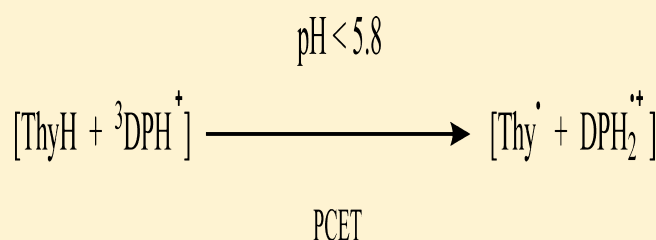


## Kinetics of the Oxidation of Thymine and Thymidine by Triplet 2,2'-Dipyridyl in Aqueous Solutions at Different pH Values

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**ABSTRACT:** The photo-oxidation of the nucleobase, thymine (Thy), and nucleoside, thymidine (dThy), by dipyridyl (DP) has been investigated in aqueous solution using time-resolved laser flash photolysis. The pH dependence of the oxidation rate constants is measured within a large pH scale. As a consequence, the chemical reactivity of the reactants existing in solution at a certain range of pH is predicted. Bimolecular rate constants of the quenching reactions between triplet dipyridyl and thymine and thymidine are, respectively,  $k_q = 2.4 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  ( $\text{pH} < 5.8$ ) and  $k_q = 1.0 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$  ( $5.8 < \text{pH} < 9.8$ ). Cyclic voltammetry was used to measure the potentials of thymine oxidation and dipyridyl reduction in water at  $\text{pH} < 7$ . Both results give hints for a proton coupled electron-transfer (PCET) reaction from thymine to triplet dipyridyl.



## INTRODUCTION

2,2'-Dipyridyl is well-known as a chelating agent for charge-transfer complexes of transition metals that has been considerably attractive. In addition, it has been widely used as a small size dye, which possesses some distinct features over the common flavin's family. Photoinitiating dipyridyl enhances the detection of CIDNP signals and transient absorption spectra powerfully for biological studies. For thymine and anthraquinone-2,6-disulfonic acid, Beckert<sup>1</sup> measured the triplet sensitized electron transfer using FT-ESR spectroscopy. Kaptein et al.<sup>2,3</sup> investigated the electron-transfer kinetics between pyrimidines and various electron donors using photo-CIDNP. Evidence for a thymine radical anion intermediate is also reported by Kaptein.<sup>4</sup> By CIDNP detecting, we confirmed that spin correlated radical pairs are formed between dipyridyl and thymine, thymidine.<sup>5</sup> The influence of amino acid side chains on the kinetics of long-distance electron transfer in peptides is pointed out in detail by Giese et al.<sup>6</sup> This group also applied Marcus theory for charge-transfer reactions in peptides.<sup>7</sup> The interaction of the triplet dipyridyl, applied for the spatial structure of protein investigations, with amino acid residues, dipeptides, and macromolecules such as bovine and human  $\alpha$ -lactalbumins can be found in the series of publications.<sup>8–16</sup>

On the other hand, the oxidation of thymine, and thymidine by photoexcited dipyridyl, similar to that of nucleobases and their nucleosides by menadion,<sup>17</sup> benzophenone,<sup>18</sup> and riboflavin,<sup>19</sup> provides the susceptible information in the direct effect of ionizing radiation on DNA. The formation of such strong oxidizing intermediates, which may induce transformations of damaged nucleobases and nucleosides, for this

reason, has been of great interest for DNA free-radical chemistry.<sup>20</sup>

Continuing investigations on the photoreaction of dipyridyl along with study on oxidation of thymine and thymidine in aqueous solution are presented in this work. The rate constants of photo-oxidation are estimated in detail, resulting in pH-dependent functions of the observed quenching rate constant. Additional hints from cyclic voltammetric measurements at  $\text{pH} < 7$  indicate a proton coupled electron transfer from thymine to the protonated triplet state of dipyridyl.

## RESULTS AND DISCUSSION

**Absorption Spectra.** The absorption spectrum of  $7 \times 10^{-5} \text{ M}$  dipyridyl at  $\text{pH} = 2$  recorded in the absence and in the presence of  $2.2 \times 10^{-3} \text{ M}$  thymine is shown in Figure 1. There is no absorption of Thy at the excitation wavelength, 308 nm, which warrants that only DP is excited by the laser beam. The absorption spectrum of a mixture of DP and Thy as compared to that of individual compound indicates that there is no association between both in the ground state. Similar behavior is observed for thymidine.

