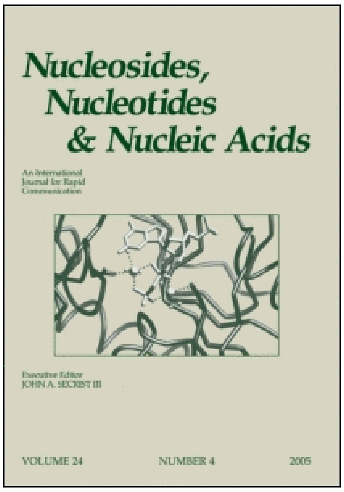

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Acid-Catalyzed Photosubstitution of 5-Fluoro-1,3-Dimethyluracil with Substituted Benzenes

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ACID-CATALYZED PHOTOSUBSTITUTION OF 5-FLUORO-1,3-DIMETHYLURACIL WITH SUBSTITUTED BENZENES[†]

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Abstract. The substantial photosubstitution of 5-fluoro-1,3-dimethyluracil with substituted benzenes is first achieved by the addition of trifluoroacetic acid to the reaction mixture. The presence of protons is essential for the formation of 5-aryl-1,3-dimethyluracils.

Protonated radical anions derived from uracil derivatives by electron attachment are of interest from synthetic and chemical points of view[1] as well as for their relevance to radiation damage to the living cell.[2] Previous work has shown that the protonated uracils behave differently depending on the halogen on the uracil ring and the reaction systems. However, the dependence of proton participation in various reactions has not been fully elucidated. We have recently reported the different types of photoreactions in the presence of acid of 5-bromo-[3] and 5-chloro-1,3-dimethyluracil[4] with substituted benzenes. In the former case, the presence of acid led to the formation of the unexpected 6-aryl isomer; the 5-isomer being the normal product in the absence of acid. However, in the latter case, with trifluoroacetic acid (TFA) present, the reaction was significantly accelerated resulting in appreciably improved yields of the 5-isomer. In an extension of this work, we now report on the photoreaction of 5-fluoro-1,3-dimethyluracil (5-FDMU) with various substituted benzenes. In the absence of TFA, the maximum

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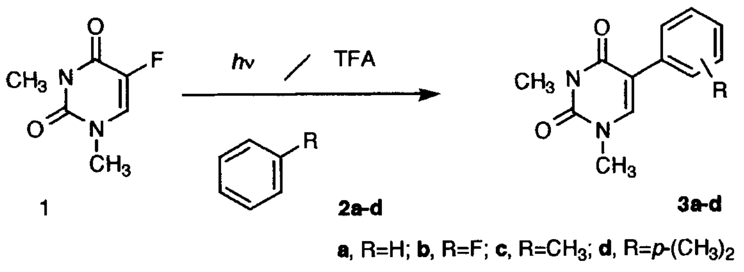
[†] Dedicated to the late Professor Tohru Ueda.



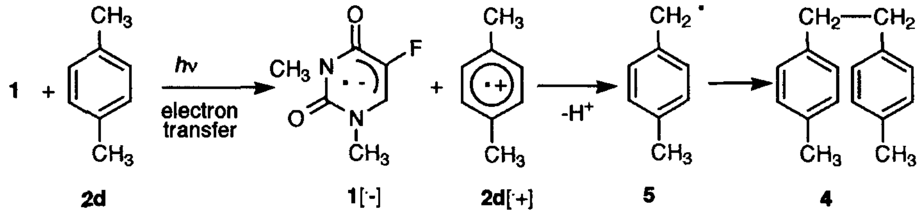
Scheme 1

Table I. Photolysis of 5-FDMU (**1**) in Substituted Benzenes (**2**)

2	TFA (mmol)	Reaction time(h)	5-ArDMU (**3**) Yields(%)	5-ArDMU (**3**) [isomer ratio(%)]	Consumed **1** (%)
2a	none	10	<0.1		5
	1.2	10	29		40
2b	none	10	<0.1		10
	0.05	10	32	[o:m:p = 30:32:38]	44
2c	none	10	0.7	[o:m:p = 70: 0:30]	10
	0.05	10	27	[o:m:p = 48:17:35]	46
2d	none	5	1.0		12
	0.05	5	13		61

degree of substitution was <0.1-1.0 %; in the presence of TFA the yields were increased to 13-32 %. Cf. Table I.

