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Photolysis of 5-Bromo-1,3-dimethyluracil in Substituted Benzenes[1]

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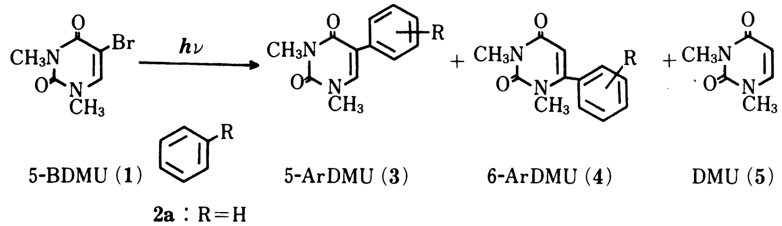
Photolysis of 5-bromo-1,3-dimethyluracil (5-BDMU) in substituted benzenes afforded the corresponding 5-aryl derivatives together with the unexpected 6-isomers as an isomeric mixture. The 6-isomers were found to be derived from the protonated 5-BDMU, presumably *via* the interaction between $LUMO_{5\text{-BDMU}}$ (in the excited triplet state) and $LUMO_{aryl}$ (in the ground state).

Keywords——5-aryl-1,3-dimethyluracil; 6-aryl-1,3-dimethyluracil; photolysis; 5-bromo-1,3-dimethyluracil; benzene; acid-catalyzed aromatic photosubstitution; frontier orbital theory; LUMO–LUMO interaction; LUMO-controlled regioselectivity; electron transfer

It is well known that the replacement of thymine in deoxyribonucleic acid (DNA) with 5-halouracil (5-halo-2,4-pyrimidinedione) increases the sensitivity of bacterial and mammalian cells to the lethal effects of ultraviolet, X-ray or γ-ray irradiation.[2] To understand the molecular basis of this phenomenon, the photochemical reactions of 5-halouracils have been studied intensively and various types of photoreactions have been reported: *inter alia* hydrogen abstraction, dimerization, and the addition of oxygen.[2] Recently, the photoreaction of nucleic acids substituted with 5-bromouracil was reported to result in photo-induced cross-linking to proteins, the importance of which in aging, carcinogenesis, and radiation biology has been reviewed.[3] As a model reaction for the photo-induced cross-linking of proteins and nucleic acids, Matsuura *et al.* carried out the photoreaction of 5-bromo-1,3-dimethyluracil (5-BDMU) in the presence of various indole derivatives and found that the uracil moiety attacked indoles at the 2-position regiospecifically to give the coupling products in fair yields.[4] These reactions were carried out in aqueous or polar media, but very little is known about the course of the reaction in less polar solutions.[5]

In the present paper, we report that the photoreaction of 5-BDMU in a solution of a substituted benzene afforded the 5-aryl-1,3-dimethyluracils (5-ArDMU) and the unexpected 6-arylated derivatives (6-ArDMU) (Chart 1), and that the acid formed during the course of the reaction was important for the formation of the 6-isomers.



2a : R=H
2b : R=CH_3
2c : R=OCH_3
2d : R=1, 4-dimethyl
2e : R=1, 2-dimethoxy

Chart 1

TABLE I. Preparative-Scale Photoreaction of 5-BDMU (**1**) in Benzenes (**2a**—**e**)

2	Reaction time (h)	Yield (%)[a]			Recovered **1** (%)[a]	Ratio of **4**/**3** (*N*)
		3	**4**	**5**		
2a	40	11	0.9	—[b]	9	0.08
2b	40	19	2.8	—[b]	5.5	0.15
2c	40	21.4	3.6	—[b]	6	0.17
2d	20	30.7	18.1	2.5	12	0.59
2e	20	15.7	0.0	2.3	28.2	0.0

a) Yield of isolated products. *b*) Not determined.

TABLE II. Physical Data for 5-Aryl- and 6-Aryl-1,3-dimethyluracils (**3** and **4**)

Compd.	mp (°C)	Crystn. solvent (Physical form)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
3a	149 (lit. 147—148)[6]	Benzene–hexane (Needles)				
4a[5,6]	102—103	Ethanol or benzene–hexane (Needles)	$C_{12}H_{12}N_2O_2$	66.65 (66.46	5.50 5.60	12.96 12.94)
3b$_2$	123—124	Hexane (Needles)	$C_{13}H_{14}N_2O_2$	67.81 (67.86	6.13 6.07	12.17 12.16)
3b$_3$	132—133	Benzene–hexane (Needles)		(67.98	6.21	12.29)
3b$_4$	121—122	Benzene–hexane (Needles)		(67.78	6.08	12.13)
4b$_2$	165	Benzene–hexane (Needles)		(67.82	6.14	12.17)
4b$_3$	167.5—168	Benzene–hexane (Needles)		(67.64	6.11	12.27)
4b$_4$	113.5—114.5	Benzene–hexane (Needles)		(67,81	6.10	12.01)
3c$_2$	123—124	Benzene–hexane (Needles)	$C_{13}H_{14}N_2O_3$	63.40 (63.57	5.73 5.68	11.38 11.43)
3c$_3$	128—129	(iso-Pro)$_2$O (Needles)		(63.25	5.68	11.41)
3c$_4$	138—139	(iso-Pro)$_2$O (Needles)		(63.36	5.69	11.59)
4c$_2$	120—121	Benzene–hexane (Needles)		(63.37	5.76	11.62)
4c$_3$	114—115	Benzene–hexane (Needles)		(63.39	5.77	11.48)
4c$_4$	87	Benzene–hexane (Fine needles)		(63.37	5.71	11.22)
3d	146	Hexane	$C_{14}H_{16}N_2O_2$	68.83 (68.78	6.60 6.70	11.47 11.43)
4d	Oil	—		(68.88	6.69	11.51)
3e$_{2,3}$	154—155	Benzene–hexane (Fine needles)	$C_{14}H_{16}N_2O_4$	60.86 (60.95	5.84 5.94	10.14 10.06)
3e$_{3,4}$	152—153.5	(iso-Pro)$_2$O–hexane (Plates)		(60.61	5.87	10.03)