**Laser Flash Photolysis.** In aqueous solution, the reactive species can be either protonated, neutral, or deprotonated depending on pH. The  $\text{pK}_a$  values that were used as boundaries to divide these pH regions and corresponding reactants can be found in Tables 1 and 2.

Kinetic traces of DP-triplet are measured at a wavelength of 325 nm where the DP-triplet state absorbs much more than the

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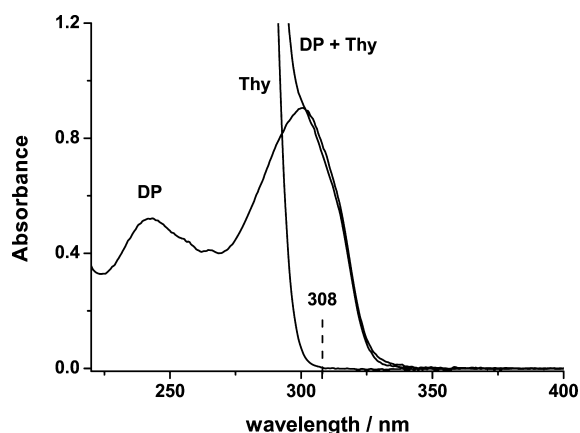


Figure 1. Absorption spectra of DP ( $7 \times 10^{-5}$  M) without and with Thy ( $2.2 \times 10^{-3}$  M) in water at pH = 2.0.

Table 1. Quenching Rate Constants of Triplet DP by Quenchers ( $k_{qi}$ )

quencher	pH region	main reactant pair	$k_{qi}$	$10^{-7} \times k_{qi} / \text{M}^{-1} \text{s}^{-1}$	
				$a$	$b$
thymine	pH < 5.8	$^3\text{DPH}^+$ and ThyH	$k_{q1}$	2.4	2.7
	5.8 < pH < 9.9	$^3\text{DP}$ and ThyH	$k_{q2}$	0.38	0.53
	9.9 < pH	$^3\text{DP}$ and Thy $^-$	$k_{q3}$	3.0	3.0
thymidine	pH < 5.8	$^3\text{DPH}^+$ and dThyH $_2$	$k_{q1}$	0.41	0.29
	5.8 < pH < 9.8	$^3\text{DP}$ and dThyH $_2$	$k_{q2}$	1.0	1.0
	9.8 < pH < 12.9	$^3\text{DP}$ and dThyH $^-$	$k_{q3}$	0.43	0.44
	12.9 < pH	$^3\text{DP}$ and dThy $^{2-}$	$k_{q4}$	0.0052 <sup>c</sup>	0

<sup>a</sup> $k_{qi}$  values resulted from simulations with  $\text{p}K_{\text{a,DPH}^+}^* = 5.8$ . <sup>b</sup> $k_{qi}$  values resulted from simulations with  $\text{p}K_{\text{a,DPH}^+}^* = 5.0$ . <sup>c</sup>That  $k_{q4}$  is small implies that the deprotonation of the deoxyribose group of dThy does not affect the quenching reaction.

Table 2.  $\text{p}K_{\text{a}}$  Values and Redox Potentials

compound	abbreviation	$\text{p}K_{\text{a}}$	potentials vs NHE (V) <sup>d</sup>
2,2'-dipyridyl	DP	4.3 <sup>a</sup>	−1.02 (pH = 2.0)
		5.8 <sup>b</sup>	−1.22 (pH = 6.1)
thymine	Thy	9.9 <sup>c</sup>	
thymidine	dThy	$\text{p}K_{\text{a}1} = 9.8$	
		$\text{p}K_{\text{a}2} = 12.9^c$	

<sup>a</sup>Reference 26. <sup>b</sup>For the triplet state, ref 10. <sup>c</sup>Reference 27. <sup>d</sup> $E(\text{Ag}/\text{AgCl})$  vs  $E(\text{NHE}) = 0.199$  V.

