electron transferred first (ETPT) or proton transferred first (PTET) or concerted (CEP), defined as electron and proton being transferred via one common transition state.[2a] The mechanism of PCET from the H-bonded systems is not expected to occur via PTET due to the large ΔpK_a (= pK_a(OH) − pK_a(COOH)) of **Ru-SA** and **Ru-PA**. For the PTET mechanism $k_{HB} = 10^{-\Delta pK_a} \times k_{ET}$,

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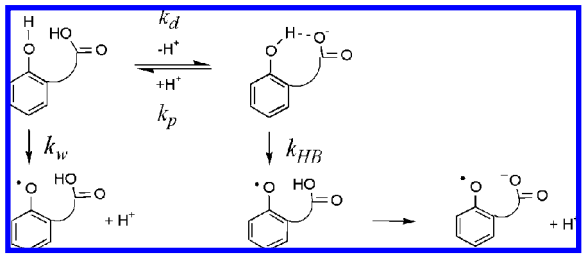
Table 1. Data for the Three Complexes Studied

	RuY	Ru-SA	Ru-PA
pK_a (OH)[a]	10	13.5[b]	10.9[b]
pK_a (COOH)[c]		3.1	4.3
$E^0_{PhO^•/PhO^-}$ vs NHE	0.72[d]	0.77[e]	0.71
k_{HB}[f]/s^{-1}		1.6×10^5	5.2×10^5
k_H/k_D[g]	1.5−3[h]	1.9	2.7

[a] pK_a of the phenolic group. [b] Reference 2c, 8. [c] pK_a of the carboxylic group. [d] Reference 9. [e] ref.[2a] [f] See eq 1. [g] Kinetic isotope effect at pH 7/pD 7. [h] Reference 10.

Scheme 1. Mechanism of HB-Gating for Y with an Internal Carboxylate Base



and with $\Delta pK_a = 10$ for **Ru-SA** this would imply an unphysical value of $k_{ET} \approx 1 \times 10^{15}$ s^{-1} from Y^-, while the observed value for ET from Y^- in **RuY** (pH > 10) is only 5×10^7 s^{-1}. Also the ETPT pathway is excluded owing to the significant kinetic isotope effects observed for k_{HB} at pH 7 (k_H/k_D in Table 1). Moreover, we concluded in our earlier studies[2a,d] that ETPT cannot compete with CEP in **RuY** at neutral pH, presumably because $\Delta G^0 \approx +0.2$ eV for the initial ET step. In **Ru-SA** and **Ru-PA** we observe an even higher rate at neutral pH than for **RuY**, but the rate of a rate-determining ET step of ETPT should not increase because of internal H-bonds. Thus, we assign the PCET to a CEP also for **Ru-SA** and **Ru-PA**, with the driving force being dependent on the reduction potential for H-bonded Y: $E°(Y•-HB/Y-B^-) = E°(Y•/Y^-) + 0.059 \times (\Delta pK_a)$ (V).

Strong H-bonds may result in reduced reorganization energy[2c,6] and/or larger proton vibrational wave function overlap[11] and effect the CEP rate constant significantly. This is first illustrated in the 10 times increased rate constant for **Ru-SA** compared to **RuY** at pH 7 despite the 0.4 eV smaller driving force for **Ru-SA**. Second, the 0.3 eV larger driving force for **Ru-PA** than **Ru-SA** results in only a 3-fold difference in k_{HB}, which suggests a compensatory effect of the strong H-bond[12] for **SA**. J. M. Mayer et al. have recently suggested that PCET is facilitated by base−phenol conjugation, which increases the H-bond strength, independently of the nature of the proton-accepting base.[13] In our results the net effect is instead that the conjugated **Ru-SA** shows a slower rate than the nonconjugated **Ru-PA**, which shows that not only the effect of H-bonding strength is important, but also the pK_a of the base.

H-Bond Gating. Interestingly, the rate constants observed at low pH revealed two disparate pH-dependences for **Ru-SA** and **Ru-PA**, respectively. For **Ru-SA** the fractions of acid (−COOH) and base ($-COO^-$) forms present around pH = pK_a (3.1) react independently. This gives biexponential kinetics with pH-dependent relative amplitudes, where the rate constant for the base (k_{HB}, Scheme 1) is much larger than the pH-dependent rate constant for the acid (k_w). Apparently, the acid-to-base conversion is much slower than PCET from the acid form ($k_d < k_w$), presumably because of the strong H-bond.[12] In contrast, for **Ru-PA** we observe single-exponential kinetics consistent with rapid deprotonation and H-bond formation ($k_d > k_w$) so that all species react via the base form with pre-equilibrium kinetics:

$$k_{obs} = f_B k_{HB} = (1 + 10^{pK_a - pH})^{-1} k_{HB} \quad (1)$$

where f_B is the fraction of base. Apparently, the direct k_w pathway cannot compete in the pH range examined, that is, $k_w < k_{obs}$. The **Ru-PA** data in Figure 1 is fitted to equation 1, giving a pK_a of ca. 4.3. The slope = 1 at low pH follows the fraction of base and should not be confused with the milder slope of **RuY** where k_w is pH-dependent in itself.

We have earlier shown[2a,6] the similarity between Y oxidation in **RuY** and Mn-depleted PSII at pH < 7, both showing a mild pH-dependence and a slow rate (Figure 1). We proposed that both are due to a CEP with bulk water as a proton acceptor. At pH > 7 it is proposed that Y_z is H-bonded to His190 (pK_a = 7) and a higher, pH-independent rate is observed.[14] This situation is now mimicked by **Ru-SA** and **Ru-PA** at intermediate pH (the "rate ladder"). The H-bond strength and the pK_a of the base determine the Y oxidation rate that is in general much faster than at low pH. Y_Z oxidation in native PSII is even faster; we believe, however, that this is not because of initial deprotonation of Y_Z as in **RuY** but rather because of an even stronger H-bond and lower reorganization energy in the more hydrophobic environment.

We have seen that PCET reactions are facilitated when the proton transfers via strong H-bond to a covalent linked base than directly to water. The reason for this behavior is presumably a combination of a stronger proton coupling and reduced reorganization energy. A detailed theoretical analysis of how the different parameters contribute to the rate enhancement is in progress.

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Supporting Information Available: Detailed description of experimental procedures; synthesis and characterization of **Ru-SA** and **Ru-PA**, transient traces and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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