TABLE III. UV[a] and MS Spectra for 5-Aryl- and 6-Aryl-1,3-dimethyluracil (**3** and **4**)

Compd.	UV (nm) λ_{max} (ε)	ε_{254}	MS (m/z, %)
3a	239 (11660), 285 (10360)	7680	216 (86, M$^+$), 158 (100)
4a	275.5 (10233)	5290	216 (76, M$^+$), 215 (71), 118 (100)
3b$_2$	206 (22340), 276 (9440)	5090	230 (98, M$^+$), 229 (33), 213 (82), 116 (100)
3b$_3$	238.5 (10390), 285 (10170)	8150	230 (100, M$^+$), 172 (82)
3b$_4$	240 (13720), 285 (10390)	9320	230 (100, M$^+$), 172 (69)
4b$_2$	207 (19780), 270.5 (10340)	6280	230 (73, M$^+$), 229 (43), 215 (51), 144 (100)
4b$_3$	207 (21660), 275 (10480)	5580	230 (100, M$^+$), 229 (92), 172 (57), 132 (89)
4b$_4$	205 (20740), 277 (11580)	7090	230 (100, M$^+$), 229 (95), 172 (55), 132 (90)
3c$_2$	211 (21330), 278 (9890)	7150	246 (100, M$^+$), 245 (10), 229 (22), 158 (76)
3c$_3$	232 (10350), 241 (11710), 286 (10400)	10350	246 (100, M$^+$), 188 (51)
3c$_4$	203 (17300), 244 (15590), 289 (10590)	12030	246 (100, M$^+$), 148 (42)
4c$_2$	211 (22570), 275 (11130)	5600	246 (100, M$^+$), 245 (26), 231 (30), 158 (59), 148 (56)
4c$_3$	213.5 (25190), 277 (11500)	5580	246 (100, M$^+$), 245 (96), 231 (13), 188 (63), 148 (94)
4c$_4$	204.5 (18940), 281.5 (13890)	9220	246 (100, M$^+$), 231 (33), 158 (86), 148 (78)
3d	208 (22390), 276 (9490)	5380	244 (100, M$^+$), 243 (32), 227 (94), 154 (43)
4d	211 (20410), 270 (10470)	7100	244 (88, M$^+$), 243 (37), 229 (100), 172 (78), 158 (58)
3e$_{2,3}$	248 (9250), 293 (8830)	13620	276 (100, M$^+$), 247 (67), 245 (84), 188 (45), 176 (95)
3e$_{3,4}$	210 (25360), 276 (10700)	6350	276 (100, M$^+$), 261 (26), 178 (31), 163 (31)

a) Measured in methanol solution.

The photoreaction of 5-BDMU (**1**) in a solution of various substituted benzenes (**2a**—**d**) gave the corresponding 5-ArDMU (**3**) and the unexpected 6-ArDMU (**4**) in various **4**:**3** ratio (N), together with the debrominated compound, 1,3-dimethyl-2,4-pyrimidinedione (1,3-dimethyluracil) (DMU) (**5**). The highest N (0.59) was observed in the reaction with *p*-xylene (**2d**), while the reaction with veratrole (**2e**) afforded only 5-ArDMU, 5-(2,3-dimethoxyphenyl)-1,3-dimethyluracil (**3e**$_{2,3}$) and 5-(3,4-dimethoxyphenyl)-1,3-dimethyluracil (**3e**$_{3,4}$) in the ratio of 4:7, and the formation of 6-ArDMU (**4e**) was not detected. By contrast, the photolysis of **1** in mono-substituted benzenes, *e.g.*, toluene (**2b**) and anisole (**2c**), resulted in the formation of all possible isomers. Thus **2b** afforded the 5-ArDMU isomers, 1,3-dimethyl-5-(x-methylphenyl)uracils (**3b**$_x$; $x=2$, 3, and 4), in the ratios of 88.5:6.5:5, and **2c** yielded the isomers, 1,3-dimethyl-5-(x-methoxyphenyl)uracils (**3c**$_x$; $x=2$, 3, and 4), in the ratios of 65:23:12. The 6-ArDMU isomers from **2b** (**4b**$_x$, $x=2$, 3, 4) were obtained in the ratios of 29:56:15, and **2c** gave the isomers **4c**$_x$, $x=2$, 3, and 4, in the ratios of 27.5:64:9. For **2b** and **2c**, $N=0.15$ and 0.17, respectively. These results are summarized in Table I.

The structure of **4a** was confirmed by comparing the physical data with those of the sample obtained by the photolysis of 6-iodo-[5] and 6-chloro-1,3-dimethyluracils (6-IDMU, 6-CDMU). Compound **3a** was identical with an authentic sample photochemically prepared from 5-iodo-1,3-dimethyluracil (5-IDMU).[5] The structural assignments of the other products (**3**, **4**) were made on the basis of the elemental analyses (Table II) and the spectra. The mass spectral (MS) and ultraviolet (UV) spectral data are listed in Table III. In the proton nuclear magnetic resonance (^{1}H-NMR) spectra, the peaks due to the C-6 olefinic proton of 5-ArDMU (**3**) appeared at 7.11—7.75 as singlets, while the peaks due to the C-5 proton of 6-ArDMU (**4**) appeared at 5.61—5.70 as singlets (Table IV-1). The assignment of the substitution sites on the benzene rings was made by analysis of the spin–spin coupling of the protons (Table IV-2).