corresponding radical.<sup>8</sup> The decay of the neutral state  $^3\text{DP}$  (at pH = 12.0) obeys the first-order kinetic law with  $k_d = 2.1 \times 10^4 \text{ s}^{-1}$ , while the protonated state  $^3\text{DPH}^+$  (at pH = 2.0) shows an admixture of first-order,  $k_d = 2.5 \times 10^4 \text{ s}^{-1}$ , and second-order,  $k_2/\epsilon = 5.4 \times 10^5 \text{ cm}^3 \text{ s}^{-1}$ , disappearances. These observations are in agreement with reported data.<sup>8</sup> In the presence of quencher, the decay of DP-triplet follows a pseudofirst-order reaction with  $k_1 = k_q^{\text{obs}} C_0$ , where  $k_q^{\text{obs}}$  is the observed quenching rate constant, which is extracted from Stern–Volmer plots.

**Oxidation of Thymine.** Time traces of  $^3\text{DP}$  with an increase in concentration of thymine and the corresponding Stern–Volmer relation are shown as Figure 2. The nature of

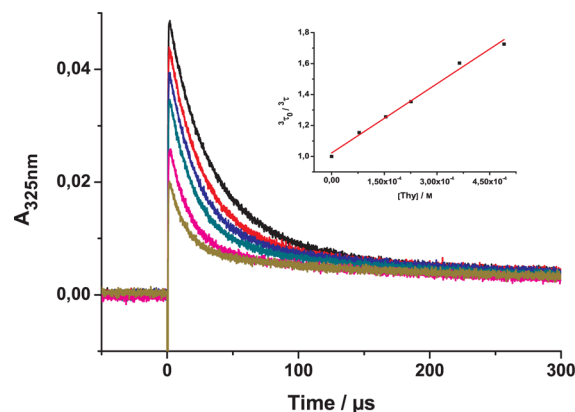


Figure 2. Decays ( $\lambda_{\text{obs}} = 325$  nm) of triplet DP ( $2 \times 10^{-3}$  M) + Thy (concentration increasing from top to bottom: 0 to  $4.9 \times 10^{-4}$  M) in water at pH = 12.0. Inset: Stern–Volmer plot.

the species that participate in the oxidation reaction is listed in Table 1. Furthermore, the pH dependence of the observed quenching rate constant,  $k_q^{\text{obs}}$ , is treated by eq 1<sup>21</sup> and is presented in Figure 3. The  $k_{qi}$  values denote the intrinsic

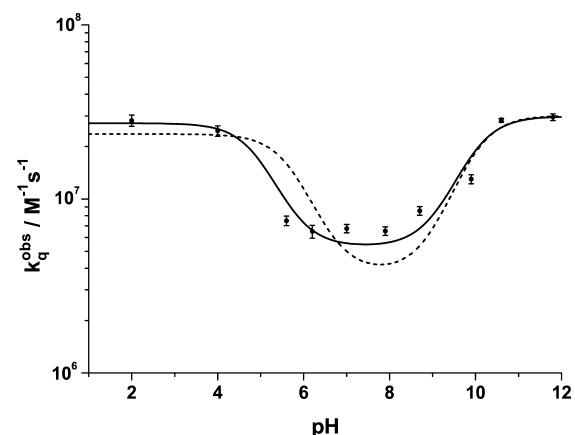


Figure 3. pH dependence of the observed quenching rate constants  $k_q^{\text{obs}}$  for the oxidation of Thy by triplet DP. The dashed line is a simulation according to eq 1 with  $\text{p}K_{\text{a,DPH}^+}^* = 5.8$ , while the solid line is the best fit with  $\text{p}K_{\text{a,DPH}^+}^* = 5.0$  (see Tables 1 and 2 for parameters). There is only a little difference between the expected and literature values.

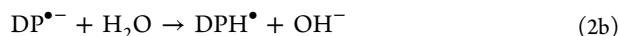
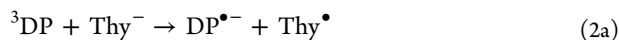
quenching rate constants for the different pH regions; see also Table 1.

$$k_q^{\text{obs}} = k_{q1} \frac{[\text{H}^+]^2}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+] + K_{\text{a}})} + k_{q2} \frac{K_{\text{a}}^*[\text{H}^+]}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+] + K_{\text{a}})} + k_{q3} \frac{K_{\text{a}}^*K_{\text{a}}}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+] + K_{\text{a}})} \quad (1)$$

It is found that the turning points of this titration curve coincide with the protonation of dipyridyl and thymine. This

fact indicates that the oxidation is influenced by the protonation of the reactants. Three pH regions can be distinguished:  $\text{pH} < 5.8$ ;  $5.8 < \text{pH} < 9.9$ ; and  $\text{pH} > 9.9$ .

