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Protonation of the Electron Adducts of Pyrimidine Derivatives[1)]

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Photolyses of 5-substituted 1,3-dimethyluracils (1a—e: a, R = F; b, R = Cl; c, R = H; d, R = CH_3; e, R = *p*-xylyl) in *p*-xylene in the presence of trifluoroacetic acid (TFA) afforded 5,6-dihydro-1,3-dimethyl-6-*p*-methylbenzyluracils (3a—d), 5,6-dihydro-1,3-dimethyl-5-*p*-methylbenzyluracils (4a—e), and 5,6-dihydro-1,3-dimethyluracils (5a—e) in varying ratios. It is suggested that the 6-isomers (3) are derived from the O(4)-protonated electron adducts of 1, while 4 and 5 are the products from the C(6)-protonated electron adducts. The ratio of (4+5) *vs.* 3 depends on the ionization potentials of the O(4)-protonated intermediates. The formation of 4+5 increases with increasing concentration of TFA.

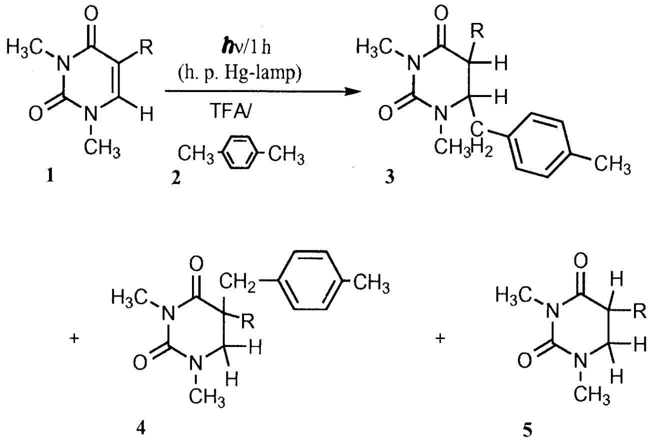
Key words acid-catalyzed photoreaction; 5-substituted 1,3-dimethyluracil; electron adduct; O(4)-protonation; C(6)-protonation

The irradiation of an aqueous solution generates various radical species such as H, OH, and e_{aq}^{-}, which cause DNA damage.[3)] Pulse radiolytic studies showed that solvated electrons (e_{aq}^{-}) react with the pyrimidine bases to form electron adducts (radical anion) (I), to which protons add either at O(4) or at C(6).[4)] In the presence of oxygen, the O(4)-protonated radicals (II) revert to the pyrimidine base, while the C(6)-protonated radicals (5,6-dihydropyrimidin-5-yl radical) (III) undergo the destruction of the pyrimidine moiety (see Chart 2).[5)] However, the degradation products have neither been isolated nor identified. Takamuku *et al.* reported that 6-hydroxymethyl-5,6-dihydropyrimidines were produced regioselectively *via* II upon the photolysis of pyrimidines in methanol in the presence of Eu(III)/(II)[6)] as well as in ionizing radiolysis,[7)] whereas no products were obtained from III. Thus, the protonated radicals behave quite differently in their formation and chemical reactivities.

We have found that photolysis of 5-chloro-1,3-dimethyluracil (5-chloro-1,3-dimethylpyrimidine-2,4-dione) (**1b**) in *p*-xylene (**2**) in the presence of a small excess of trifluoroacetic acid (TFA) (2 molar eq) afforded 1,3-dimethyl-5-(*p*-methylbenzyl)-5-(*p*-xylyl)uracil (**4e**) and the 5,6-dihydro-5-*p*-xylyl derivative (**5e**) together with 1,3-dimethyl-5-(*p*-xylyl)uracil (**1e**).[8)] Furthermore, we recently reported[9)] that the photoreaction of 1,3-dimethyl-5-fluorouracil (**1a**) and **2** in the presence of TFA (2 molar eq) produced 4,4′-dimethylbibenzyl (**6**) as a by-product, the formation of which can be well explained in terms of a mechanism involving an electron transfer from **2** to **1a**, followed by deprotonation from the radical cation of **2** (IV) and dimerization of the resulting *p*-methylbenzyl radicals (V). These findings suggested that modification of the present TFA-assisted photoredox reaction of uracil derivatives would provide a new aspect to the protonation of the electron adducts of pyrimidines. We now report our findings that photolyses of 5-substituted 1,3-dimethyluracils (**1a**—**e**: **a**, R = F; **b**, R = Cl; **c**, R = H; **d**, R = CH_3; **e**, R = *p*-xylyl) in *p*-xylene (**2**) in the presence of a large excess of TFA (48 eq) afford 5-substituted 5,6-dihydro-6-*p*-methylbenzyluracils (**3a**—**d**), the 5-*p*-methylbenzyl derivatives (**4a**—**e**), and 5,6-dihydrouracils (**5a**—**e**) in varying ratios. The 6-benzyl adducts **3** were found to be derived *via* O(4)-protonation, while the 5-isomers (**4**) and dihydro derivatives (**5**) are suggested to be produced from 5,6-dihydrouracil-5-yl radicals (III) or their O(4)-protonated forms (III-H^{+}), which may be derived from II by C(6)-protonation.