In order to explore the factors affecting the substitution at the 6-position of **1**, we investigated the time course of the photoreaction of **1** in *p*-xylene (**2d**), and found that the

TABLE IV-1. ^{1}H-NMR Chemical Shifts, δ (ppm), for 5-Aryl- and 6-Aryl-1,3-dimethyluracil (**3** and **4**)

Compd.	1N–CH$_3$	3N–CH$_3$	5-H	6-H	2′-H	3′-H	4′-H	5′-H	6′-H	Ar–CH$_3$	–OCH$_3$
3b$_2$[a,c,g]	3.42	3.44	—	7.12	—	7.24	7.27	7.19	7.11	2.23	
3b$_3$[b,c]	3.36	3.45	—	7.71	7.33	—	7.13	7.25	7.30	2.33	
3b$_4$[b,c]	3.36	3.45	—	7.70	7.40	7.19	—	7.19	7.40	2.34	
4b$_2$[a,c]	3.07	3.42	5.65	—	—	7.16	7.30	7.39	7.31	2.24	
4b$_3$[b,c]	3.20	3.35	5.64	—	7.27	—	7.23	7.40	7.36	2.41	
4b$_4$[a,d]	3.22	3.40	5.57	—	7.41	7.17	—	7.17	7.41	2.42	
3c$_2$[b,e]	3.34	3.42	—	7.56	—	7.02	7.33	6.96	7.21		3.77
3c$_3$[b,e]	3.37	3.46	—	7.75	7.13	—	6.88	7.28	7.08		3.81
3c$_4$[b,d]	3.37	3.45	—	7.64	7.44	6.92	—	6.92	7.44		3.81
4c$_2$[b,c]	3.12	3.35	5.61	—	—	7.15	7.53	7.09	7.27		3.87
4c$_3$[a,c]	3.23	3.40	5.70	—	7.00	—	6.99	7.43	7.09		3.84
4c$_4$[b,d]	3.23	3.41	5.63	—	7.37	7.05	—	7.05	7.37		3.85
3d[a,f]	3.42	3.45	—	7.11	—	7.13	7.09	—	6.93	2.18, 2.31	
4d[a,f]	3.08	3.42	5.64	—	—	7.18	7.18	—	6.96	2.18, 2.35	
3e$_{2,3}$[a,f]	3.43	3.44	—	7.32	—	—	6.93	7.07	6.92		3.70, 3.76
3e$_{3,4}$[a,f]	3.43	3.48	—	7.27	7.14	—	—	6.88	6.98		3.90, 3.91

a) CDCl$_3$. *b*) CD$_3$OD. *c*) 500 MHz. *d*) 90 MHz. *e*) 200 MHz. *f*) 270 MHz. *g*) 2′-H was assigned by the observation of the nuclear Overhauser effect (NOE) on irradiation at Ar–CH$_3$.

TABLE IV-2. Spin–Spin Coupling Constants (J = Hz) for 5-Aryl- and 6-Aryl-1,3-dimethyluracils (**3** and **4**)

	2′–3′	2′–4′	2′–5′	2′–6′	3′–4′	3′–5′	3′–6′	4′–5′	4′–6′	5′–6′
3b$_2$	—	—	—	—	7.7	0.9	0.2	7.5	1.3	7.7
3b$_3$	—	0.8	0.3	0.7	—	—	—	7.6	0.3	7.5
3b$_4$	8.2	—	0.5	1.3	—	1.3	0.5	—	—	8.2
4b$_2$	—	—	—	—	7.8	1.4	1.0	7.8	0.7	7.3
4b$_3$	—	0.8	0.4	1.2	—	—	—	7.6	0.5	7.6
4b$_4$	8.8	—	0.5	1.3	—	1.3	0.5	—	—	8.8
3c$_2$	—	—	—	—	8.5	0.7	0.2	7.5	1.6	7.4
3c$_3$	—	1.8	0.1	1.7	—	—	—	7.5	1.4	7.8
3c$_4$	8.9	—	0.5	2.4	—	2.4	0.5	—	—	8.9
4c$_2$	—	—	—	—	8.4	0.8	0.1	7.5	1.7	7.5
4c$_3$	—	1.2	0.3	2.4	—	—	—	7.3	1.0	7.8
4c$_4$	8.8	—	0.5	2.2	—	2.2	0.5	—	—	8.8
3d	—	—	—	—	7.8	—	0.1	—	0.9	—
4d	—	—	—	—	—[a]	—	—[a]	—	—[a]	—
3e$_{2,3}$	—	—	—	—	—	—	—	7.7	1.4	8.2
3e$_{3,4}$	—	—	0.2	2.0	—	—	—	—	—	8.3

a) Could not be determined (broad singlet).

production of the 6-isomer (**4d**) began after the formation of the 5-isomer (**3d**) (Fig. 1).

To clarify whether 6-ArDMU (**4**) resulted from the isomerization of 5-ArDMU (**3**), we examined the possibility of the photoisomerization of **3d** to **4d** by carrying out the photolysis of **3d** in xylene (**2d**) solution. No **4d** was detected. The possibility of contaminant-catalyzed isomerization of **3** to **4** was also eliminated by conducting the photolysis of **3d** under the same conditions employed for the present reaction (10 h). In this run, 2-^{14}C-labeled **3d** (**3d**[^{14}C]) was added initially to a solution undergoing the photoreaction of **1** with **2d**. However, no radioactivity was detected in **4d** produced in this reaction; this is an indication that **3d** did not undergo isomerization.