Solutions of 5-FDMU (**1**) in 5 ml of substituted benzenes (**2a**, benzene; **2b**, fluorobenzene; **2c**, toluene; **2d**, p-xylene) were irradiated in the presence and in the absence of TFA (Scheme 1). The reaction with **2a** in the absence of TFA gave barely detectable 5-phenyl-1,3-dimethyluracil (**3a**) (<0.1%). By contrast, the reaction in the presence of TFA afforded **3a** in 29 % yield. A very similar result was obtained for the reaction with **2b**; in this case the product consisted of a regioisomeric mixture

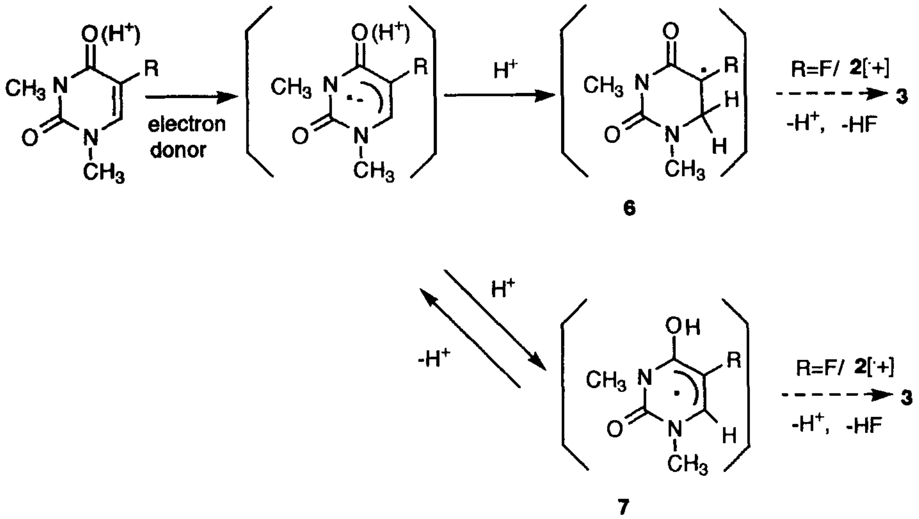


Scheme 2

of 5-(2-, 3-, and 4-fluorophenyl)-1,3-dimethyluracils (**3b**$_{\text{i-iii}}$). Similarly the photoreaction in **2c** and **2d** in the absence of TFA produced 5-(2-, 3-, and 4-tolyl)-1,3-dimethyluracils (**3c**$_{\text{i-iii}}$), and 5-(p-xylyl)-1,3-dimethyluracils (**3d**) in detectable yields; whereas in the presence of TFA substantially higher yields were obtained. Cf. Table I.

Interestingly the formation of some amounts of bi-p-methylbenzyl (**4**) (6.4×10^{-4} mmol) was detected in the reactions with **2d** in the absence of TFA. Since the formation of **4** might be the result of the coupling of p-methylbenzyl radical (**5**), derived from the initially generated radical cations **2d**[$\cdot^{+}$] with the radical anion of **1** (**1**[$\cdot^{-}$]) via electron transfer by deprotonation (Scheme 2),[5] it is reasonable to assume that protons are present in the reaction mixture. In fact no **3d** was detected in the reaction in the presence of 10% aqueous K_2CO_3 (0.1 ml).

Thus it was suggested that the presence of a proton might be essential for the formation of 5-ArDMU (**3**) in the present reaction. In order to confirm the importance of the presence of protons for the formation of 5-ArDMU (**3**), the photolyses of **1** were performed in equivolume solutions of **2a** and various media under the conditions employed above (10 h). In the aprotic solvents, acetonitrile and cyclohexane, no **3a** was detected, while in methanol **3a** was obtained in 13 % yield (based on 48 % **1** consumed). Furthermore, in the presence of TFA (0.05 mmol) the reaction in cyclohexane resulted in the formation of **3a** in appreciable yield (79 %, based on 52% **1** consumed). These findings suggest that the present reaction may involve the σ-radical (**6**), which is reported to be produced from the radical anion of uracil derivatives by C-6 protonation in competition with the formation of the π-radical (**7**) by O-protonation (Scheme 3).[2b] However it seems unlikely that **3** resulted from a cou-