Photoreaction of **1a** with **2** in the presence of TFA afforded 5,6-dihydro-1,3-dimethyl-5-fluoro-6-(*p*-methylbenzyl)uracil (**3a**) (22.8%), 5,6-dihydro-1,3-dimethyl-5-fluoro-5-(*p*-methylbenzyl)uracil (**4a**) (9.4%), and 5,6-dihydro-1,3-dimethyl-5-fluorouracil (**5a**) (8.4%), together with the substitution product **1e** (1.4%) (Chart 1). Similarly, photolysis of **1b** gave 5-chloro-5,6-dihydro-1,3-dimethyl-6-(*p*-methylbenzyl)uracil **3b** (5.3%), 5-chloro-5,6-dihydro-1,3-dimethyl-5-(*p*-methylbenzyl)uracil (**4b**) (3.8%) and 5-chloro-5,6-dihydro-1,3-dimethyluracil (**5b**) (15.5%), together with **1e** (13.1%). Other pyrimidines (**1c**, **1d**, and **1e**) gave the corresponding dihydrouracils, **3c**—**d**, **4c**—**e**, and **5c**—**e**, in varying yields (Chart 1 and Table 1). The reaction of **1b** with **2** was accompanied with the formation of **4e** and **5e** derived from **1e**.

Photoreactions of **1**(**c**, **d**) with **2** in the presence of TFA-*d* showed that deuterium uptake into **3c** and **d** was predominant at C(5) (119% for **c** and 89% for **d**, re-



R: **a**, F; **b**, Cl; **c**, H; **d**, CH_3; **e**, *p*-xylyl

Chart 1

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Table 1. Photoreaction of 1,3-Dimethyl-5-substituted Uracils (**1**) in *p*-Xylene (**2**) in the Presence of TFA

Starting compd. **1**	Yield (%) of **3**	**4**	**5**	**1e**	**6** (mmol)	Consumed **1** (%)	Ratio of **3**/(**4**+**5**)
a	22.8	9.4	8.4	1.4[a]	0.0025	56	1.28
b	5.3	3.8	15.5	13.1[a]	0.006	70	0.27
c	3.3	4.7	33.5	—	0.007	63	0.09
d	6.0	16.5	22.1	—	0.0035	52	0.16
e	—	22.5	20.2	—	0.003	47	*ca.*0

[a] In the reaction with **1a**, **5e** (0.5%) was obtained, while in the reaction with **1b**, **4e** and **5e** were produced as by-products in 2.2% and 3.5% yields, respectively.

Table 2. Deuterium Incorporation (%) into the Products of the Photoreaction of **1c** in *p*-Xylene (**2**) in the Presence of TFA-*d*[a]

Sites	Product **3c**	**4c**	**5c**	**1c**
C(5)	119	18	14	30
C(6)	0	100	76	0

[a] Determined from the ^{1}H-NMR spectra.

Table 3. Deuterium Incorporation (%) into the Products at Sites C(5) and C(6) by the Photoreaction of **1d** in **2** in the Presence of TFA-*d*[a]

Sites	Product **3d**	**4d**	**5d**
C(5)	89	—	15
C(6)	0	62	71

[a] Determined from the ^{1}H-NMR spectra.