We then examined the effect of a contaminant on the formation of 6-ArDMU (**4**).

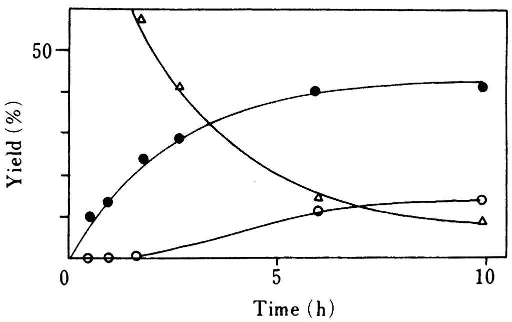


Fig. 1. Time Course of the Photoreaction of 5-BDMU (**1**) in *p*-Xylene (**2d**)

△=**1**, ●=**3d**, ○=**4d**.

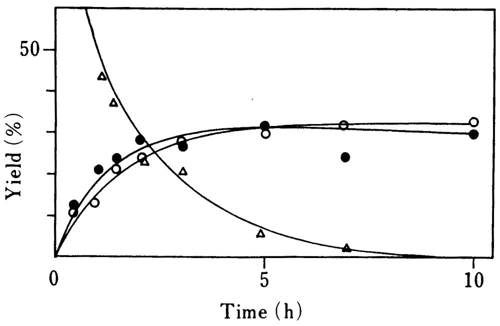


Fig. 2. Time Course of the Photoreaction of 5-BDMU (**1**) in *p*-Xylene (**2d**) in the Presence of HBr

△=**1**, ●=**3d**, ○=**4d**.

Table V. The Photolysis of **1** (5 mg, 0.023 mmol) in *p*-Xylene (**2d**) (5 ml) in the Presence of Additives

Additive (mmol)	Reaction time (h)	Yield (%) **3**	Yield (%) **4**	Yield (%) **5**	Recovery of **1** (%)
None	4	39	7.5	4	28.5
None	10	41	14	3	9
HBr gas (sat.)	2	29	24	5	24.5
TFA (2.7)	4	41	16	3	18
Pyridine (0.6)	4	23	—[a]	4	42
10% aq. K_2CO_3 (1 ml)	10	42	—[a]	8	2
Piperylene (0.16)	10	51	7	5	9
Piperylene (0.32)	10	50	—[a]	6	14
Piperylene (0.32)+TFA (2.7)	4	32	—[a]	4	9
Air (sat.)	10	33	—[a]	6	15
Air (sat.)+TFA (2.7)	4	34	—[a]	2	29

a) Not detected.

Among various possible contaminants, hydrogen bromide was found to be effective for the formation of **4**. In the presence of initially added hydrogen bromide in the reaction of **1** and **2d**, the time lag disappeared and both **3d** and **4d** were formed simultaneously, resulting in a final $N=1.1$ (10 h), significantly higher than in the absence of added acid ($N=$ *ca.* 0.34, 10 h) (Fig. 2).

Trifluoroacetic acid (TFA) also accelerated the formation of **4d**, but less effectively ($N=$ 0.56—0.65 after 10 h). The formation of **4d** was completely blocked by the addition of base (pyridine, aqueous potassium carbonate) (Table V). This indicates that the presence of acid is essential for the formation of 6-ArDMU (**4**).

A new charge transfer absorption spectrum was not observed for a mixture of **1** and **2d** in cyclohexane either in the presence or in the absence of TFA. However, the UV spectrum of **1** was shifted 5 nm to the red in cyclohexane by the addition of TFA (Fig. 3), while no change was observed in methanol. That the protonation of **1** is essential for the formation of **4** is supported by the facts that (a) **1** was not protonated in methanol, (b) nor was any **4** detected in the photoreaction of **1** with **2d** in methanol solution (Table VI).

Addition of piperylene (0.16 mmol) to a solution of **1** (0.023 mmol) in **2d** (5 ml)

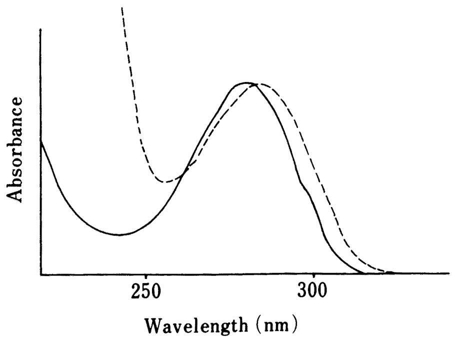


Fig. 3. Effect of TFA (0.13 mM) on the UV Spectrum of **1** (0.15 mM) in Cyclohexane

——, **1** without TFA; ----, **1**+TFA.