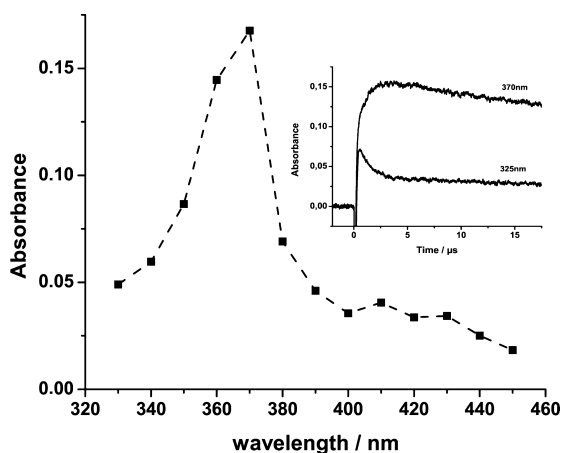
At  $\text{pH} > 9.9$ , the triplet dipyridyl and thymine exist in their neutral and deprotonated forms, respectively. It is clear that the primary photo-oxidation step of thymine by  $^3\text{DP}$  is an electron-transfer reaction. The formed radical anion,  $\text{DP}^{\bullet-}$ , is a strong base ( $\text{p}K_{\text{a,DPH}^\bullet} \approx 24$ ),<sup>22</sup> immediately protonated.<sup>9</sup>



On the other hand, it is concluded that the reactivity of triplet dipyridyl and thymine is highest in this range of pH (see Figure 3 and Table 1).

Between  $5.8 < \text{pH} < 9.9$ , both triplet dipyridyl and thymine exist as neutral species. The species resulting from the reduction of DP are expected as the neutral radical  $\text{DPH}^\bullet$  ( $\lambda_{\text{max}} = 365$  and  $470$  nm<sup>8</sup>). However, it could not be found in our experiment, and this has been attributed to the fast escape of radical ions from the charge-transfer successor complex. The primary photochemical step between  $^3\text{DP}$  and ThyH would react in a similar way (i.e., hydrogen abstraction) to that of triplet dipyridyl and *N*-acetyl tyrosine as suggested by Tsentelovich et al.<sup>8</sup>

At  $\text{pH} < 5.8$ , both the triplet dipyridyl and the thymine exist in the  $^3\text{DPH}^+$  and ThyH forms, respectively. The long-living transient, radical cation  $\text{DPH}_2^{\bullet+}$  ( $\lambda_{\text{max}} = 370$  nm), is observed, and its absorption spectrum is shown in Figure 4.<sup>9</sup> The

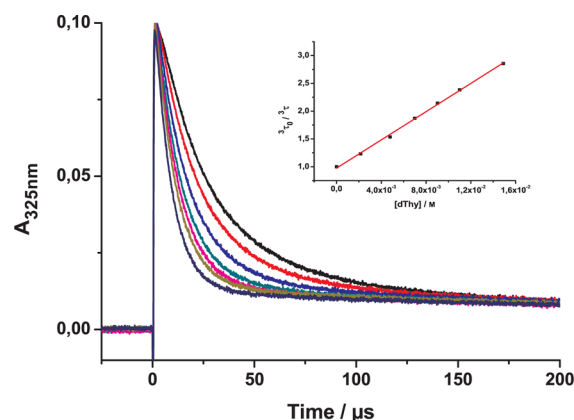


**Figure 4.** Transient absorption spectrum obtained at  $2 \mu\text{s}$  after irradiation of DP ( $7.0 \times 10^{-5}$  M) + Thy ( $7.5 \times 10^{-3}$  M) at  $\text{pH} = 2.0$ . Inset: Decay profiles observed at  $\lambda_{\text{obs}} = 325$  and  $370$  nm.

formation of this radical may be explained by the different mechanisms through which the same radical cation is formed by reduction: (i) hydrogen atom transfer; and (ii) proton coupled electron transfer (PCET) by means of either concerted proton and electron-transfer (CPET) pathway or stepwise pathway, electron transfer followed by proton transfer (ETPT), or proton transfer followed by electron transfer (PTET). Noting that, regardless of the activation energy barrier, case (i) and case (ii) are equal.<sup>9</sup> Moreover, the PTET mechanism can be ruled out because thymine would prefer its deprotonation at  $\text{pH} > \text{p}K_{\text{a}} = 9.9$ . As discussed later, the possibility of the favorable pathway will be evaluated from the electrochemical results.