Table 4. Ionization Potentials (eV) of Ia—f and IIa—f

	a	**b**	**c**	**d**	**f**
I	2.312	2.331	2.006	2.034	2.451
II	7.999	7.856	7.663	7.664	7.632

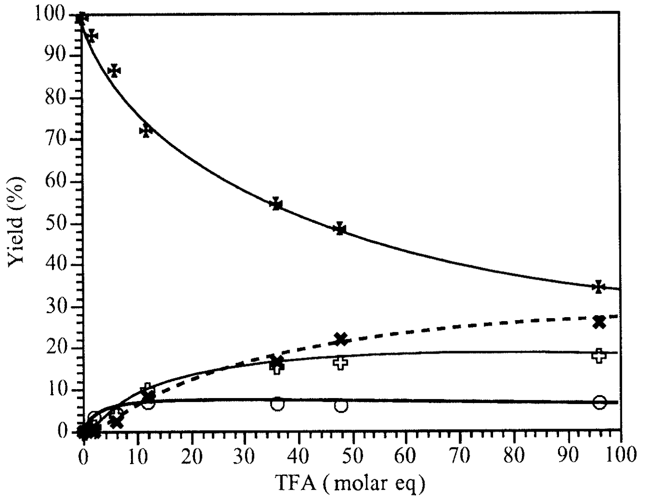

Fig. 1. Photoreaction of **1d** in **2** in the Presence of Varying Amounts of TFA (1 h)

✤,**1d**; ○, **3d**; ✧, **4d**; ✖, **5d**.

spectively), while in **4**(**c**, **d**) it occurred preferentially at C(6) (100% for **c** and 62% for **d**) as well as in **5**(**c**, **d**) (76% for **c** and 71% for **d**) (Tables 2 and 3). These observations suggest that O(4)-protonation participates importantly in the formation of **3**, while C(6)-protonation is significant for the formation of **4** and **5**. The deuterons incorporated into **3c** (19% of 119%), **4c** (18%), and **5c** (14%) at C(5) are presumed to originate mainly from those incorporated initially into **1c**, since deuterium exchange at C(5) in the recovered **1c** amounted to 30%.

Von Sonntag *et al.*[4] reported that the radical anion I formed in the radiolysis of an aqueous solution of **1**(**c**, **d**) can protonate rapidly at O(4) to give II, while a slower protonation occurs at C(6) to give III, and the deprotonation at carbon is much slower than that at oxygen at neutral pH, so that I and II are ultimately converted into III (see Chart 2). However, in view of the basicity of the radical I,[10] it seems unlikely that II could readily deprotonate from O(4) to form I, and reprotonate at C(6), leading to the key intermediate III-H$^+$, in the presence of a strong acid in the aprotic solvent. Interestingly, the ratio of **3** *vs.* (**4**+**5**) tends to decrease as the electron-donating character of the substituent at C(5) increases (see Table 1). It was assumed that the ratios reflect the feasibility of protonation of the intermediate radicals. According to the frontier orbital theory, protonation may depend on the ionization potentials of the substrates.[11] Hence, we performed MO calculations[12] for the possible intermediates I and II. In place of IIe, IIf (R=Ph) was used as a model to simplify the calculation (Table 4). Changes in the ratios apparently depend on the order of the calculated ionization potentials of the radicals II(**a**—**d** and **f**). The observation that the reaction of **1e** gave predominantly C(6)-protonation products, **4e** and **5e**, could not be interpreted solely in terms of the ionization potential. Presumably the resonance effects of the phenyl group are more important for the formation of the radical III-H$^+$.

In order to obtain further insight into the reaction mechanism, we carried out photolyses of **1d** in **2** in the presence of various amounts of TFA. As shown in Fig. 1 (see also Table 5), the formation of **3d**, **4d**, and **5d** is strongly dependent on TFA concentration; formation of the products was accelerated in the order of **3d** (2.9%)>**4d** (1.3%)>**5d** (0.0%) in the presence of a small amount of TFA (2 molar eq), while **5d** was produced predominantly when larger amounts of TFA (>36 molar eq) were used. These observations could be explained as follows (Chart 2). a) In the presence of a small amount of TFA, the protonation of **1d**[13] would promote electron transfer from **2** to **1d** to form a pair of II and the radical cation IV. The radical cation (IV) so produced would release its proton to give V, coupling of which to the O(4)-protonated radical II would result in the formation of **3d**. b) As the amount of TFA is increased, the initially produced radical (II) becomes susceptible to further protonation at C(6) to form the radical III-H$^+$, and this (or its deprotonated derivative III) would give rise to the formation of **4d**, in competition with the formation of the