TABLE VI. The Photoreaction of **1** and *p*-Xylene (**2d**) (2 ml) in Various Solvents (8 ml) (10 h)

1 (mg)	Solvent	Yield (%)			Recovery of **1** (%)
		3d	**4d**	**5**	
2.5	Cyclohexane	36	7.3	12	10
5	Ether	23	0.7	31	27
5	Ethyl acetate	35	0.1	11	39
5	Acetonitrile	41	0	5	31
5	Methanol	52	0	11	7

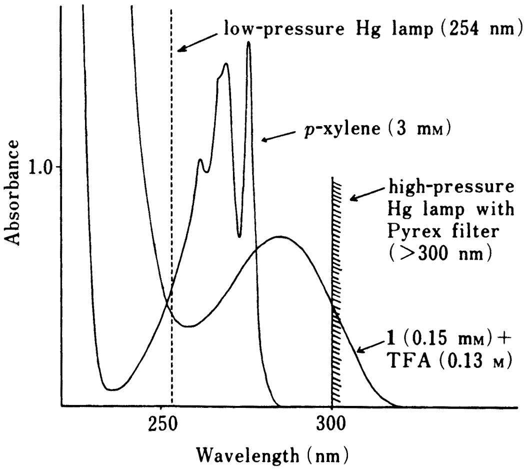


Fig. 4. UV Spectra of *p*-Xylene (**2d**) and the Protonated **1** (**1**-H$^+$) in Cyclohexane

TABLE VII. Photolysis of **1** (5 mg) in Xylene (**2d**) with a Low-Pressure Mercury Lamp for 16 h (Argon) under Various Conditions

Additive	Yield (%)			Recovery of **1**
	3	**4**	**5**	
None	50	—$^{d)}$	5	4
Air$^{a)}$	48	—$^{d)}$	8	12
TFA$^{b)}$	36	—$^{d)}$	2	1
Piperylene$^{c)}$	48	—$^{d)}$	7	6.5

a) Saturated. *b*) 1.3 mmol. *c*) 0.32 mmol. *d*) Not detected.

suppressed the formation of **4d** appreciably, and no production of **4d** was detected with 0.32 mmol of piperylene (Table V). The formation of **4d** was also suppressed in the reaction under air. On the other hand, the triplet quenchers, piperylene and air, were ineffective on the formation of **3d** in the reaction of **1** and **2d**, either in the presence or absence of acid.

In order to investigate the reaction of the excited **2d** with **1** in the ground state, a solution of **1** in **2d** was photolyzed with a low-pressure mercury lamp (254 nm) in the place of a high-pressure mercury lamp with a Pyrex filter (>300 nm). Interestingly, the formation of **4d** was not detected under these conditions, even in the presence of acid, whilst **3d** was generated in an appreciable yield (Table VII); under the former conditions most of the incident light is absorbed by **1**, while under the latter conditions the incident light is absorbed essentially (>99%) by **2d** used as the solvent (Fig. 4). The addition of piperylene had no effect on the formation of **3d** under these conditions.

These results suggest that the excitation of the protonated **1** (**1**-H$^+$) leads to the formation of **4d** *via* the triplet state and **3d** *via* the singlet state, while the excitation of either the nonprotonated **1** or **2d** results in the production of **3d** *via* the singlet state.

Although the possible pathway for the transfer of energy from excited **1**-H$^+$ (in the triplet state) to xylene (**2d**) in the ground state, a mechanism that would lead to the formation of **4**, could not be eliminated completely, the fact that the phosphorescence of **2d**, whose emission

Table VIII. The Net Charges and the Frontier Orbital Coefficients for 5-CDMU, 5-CDMU-H$^+$, **2c**, and **2c** [· +] (CNDO/2)[a)]

	5-CDMU			5-CDMU-H$^+$			**2c**			**2c** [· +][b)]	
	HOMO	LUMO	NC	HOMO	LUMO	NC	HOMO	LUMO	NC	SOMO	NC
EV (eV)	−12.219	1.726		−17.541	−5.086		−12.474	3.970		−11.151	
Coefficient											
Site 1	−0.5445	0.2227	−0.1175	0.5124	−0.2968	−0.0741	−0.4278	0.0447	0.1751	0.4568	0.4559
2	0.0137	0.0379	0.4107	−0.0748	0.0233	0.4129	−0.3103	−0.5032	−0.0506	0.3446	−0.0642
3	0.1715	−0.2077	−0.1547	0.3243	0.3134	−0.0956	0.2241	0.4898	0.0291	−0.2350	−0.0520
4	−0.0990	0.4507	0.3316	−0.0624	−0.6385	0.4207	0.4843	0.0184	−0.0160	−0.5356	0.1674
5	0.4444	0.3518	0.0341	−0.3940	−0.0711	0.0068	0.1606	−0.5239	0.0277	−0.1606	0.0219
6	0.2323	−0.6296	0.1418	−0.0799	0.5513	0.2086	−0.3367	0.4793	−0.0422	0.3735	−0.0092
TE (eV)		−3692.800			−3707.309			−2019.887		−1307.915	

a) The following abbreviations are used. NC, net charge; EV, eigen value; TE, total energy. *b*) MINDO/3.

maximum is at 402 nm (excitation at 275 nm) was not observed in the region of 350—500 nm with excitation of **1**-H$^+$ at 300 nm[7)] supports the belief that **4** is derived from the triplet excited state of **1**-H$^+$.

We then attempted to explore the reaction pathway on the basis of the observed isomer distributions for 5-ArDMU derived from the mono-substituted benzenes (**2b**, **2c**), wherein substitution occurred mainly at the *ortho*-position. On the other hand, *meta*-favored substitution occurred for 6-ArDMU (**4**). Recently, Mutai *et al.* have successfully interpreted the regioselectivities and the mechanisms of the nucleophilic aromatic photosubstitutions,[8)] which have been widely investigated by Cornelisse *et al.*,[9)] in terms of two rules using the frontier molecular orbital theory. Rule 1 involves the direct addition of a nucleophile to an excited benzene, where the regioselectivity is governed by the highest occupied molecular orbital (HOMO) of the substrates, and rule 2 regards reactions involving electron transfer, where the regioselectivity is lowest unoccupied molecular orbital (LUMO)-controlled. On the other hand, the *meta*-orientation of the photo-induced isotopic proton exchange reactions of toluene (**2b**) and anisole (**2c**) reported by Havinga and his colleagues[9c,10)] has been recognized as typical electrophilic aromatic photosubstitution reactions.[9c,11)] This reaction has been successfully explained by Fleming in terms of the interaction of the LUMO of a benzene and the LUMO of the proton in terms of the frontier electron densities of the Hückel molecular orbitals.[12,13)]