Scheme 3

pling between 5-fluoro-5,6-dihydro-1,3-dimethyluracil-5-yl radical (**6**, R=F) and the radical cation **2**[$\cdot^{+}$];6) since no deuterium (D) was found to be incorporated in **3a** at the C-6 upon irradiation of the solution of **1** in **2a** in the presence of d-TFA. Presumably a proton participates importantly in the excited states of **1** or in the exciplex formation between **1** and **2**. The results that the reaction in the presence of TFA (0.05 mmol) in cyclohexane proceeded more efficiently than the reaction in methanol (2.5 ml) may suggest that TFA is not only important in the excited states but in the ground states. In fact the ultraviolet (uv) spectrum of **1** (λ_{max} 268 nm) shifted ca. 5 nm to the red in cyclohexane by the addition of TFA, indicating that **1** may form the protonated **1** or the charge transfer complex with added TFA in the ground state. It is noteworthy that the present reaction provides the first substantial aromatic photosubstitution of 5-FDMU at the C-F bond,7) wherein acid serves essentially.

Further work to elucidate the general features of the acid-catalyzed photoreaction of halouracils is now in progress.

EXPERIMENTAL

Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were measured with a EX400 (400 MHz, JEOL) spectrometer, and chemical shifts were given on the δ (ppm) scales with tetramethylsilane as an internal standard. Abbreviations are used as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Mass spectra (ms) were determined on a JEOL QH-100 mass spectrometer. Uv spectra was taken on a Shimadzu UV-240 at room temperature. High-performance liquid chromatograpy (hplc) was performed with a Shimadzu HPLC system (pump, LC-5A ; detector, SPD-2A; controller, SIL-6A) equipped with a pre-packed column (Wakosil II-5C18, 4.6 mm *i.d.* x 250 mm, Wako), using caffeine as an internal standard. Uv-irradiation was carried out with a 500 W high-pressure mercury lamp (Eiko-sha) at room temperature.

General Procedure for the Photolysis of 5-Fluoro-1,3-dimethyluracil (1) in Substituted Benzenes (2a-d) ———A solution of **1** (3.95 mg, 0.025 mmol) in **2a-d** (5ml) or in **2a** and a solvent (2.5 ml + 2.5 ml) was irradiated externally in a degassed Pyrex tube using a merry-go-round apparatus (Eiko-sha) in the presence or in the absence of trifluoroacetic acid (TFA). The reaction mixture was evaporated under reduced pressure and the residual oil was submitted to hplc (methanol-H_2O, 25-100%) with monitoring at 254 nm. The products (**3a-d**) were identified by comparison of their spectroscopic (MS) and chromatographic behavior with the authentic samples prepared by the photolysis of 5-bromo-1,3-dimethyluracil in **2a**, **c** and **d**,[3)] and 5-iodo-1,3-dimethyluracil in **2b**, respectively.

Preparation of 5-(2-, 3-, and 4-Fluorophenyl)-1,3-dimethyluracils ($\mathbf{3b_i}$, $\mathbf{3b_{ii}}$, and $\mathbf{3b_{iii}}$) ———A solution of a mixture of 5-iodo-1,3-dimethyluracil (5-IDMU) (133 mg, 0.5 mmol) in fluorobenzene (**2b**) (100 ml) was irradiated externally under argon in a doughnut-type Pyrex vessel for 2 h. The reaction mixture was evaporated under reduced pressure and the residual oil was passed through a short column of silica gel (Kieselgel60 F_{254}, Merck) (10 g) first with hexane (25 ml) and then with ether (150 ml). The ether eluate (116 mg) was submitted to silica gel column chromatography with ether-hexane (1 : 1) on the hplc apparatus equipped with a pre-packed column (Shim-Pac Prep-Sil, Shimadzu) to furnish $\mathbf{3b_i}$ (47.3

mg, 40.4 %), 5-IDMU (14.2 mg, 10.7 %), **3b$_{ii}$** (31.8 mg, 27.2 %), and **3b$_{iii}$** (18.0 mg, 15.4 %), subsequently.