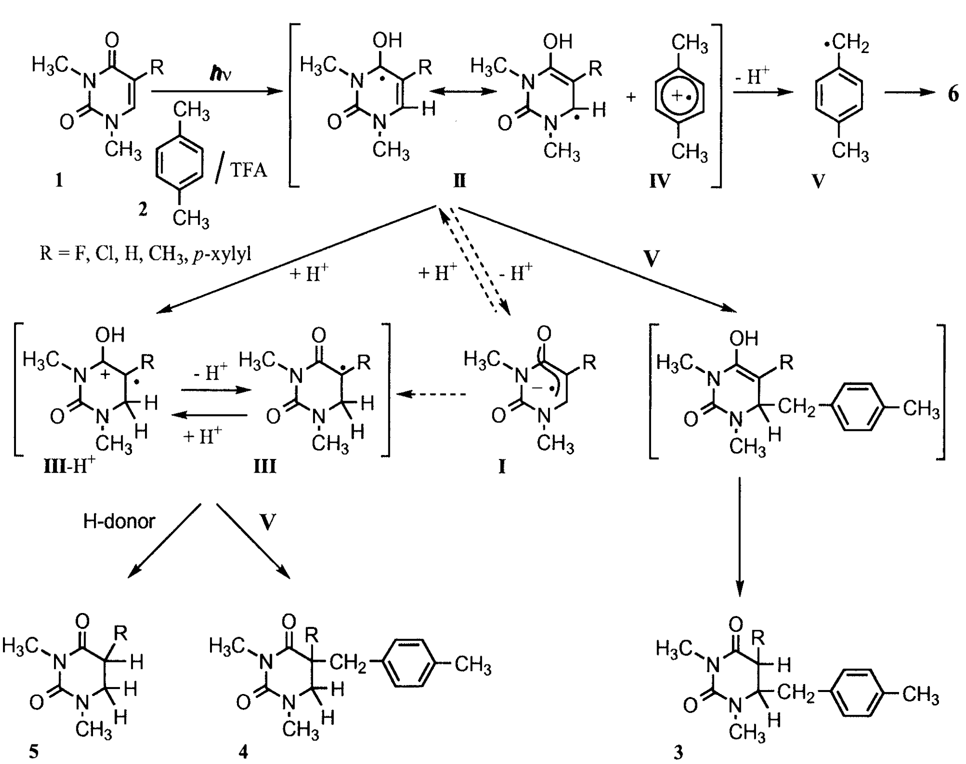

Chart 2

hydrogen abstraction product **5d**. c) In the presence of a larger excess of TFA (>36 molar eq), protons would still accelerate the generation of the radical pair of II and IV and further conversion of the former (II) into III-H$^+$ would occur, resulting in the increased yield of **5d**. On the other hand, the excess acid would suppress the deprotonation from IV to form V, resulting in no further increase in the yield of **4d**.

In contrast to the behavior of the electron adducts of pyrimidine bases in aqueous solutions, the present reaction appears to produce the C(6)-protonated radicals III-H$^+$ directly from II through C(6)-protonation. The extent of their formation depends strongly on the quantity of TFA added.

Experimental

^{1}H-NMR spectra were measured with a JEOL JNM-EX400 (400 MHz) spectrometer, and chemical shifts are given on the δ (ppm) scale with tetramethylsilane as an internal standard. Mass spectra (MS) and high resolution MS (HR-MS) were determined on a Shimadzu GCMS 9100-MK spectrometer. UV spectra were taken on a Shimadzu UV-240 instrument at room temperature. Gas-liquid chromatography (GLC) was performed with a capillary column (CPB1-M50-025, Shimadzu) on a Shimadzu GC-7A gas chromatograph equipped with a hydrogen flame-ionization detector using helium as a carrier gas. Short-column chromatography was conducted on Kieselgel Si-60 (Merck). Reverse-phase liquid chromatography (RP-LC) was carried out on a Shim-pac Prep-ODS (25 cm × 20 mm i.d.) (Shimadzu) with aqueous methanol, using a Shimadzu LC-6A apparatus with monitoring at 254 nm. Silica gel LC (Si-LC) was conducted on a Shim-pac Prep-Sil (25 cm × 20 mm i.d.), using the same apparatus.

General Procedure for the Analytical-Scale Photoreactions: Photolyses of 5-Substituted 1,3-Dimethyluracils (1a—e) in *p*-Xylene (2) in the Presence of Trifluoroacetic Acid (TFA) A solution of **1** (0.025 mmol) in **2** (5 ml) in the presence of TFA (1.2 mmol) was irradiated externally with a 500 W high-pressure mercury lamp (>300 nm) (Eiko-sha) in a degassed Pyrex tube on a merry-go-round apparatus for 1 h, and the reaction mixture was subjected to GLC analysis.