Using this approach, we have made molecular orbital (MO) calculations for the chloro analogue of **1** (5-CDMU) and the 5-CDMU protonated at the C-4 carbonyl (5-CDMU-H$^+$), instead of **1** and **1**-H$^+$, and for **2c** by using the CNDO/2 method.[14)]

As shown in Table VIII, both 5-CDMU and 5-CDMU-H$^+$ have the largest coefficients in the LUMOs at the 6-positions, while the coefficients of the LUMO of **2c** (LUMO$_{\mathbf{2c}}$) are large at the *meta*- and at the *ortho*-positions. If it is assumed that, upon irradiation, one electron is promoted from the HOMO of **1** (HOMO$_{\mathbf{1}}$) to the corresponding LUMO of **1** (LUMO$_{\mathbf{1}}$) to make the low-energy single occupied MO (LSOMO$_{\mathbf{1}}$ = HOMO$_{\mathbf{1}}$ before excitation) and the high-energy singly occupied MO (HSOMO$_{\mathbf{1}}$ = LUMO$_{\mathbf{1}}$ before excitation), respectively, then the latter orbital (HSOMO$_{\mathbf{1}}$) is expected to lead to the productive interaction directly at the 6-position with the LUMO$_{\mathbf{2c}}$ predominantly at the *meta*-position to form a σ-complex in one step, thus generating **4c** (Fig. 5). This process can be regarded as corresponding to the rule 1 of Mutai *et al.* If the competing electron transfer from the HOMO$_{\mathbf{2c}}$ to the LSOMO$_{\mathbf{1}}$ takes place initially (Fig. 6), the resulting radical anion of **1** (**1**[· −]) would give rise to the formation of the 1,3-dimethyluracil 5-radical (**6**) *via* the smooth elimination of the bromide anion. This would lead to facile coupling with the counterpart of the electron transfer, the radical cation

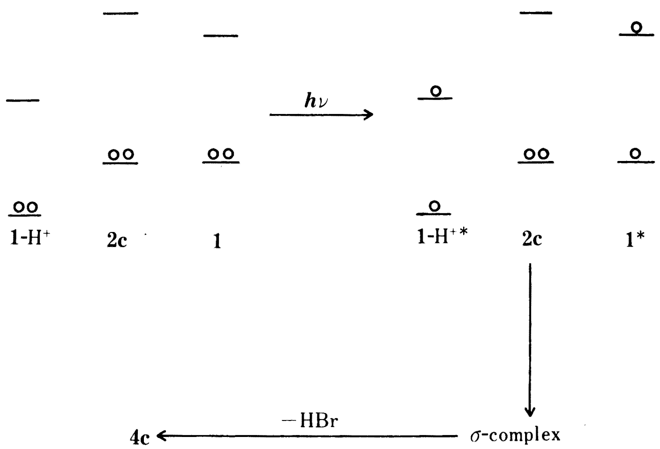


Fig. 5. Schematic Illustration of the Reaction of **1** and **1**-H$^+$ with **2c**, Leading to **4c** through Frontier Orbital Interaction

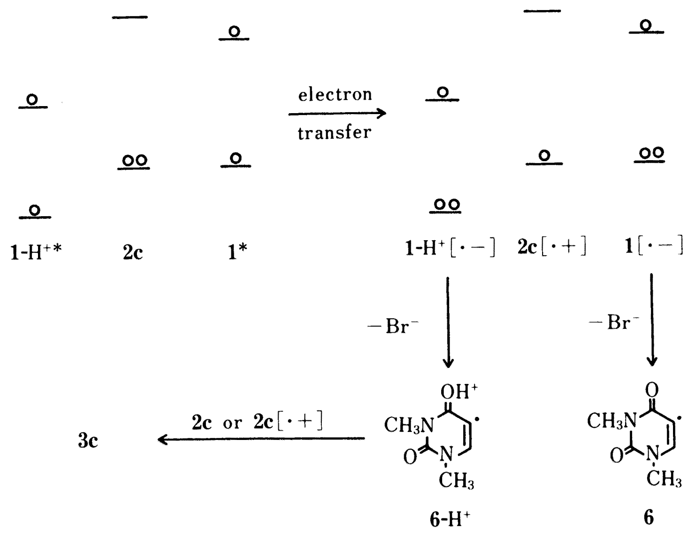


Fig. 6. Schematic Illustration of the Electron Transfer Process for the Photoreaction of **1** (**1**-H$^+$) with **2c**

of **2c** (**2c**[· +]) preferentially at the *ortho*-position to give the *ortho* isomer of **3c** as the major isomer, as has been reported for the photoreaction of **1** with indoles.[4] This procedure corresponds to the above "rule 2." The same sequence will apply to **1**-H$^+$.