3b$_i$; mp 142-143°C (from hexane). Anal. Calcd for $C_{12}H_{11}N_2O_2F$: C, 61.53; H, 4.73; N, 11.96. Found C, 61.52; H, 4.61; N, 11.89. ^{1}H-Nmr ($CDCl_3$) δ: 3.43 and 3.47 (3Hx2, s, N-CH_3), 7.12 (1H, ddd, J = 10.2, 8.2, 1.2 Hz, 3'-H), 7.17 (1H, ddd, J = 7.7, 7.5, 1.2 Hz, 5'-H), 7.32 (1H, dddd, J = 8.2, 7.5, 5.5, 1.8 Hz, 4'-H), 7.36 (1H, d, J = 1.5 Hz, 6-H), 7.47 (1H, ddd, J = 7.7, 7.6, 1.8 Hz, 6'-H). Ms m/z (%): 234 (M^+, 100), 177 (33), 158 (70), 136 (36), 107 (71). Uv λ_{max} (ethanol): 230 (9900) and 278 (11000) nm (ε).

3b$_{ii}$; mp 210-212°C (from ethanol). Anal. Calcd for Calcd for $C_{12}H_{11}N_2O_2F$: C, 61.53; H, 4.73; N, 11.96. Found C, 61.58; H, 4.62; N, 11.82. ^{1}H-Nmr (acetone-d_6) δ: 3.31 and 3.50 (3Hx2, s, N-CH_3), 7.05 (1H, tdd, J = 8.5, 2.8, 0.9 Hz, 4'-H), 7.39 (1H, ddd, J = 8.5, 8.1, 6.2 Hz, 5'-H), 7.46 (1H, ddd, J = 8.1, 1.3, 0.9 Hz, 6'-H). 7.47 (1H, ddd, J = 9.9, 2.8, 1.3 Hz, 2'-H), 7.95 (1H, s, 6-H). Ms m/z (%): 234 (M^+, 100), 176 (75), 136 (67). Uv λ_{max} (ethanol): 242(10800) and 287(10900) nm(ε).

3b$_{iii}$; mp 141-142°C (from i-propanol). Anal. Calcd for $C_{12}H_{11}N_2O_2F$: C, 61.53; H, 4.73; N, 11.96. Found C, 61.65; H, 4.71; N, 11.83. ^{1}H-Nmr (acetone-d_6) δ: 3.31 and 3.48 (3Hx2, s, N-CH_3), 7.13 (2H, dddd, J = 9.0, 8.8, 2.5, 0.09 Hz, 3'-H and 5'-H), 7.64 (2H, dddd, J = 8.8, 5.1, 2.5, 0.09 Hz, 2'-H and 6'-H), 7.85 (1H, s, 6-H). Ms m/z (%): 234 (M^+, 100), 176 (31), 136 (40). Uv λ_{max} (ethanol): 237(11000) and 282(9770) nm(ε).

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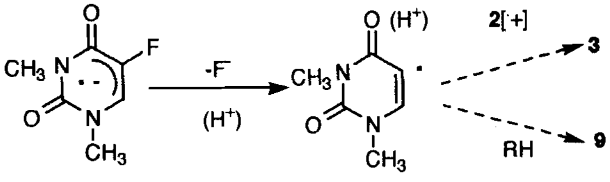
6. In view of the ESR study$^{2c,8)}$ and the MO calculation$^{9)}$ for **1**[$\cdot^-$] and its protonated derivative, showing that **1**[$\cdot^-$] would be difficult to dissociate to 1,3-dimethyluracyl-5-yl radical (**8**) under acidic conditions, it seems unlikely that the formation of **3** is the result of the coupling of **8**, derived from **1**[$\cdot^-$] by elimination of fluoride ion (F^-), and **2**[$\cdot^+$] (Scheme 4). The fact that no formation of 1,3-dimethyluracil (**9**) was detected may support the above basis.



1[·-] **8**

Scheme 4

7. Various photochemical studies including hydration, cycloaddition and dimerization have been reported for 5-fluorouracil and its dimethyl derivative 5-FDMU which, however, can be regarded as chemistry of the olefinic part: see references in; S. Y. Wang, "Photochemistry and Photobiology of Nucleic Acid" Vol. 1, ed. by S. Y. Wang, Academic Press, New York, 1976, Chapter 6; W. M. Horspool, "Enone Cycloadditions and Rearrangements: Photoreactions of Dienones and Quinones" in "Photochemistry", ed. by D. Bryce-Smith, The Royal Society of Chemistry, London, Vols. 12, 16, and 17, 1982, 1985, and 1986; A. J. Wexler, R. J. Balchunis, and J. S. Swenton, *J. Org. Chem.*, **49**, 2733 (1984).
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9. Unpublished data. For chloro derivatives, see ref. 3b).

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