Otherwise, it can be seen that the reaction rate constant of thymine with  $\text{DPH}^+$  is higher than that with  $^3\text{DP}$  (see Figure 3 and Table 1). The interpretation of this behavior is related to the dissociation constant of the neutral radical  $\text{DPH}^\bullet$  ( $\text{p}K_{\text{a,DPH}^\bullet} \approx 24$ ) and the equilibrium constant of triplet dipyridyl ( $\text{p}K_{\text{a}}^* = 5.8$ ) given by Chibisov.<sup>23</sup> For  $\text{p}K_{\text{a,DPH}^\bullet} > \text{p}K_{\text{a}}^*$ ,  $k_{\text{q1}}$  is larger than  $k_{\text{q2}}$  (see Table 1).

**Oxidation of Thymidine.** The initial reactive species existing in solution at different pH values are shown in Table 1. Decays of  $^3\text{DP}$ -triplet and Stern–Volmer plots in the presence of dThy are demonstrated in Figure 5. Taking the  $\text{p}K$  values



**Figure 5.** Decays ( $\lambda_{\text{abs}} = 325$  nm) for the DP + dThy system in water  $\text{pH} = 2.0$ . Concentration of dThy increases from top to bottom: 0 to  $1.5 \times 10^{-2}$  M. Inset: Stern–Volmer plot.

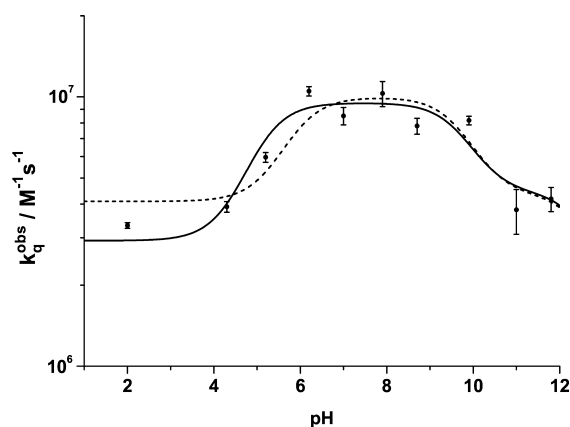
into account, the pH dependence of the oxidation rate constant,  $k_{\text{q}}^{\text{obs}}$ , can be expressed by the eq 3<sup>21</sup> and is represented in Figure 6.

$$k_{\text{q}}^{\text{obs}} = k_{\text{q1}} \frac{[\text{H}^+]^3}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+]^2 + K_{\text{a1}}[\text{H}^+] + K_{\text{a1}}K_{\text{a2}})} + k_{\text{q2}} \frac{K_{\text{a}}^*[\text{H}^+]^2}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+]^2 + K_{\text{a1}}[\text{H}^+] + K_{\text{a1}}K_{\text{a2}})} + k_{\text{q3}} \frac{K_{\text{a}}^*K_{\text{a1}}[\text{H}^+]}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+]^2 + K_{\text{a1}}[\text{H}^+] + K_{\text{a1}}K_{\text{a2}})} + k_{\text{q4}} \frac{K_{\text{a}}^*K_{\text{a1}}K_{\text{a2}}}{([\text{H}^+] + K_{\text{a}}^*)([\text{H}^+]^2 + K_{\text{a1}}[\text{H}^+] + K_{\text{a1}}K_{\text{a2}})} \quad (3)$$

The main reactions in each pH region and their corresponding quenching rate constants,  $k_{\text{qi}}$ , obtained by the best fit (solid line, Figure 6) are summarized in Table 1. It is important to note that  $k_{\text{q3}} = 5.2 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$  is about 2 orders of magnitude lower than others. This implies its small contribution to the overall quenching rate constant. In other words, the oxidation reaction is not affected by the protonation state of the deoxyribose group ( $\text{p}K_{\text{a2}} = 12.9$ ) of dThy. Note that  $\text{p}K_{\text{a,thymine}} \approx \text{p}K_{\text{a1,thymine}}$  (see Table 2). Therefore, similar pH-depending regions and mechanisms as compared to that of the triplet dipyridyl–thymine reaction are predicted for the photo-oxidation of thymidine.