Table 5. Photoreaction of **1d** in **2** in the Presence of Various Amounts of TFA

TFA (molar eq)	Yield (%) of			Unreacted **1d** (%)
	3d	**4d**	**5d**	
0	0.0	0.0	0.0	99.0
2	0.0	2.9	1.3	94.7
6	2.3	4.0	4.2	86.3
12	8.1	6.7	10.0	72.0
36	16.5	6.1	15.4	54.6
48	22.1	6.0	16.5	48.3
96	25.6	6.3	18.0	34.2

Photolyses of 1d in 2 in the Presence of Various Amounts of TFA Photolyses of **1d** were performed according to the procedure described above but in the presence of various amounts of TFA [2(=0.05 mmol), 6, 12, 36, 48, and 96 molar eq]. The results are listed in Table 5.

General Procedure for the Preparative-Scale Photoreactions A solution of **1** (1 mmol) in **2** (200 ml) in the presence of TFA (3.57 ml, 48 mmol) was irradiated in a doughnut-type Pyrex vessel with a 500 W high-pressure mercury lamp under an argon atmosphere (**a**, 10 h; **b**, 5 h; **c** and **d**,[1a)] 20 h). In the case of **1e**, the following reaction conditions were employed; **1e** (0.66 mmol), **2** (160 ml), TFA (2.8 ml, 38 mmol), 5 h.[8)]

Preparation of 3a, 4a, and 5a After removal of the solvent, the reaction mixture was passed through a short column of silica gel with hexane, and then with 5% ethanol–ethyl acetate. The ethanol–ethyl acetate eluate was submitted to Si-LC (10% ethyl acetate–dichloromethane) to give the 5-*p*-methylbenzyl derivatives **4a** (19.8 mg, 7.5%), **5e** (30 mg, 12.2%) and a mixture of **5a**, **1e** and **3a**, respectively. The RP-LC (38% methanol–H_2O) of the mixture afforded **5a** (17.8 mg, 11.1%), **1e** (4.1 mg, 1.7%) and **3a** (39.1 mg, 14.8%), successively.

5,6-Dihydro-1,3-dimethyl-5-fluoro-6-(*p*-methylbenzyl)uracil (**3a**): Colorless oil. MS *m*/*z* (%): 264 (M^+, 7), 159 (60), 106 (59), 105 (100), 102 (78). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, Ar-CH_3), 2.77 (1H, dd, $J=14.2$, 7.3 Hz, Ar-CH_2–), 2.85 (3H, s, N–CH_3), 2.90 (3H, s, N–CH_3), 3.03 (1H, dd, $J=14.2$, 3.4 Hz, $J_{F-H}=7.3$ Hz, Ar-CH_2–), 3.91 (1H, ddd, $J=7.3$, 7.3, 3.4 Hz, H-6), 5.18 (1H, d, $J=7.3$ Hz, $J_{F-H}=47.4$ Hz, H-5), 7.00 (2H, d, $J=8.1$ Hz, Ar-H), 7.11 (2H, d, $J=8.1$ Hz, Ar-H). *Anal.* Calcd for $C_{14}H_{17}FN_2O_2$: C, 63.62; H, 6.48; N, 10.60. Found: C, 63.78; H, 6.66; N, 10.60.

5,6-Dihydro-1,3-dimethyl-5-fluoro-5-(*p*-methylbenzyl)uracil (**4a**): Colorless oil. MS *m*/*z* (%): 264 (M^+, 10), 144 (83), 229 (31), 105 (100). ^{1}H-NMR (acetone-d_6) δ: 2.31 (3H, s, Ar-CH_3), 2.94 (3H, s, N–CH_3), 3.11 (3H, s, N–CH_3), 3.14 (1H, d, J=14.7 Hz, J_{F-H}=30.8 Hz, Ar-CH_2–), 3.33 (1H, d, J=14.7 Hz, Ar-CH_2–), 3.39 (1H, d, J=13.2 Hz, J_{F-H}=13.2 Hz, H-6), 3.49 (1H, d, J=13.2 Hz, J_{F-H}=20.5 Hz, H-6), 7.16 (4H, s, Ar-H). HR-MS: *Anal.* Calcd for $C_{14}H_{17}FN_2O_2$: 264.1273. Found: 264.1265.