Although the formation of **4** occurred only from **1**-H$^+$, this observation could not be explained on the above basis. In view of the perturbation that exists when the interacting orbitals are close in energy,[15] **4** should have been produced preferentially by the reaction with **1** rather than with **1**-H$^+$, for the energies of the latter interacting orbitals are closer than for the former.[16] This discrepancy could be explained partially in terms of arguments that are based on the results of the calculations on the chloro derivatives as models for the bromo compounds. It might be improper to discuss the reactivities in the excited states based only on the results of calculations that do not involve the configuration interaction (CI) method. The more important factor must be that the above consideration, based on the frontier orbital

TABLE IX. Molecular Orbitals for the Radicals Derived from 5-CDMU (MINDO/3)[a]

	5-CDMU [· −]		5-CDMU-H$^+$ [· −]		**6**		**6**-H$^+$	
	ED	(NC)	ED	(NC)	ED	(NC)	ED	(NC)
Site 5	0.1781	(−0.0463)	0.1353	(−0.0753)	0.5568	(−0.2510)	0.5812	(−0.2605)
6	0.0588	(0.0567)	0.0036	(0.1404)	0.0255	(0.1474)	0.0358	(0.2298)
TE (eV)	−2219.448		−2232.552		−1869.217		−1877.393	
EV (eV)	1.574		−3.058		−5.409		−10.255	

a) The following abbreviations are used. ED, electron density; NC, net charge; TE, total energy; EV, eigen value.

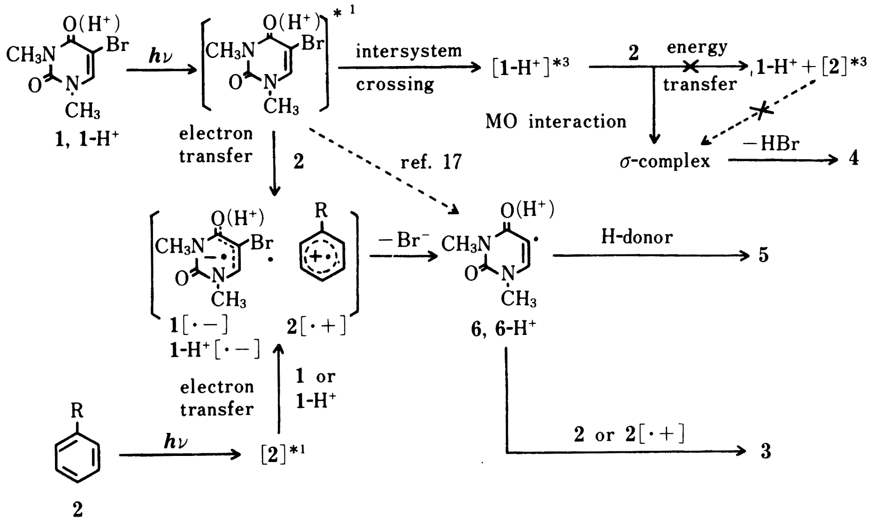


Chart 2

theory, is concerned with the initial stage of the reaction and not the subsequent reaction pathways.

Hence, our attention was directed to the intermediate molecules generated in the course of the electron transfer process (Chart 2), and the MO calculations of the intermediate radicals, the radical anion of 5-CDMU (5-CDMU[· −]) (as the model for **1**[· −]), **6**, and their protonated derivatives, 5-CDMU-H$^+$[· −] and **6**-H$^+$, using the MINDO/3 method.[14] The results of these calculations are shown in Table IX.

Although the attempt to explain the conflict on the basis of the coefficients or the gross atomic populations seemed unsuccessful, it was shown that the total energy change involving the generation of **6**-H$^+$ by eliminating the chloride anion from 5-CDMU-H$^+$[· −], which was derived from 5-CDMU-H$^+$ *via* the electron transfer from **2c**, resulted in a 4.93 eV loss greater than that of **6** from 5-CDMU[· −]. Presumably, the non-protonated **1**[· −], produced *via* electron transfer, smoothly eliminated the bromide anion to yield 5-ArDMU (**3**) exclusively, while the formation of **4** from **1**-H$^+$ *via* the one-step formation of a σ-complex through a direct interaction between the excited **1**-H$^+$ and **2** may be caused by the difficulties of the elimination of the bromide anion from **1**-H$^+$[· −] generated in the competing process involving the electron transfer from **2**.

Though the experimental evidence for the electron transfer mechanism is only partial, the fact that the yield of **3d** in the photoreaction of **1** with **2d** in various solvents was raised as the solvent polarity increased (Table VI) may support this mechanism for the formation of **3d**.

A probable pathway of the present reaction can be summarized as illustrated in Chart 2.

It is noteworthy that the present acid-catalyzed aromatic photosubstitution reaction with **1**, affording the *meta*-favoring substitution products (**4**) possibly through the interaction between the LUMO of ground state benzenes and the LUMO of excited **1**,[18] may represent a new type of photo-induced *meta*-favoring substitution reaction on a benzene with an electron-donating substrate.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were measured with JEOL JNM-GX500 (500 MHz), JNM-GX 270 (270 MHz), JNM-FX 200 (200 MHz), and JNM-FX 90 (90 MHz) spectrometers, and chemical shifts were given on the δ (ppm) scale with tetramethylsilane as an internal standard. MS were determined on a Shimadzu LKB-9000 GC-mass spectrometer. UV spectra were taken on a Shimadzu UV-240 at room temperature and phosphorescence spectra were measured on a Hitachi 650-60 in a liquid nitrogen bath (−195.8 °C). Radioactivities were measured on an Aloka liquid-scintillation system (LSC-903). Analytical high-pressure liquid chromatography (HPLC) was performed on a Shimadzu LC-5A apparatus with a Hibar column (LiChrosorb RP-18, Merck) eluting with aqueous methanol (30%—70%) and monitoring at 254 nm. Column chromatography was conducted with the same apparatus but on pre-packed silica gel (Lichroprep Si-60, Merck) and a C-8 reverse-phase (Lichrosorb RP-8, Merck) column. Thin layer chromatography (TLC) was carried out on Kieselgel 60 F_{254} (Merck) TLC plates. UV-irradiation was carried out with an Eiko-sha 500 W high-pressure mercury lamp (>300 nm) in a degassed (10^{-2} Torr) Pyrex tube using a merry-go-round apparatus (Eiko-sha) at room temperature, unless otherwise cited herein, while the UV-irradiation with an Eiko-sha 60 W low-pressure mercury lamp (254 nm) was carried out in a quartz test tube under argon (1 atm).