In contrast, DP-triplet quenching rate constants (see Table 1) for thymidine show a different behavior as compared to those for thymine.

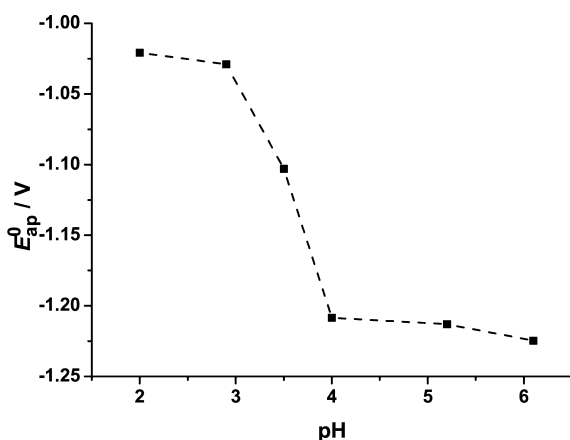
**Cyclic Voltammetric Investigation.** As mentioned earlier, to check the feasible mechanisms of the thymine photo-



**Figure 6.** pH dependence of the observed quenching rate constant  $k_q^{\text{obs}}$  for the reaction of triplet DP with dThy. The dashed line is a simulation according to eq 3 with  $pK_{a,\text{DPH}^+}^* = 5.8$ , while the solid line is the best fit with  $pK_{a,\text{DPH}^+}^* = 5.0$  (see Tables 1 and 2 for parameters). There is only a little difference between the expected and literature values.

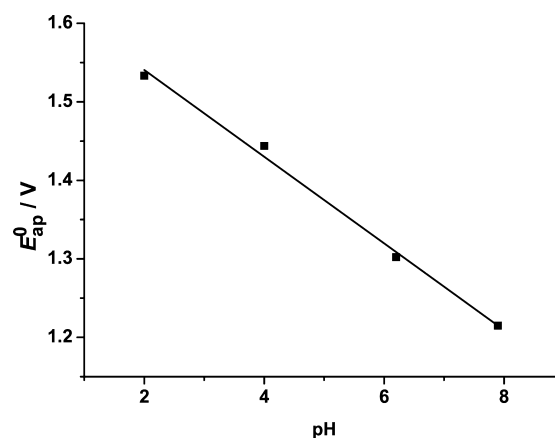
oxidation by triplet dipyridyl, the pH-dependent redox potentials of DP and thymine have been investigated at pH < 7. Oxidation of thymidine is not possible in aqueous solution at pH < 7.

Figure 7 shows the variation of the apparent standard reduction potential of DP,  $E_{\text{ap,DP}}^0$ , with pH. As seen in Figure 7,



**Figure 7.** Variation of the apparent standard reduction potential (vs NHE) of DP (1 mM) with pH.

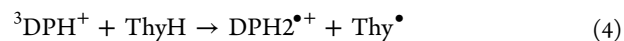
the apparent standard reduction potential of DP is assigned to be constant (within experimental error,  $\pm 20$  mV) between the pH ranges of 2–3 and 4–6 as well. A change of  $E_{\text{ap,DP}}^0$  occurs at pH  $\approx 3$ –4 corresponding to the deprotonation of  $\text{DPH}^+$  to the neutral DP. This is reasonable because dipyridyl has a  $pK_a$  value of 4.3. We determine  $E_{\text{DPH}^+}^0 = -1.02$  V vs NHE (taken at pH = 2.0). This value is comparable to the published one,  $E_{\text{DPH}^+}^0 = -0.97$  V vs NHE by Krishnan et al.<sup>22</sup> using pulse-radiolysis technique. In Figure 8, the pH dependence of the apparent standard oxidation potential of thymine is given.<sup>18</sup> It shows a linear variation of  $E_{\text{ap,thy}}^0$  with pH characterized by a slope of  $-55.2$  mV per pH unit. This observation indicates a one-proton coupled one-electron transfer (PCET) during the oxidation of thymine.<sup>24,25</sup> The  $pK_{a,\text{thyH}\bullet+} = 3.2$ <sup>20</sup> of thymine radical cation from the literature is not in agreement with our results. Without knowing of the  $pK_{a,\text{thyH}\bullet+}$  value, it is not possible to calculate