5,6-Dihydro-1,3-dimethyl-5-fluorouracil (**5a**): mp 46.5—47.5 °C (lit. 51 °C).[14] MS *m*/*z* (%): 160 (M^+, 76), 46 (100). ^{1}H-NMR ($CDCl_3$): δ 3.10 (3H, s, N–CH_3), 3.21 (3H, s, N–CH_3), 3.55—3.73 (2H, m, H-6), 5.06 (1H, dd, J=7.8, 5.4 Hz, J_{F-H}=47.4 Hz, H-5). HR-MS: *Anal.* Calcd for $C_6H_9FN_2O_2$: 160.0648. Found: 160.0661.

Preparation of 3b, 4b, and 5b (Preparative-Scale Photoreaction of 1b in 2) After photolysis of **1b** (174.5 mg, 1 mmol) (5 h), successive chromatography in the same manner as described above gave the 5-*p*-methylbenzyl derivatives **4e** (19.3 mg, 5.5%) and **4b** (13.7 mg, 4.9%), the 6-isomer **3b** (23 mg, 8.2%), the substituted product **1e** (12 mg, 4.9%), and the 5,6-dihydro derivatives **5e** (23.1 mg, 9.4%) and **5b** (19.7 mg, 11.1%).

5-Chloro-5,6-dihydro-1,3-dimethyl-6-(*p*-methylbenzyl)uracil (**3b**): Colorless oil. MS *m*/*z* (%): 283 (0.4), 282 (M^+, 0.9), 281 (1.3), 280 (M^+, 2.3), 246 (15), 245 (2.4), 177 (13), 175 (38), 141 (52), 140 (26), 120 (10), 118 (31), 106 (35), 105 (100). ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s, Ar-CH_3), 2.88 (3H, s, N–CH_3), 2.91 (1H, dd, J=13.5, 6.9 Hz, Ar-CH_2–), 2.97 (3H, s, N–CH_3), 3.12 (1H, dd, J=13.5, 5.6 Hz, Ar-CH_2–), 3.82 (1H, ddd, J=6.9, 5.6, 5.2 Hz, H-6), 4.67 (1H, d, J=5.2 Hz, H-5), 7.03 (2H, d like, J=7.9 Hz, Ar-H), 7.12 (2H, d like, J=7.9 Hz, Ar-H). HR-MS: *Anal.* Calcd for $C_{14}H_{17}ClN_2O_2$: 280.0978. Found: 280.0966.

5-Chloro-5,6-dihydro-1,3-dimethyl-5-(*p*-methylbenzyl)uracil (**4b**): mp 113—115 °C (recrystallized from hexane). MS *m*/*z* (%): 283 (0.3), 282 (M^+, 0.7), 281 (0.8), 280 (M^+, 1.5), 245 (100), 244 (61), 131 (29), 105 (98). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, Ar-CH_3), 3.03 (3H, s, N–CH_3), 3.22 (3H, s, N–CH_3), 3.41 (2H, s, Ar-CH_2–), 3.44 (1H, d, J=14.1 Hz, H-6), 3.58 (1H, d, J=14.1 Hz, H-6), 7.14 (4H, s, Ar-H). HR-MS: *Anal.* Calcd for $C_{14}H_{17}ClN_2O_2$: 280.0978. Found: 280.0979.

5-Chloro-5,6-dihydro-1,3-dimethyluracil (**5b**): Colorless oil. MS *m*/*z* (%): 178 (M^+, 38), 176 (M^+, 100), 141 (10), 119 (20), 62 (36); HR-MS: *Anal.* Calcd for $C_6H_9ClN_2O_2$: 176.0358. Found: 176.0352.

Deuterium Labeling Experiment The photoreaction of 1,3-dimethyluracil or 1,3-dimethylthymine (**1c** or **1d**) in *p*-xylene (**2**) in the presence of trifluoroacetic acid-*d* (TFA-*d*) was conducted preparatively in the same manner as described above. Deuterium incorporation into the products was determined by ^{1}H-NMR spectroscopy.

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13) Upon addition of TFA (2 molar eq), the UV peak of **1d** (λ_{max} 266 nm) shifted to the red by *ca.* 5 nm at the longer wavelength region from the λ_{max} in cyclohexane, as found for **1a**, and the ^{13}C-NMR spectra showed remarkable shifts of the peaks due to C-4 and C-6: ^{13}C-NMR ($CDCl_3$) δ 164.0 to 165.4 (C-4); δ 138.9 to 140.5 (C-6).
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