**Figure 8.** The apparent standard oxidation potential (vs NHE) of thymine (1 mM) as a function of pH. Solid line: Linear fit.

the corresponding driving forces. Therefore, distinction between concerted proton and electron transfer (CPET) or electron transfer followed by proton transfer (ETPT) is not possible. However, the  $pK_{a,\text{thyH}\bullet+}$  value does not influence the experimental rate constants.

Thus, the above analysis leads to the assumption that the primary photoreduction between thymine (and thymidine) and triplet dipyridyl at pH < 5.8 is a proton coupled electron-transfer reaction.



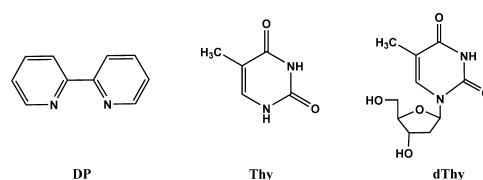
## CONCLUSION

Photo-oxidation of thymine and thymidine by 2,2'-dipyridyl in aqueous solution at different pH values was investigated using time-resolved laser flash photolysis. A relationship between the quenching rate constants and pH has been established over a wide range. The formation of the radical cation  $\text{DPH}_2^{\bullet+}$  ( $\lambda_{\text{max}} = 370$  nm) is observed at pH < 5.8. Additional information from the pH-dependent redox potentials of 2,2'-dipyridyl and thymine obtained from cyclic voltammetry suggests that a proton coupled electron transfer (PCET) from thymine to triplet dipyridyl takes place.

## EXPERIMENTAL SECTION

**Materials.** Abbreviations used in this Article can be found in Table 2. 2,2'-Dipyridyl ( $\geq 99\%$ ) purchased from Sigma-Aldrich was recrystallized in cyclohexane. Thymine (97%) and thymidine (99%) obtained from Alfa-Aesar were used as received. In Figure 9, structures of the compounds used are given.

All experiments were carried out at room temperature in buffered aqueous solutions. The 0.01 M buffer solutions employed covering a pH range from 3.0 to 11.0 with (a)  $\text{HCl-KH}_2\text{PO}_4$ , pH = 3.0–5.0; (b)  $\text{KH}_2\text{PO}_4\text{-Na}_2\text{HPO}_4$ , pH = 5.0–



**Figure 9.** Structure of the compounds.



9.0; and (c)  $\text{Na}_2\text{HPO}_4\text{--NaOH}$ , pH = 9.0–11.0. pH = 2.0 and pH = 12.0 were adjusted with aqueous HCl and NaOH, respectively. The pH value was checked with a WTW-type-S22 pH meter. Bidistilled water was used to prepare the samples.

**Spectroscopic Methods.** Absorption spectra were recorded with a Shimadzu UV-3101-PC spectrophotometer. Transient absorption spectra were obtained by time-resolved laser spectroscopy using a Lambda Physik LPX-120 XeCl-excimer laser (308 nm, pulse energy up to 100 mJ, pulse width 10 ns). The monitoring system includes a UV-LED 325 nm (or xenon lamp 150 W), a Hamamatsu PMT, R955 photomultiplier tube, (or PMT synchronized a OBB/PTI monochromator model 101/102), and a digital storage oscilloscope LeCroy, type 9410A. Irradiation was employed in a  $1 \times 1$  cm rectangular quartz cell. All solutions were treated identically and deoxygenated by bubbling with high-purity argon gas for 15 min.

**Cyclic Voltammetry.** Cyclic voltammetric measurements were performed with an Autolab-PGES AUT 73227 potentiostat (Metrohm). A conventional three-electrode cell configuration was used: a Pt counter electrode, a Ag/AgCl reference electrode, and a glassy carbon working electrode ( $0.03 \text{ cm}^2$  area). The working electrode was polished with diamond paste in water after each single scan to remove possible follow-up products of the oxidative/reductive process on the electrode surface. The background current was always subtracted from the current response for further calculation.

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### Notes

The authors declare no competing financial interest.

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