Materials——5-BDMU (**1**) was prepared from uracil (Aldrich) according to the reported procedure.[19] 5-BDMU[2-^{14}C] (1.13 Ci/mmol) (9.1 g) was prepared from *ca.* 90 Ci of uracil [2-^{14}C] (New England Nuclear Corp.) diluted with cold uracil (9.9 g), according to the above procedure. 6-CDMU is commercially available (Aldrich). 6-IDMU was prepared from 6-CDMU (6 g) and sodium iodide (20 g), according to the procedure of Pfleiderer and Deiss,[20] by refluxing in dimethylacetamide in place of dimethylformamide for 2 h at 195 °C; yield 50% after recrystallization from ethanol. Hydrogen bromide (HBr) was prepared according to the cited method.[21]

General Procedure for the Preparative-Scale Photoreaction of 5-BDMU (1) with a Substituted Benzene (2a—e)——A solution of **1** (200 mg) in **2** (150 ml) was irradiated with a 500 W high-pressure mercury lamp in a doughnut-type Pyrex vessel (>300 nm) at room temperature under an argon atmosphere. After evaporation of the solvent, the reaction mixture was subjected to column chromatography.

Photoreaction of 1 with Benzene (2a)——The reaction mixture was submitted to HPLC on a reverse-phase column with 30% aqueous methanol to afford 1,3-dimethyl-5-phenyluracil (**3a**) (21.6 mg, 11%), 1,3-dimethyl-6-phenyluracil (**4a**) (1.8 mg, 0.9%), and 1,3-dimethyluracil (**5**) together with recovered **1** (17.6 mg, 8.8%).

Photoreaction of 1 in Toluene (2b)——After removal of the solvent, the resulting oil in ether was passed through a short column of alumina (aluminumoxid 90 neutral I, Merck). Some losses of the debrominated compound **5** occurred in this procedure. The eluate was subjected to reverse-phase column chromatography and eluted with 40% aqueous methanol to afford recovered **1** (11 mg, 5.5%), **3b$_2$** (35 mg, 16.7%), a mixture of **3b$_3$**, **3b$_4$**, and **4b$_2$** (f-1), and a mixture of **4b$_3$** and **4b$_4$** (f-2), successively. Then f-1 and f-2 were separately subjected to silica gel column chromatography. Thus f-1 with hexane–ether (2:3) gave **3b$_3$** (2.6 mg, 1.2%), **3b$_4$** (1.9 mg, 0.9%), **4b$_2$** (1.7 mg, 0.8%), successively, and f-2 with hexane–ethyl acetate (5:1) gave **4b$_3$** (3.3 mg, 1.6%) and **4b$_4$** (0.9 mg, 0.4%), successively.

Photoreaction of 1 in Anisole (2c)——After removal of the solvent, the resulting oil in ethyl acetate was passed through a short column of alumina. Reverse-phase column chromatography of the eluate (138.6 mg) with 35% aqueous methanol afforded **1** (58 mg, 29%), **3c$_2$** (32 mg, 14%), and a mixture of **3c$_3$** and **3c$_4$** (f-1), and then a mixture of **4c$_2$**, **4c$_3$**, and **4c$_4$** (f-2), successively. Then f-1 was submitted to column chromatography with hexane–acetone (4:1) to give **3c$_3$** (12 mg, 5%) and **3c$_4$** (6.5 mg, 2.6%). Similarly f-2 was chromatographed on silica gel with hexane–ethyl acetate (8:3) to yield a mixture of **4c$_2$** and **4c$_3$**, and then pure **4c$_4$** (0.8 mg, 0.3%). Rechromatography of the mixture using dichloromethane (CH_2Cl_2)–isopropanol (100:1) separated **4c$_2$** (2.3 mg, 1%) and **4c$_3$** (5.2 mg, 2.3%).

Photoreaction of 1 in Xylene (2d)——The residual oil was submitted to silica gel column chromatography with a mixture of hexane–ether–CH_2Cl_2 (4:3:3) to give 1,3-dimethyl-6-(2,5-dimethylphenyl)uracil (**4d**) (40.3 mg, 18.1%) and 1,3-dimethyl-5-(2,5-dimethylphenyl)uracil (**3d**) (68.5 mg, 30.7%), together with recovered **1** (24.6 mg, 12.3%) and **5** (3.2 mg, 2.5%), successively.

Photoreaction of 1 in Veratrole (2e)——Following removal of the solvent, the residual oil was passed through a short column of alumina (CH_2Cl_2); the eluate was subjected to silica gel column chromatography with hexane–ethyl acetate–ethanol (20:5:1) to afford **3e$_{2,3}$** (16.1 mg, 6.4%) and **3e$_{3,4}$** (24.3 mg, 9.3%), together with recovered **1** (56.3 mg, 28.2%) and **5** (2.9 mg, 2.3%), successively.

Photolysis of 6-CDMU and 6-IDMU in Benzene (2a)——A solution of 6-CDMU (200 mg) in **2a** (150 ml) was irradiated for 40 h under an argon atmosphere. The reaction mixture was concentrated under reduced pressure and the residual oil was passed through a short column of silica gel with ether. The eluate on reverse-phase column chromatography (40% aqueous methanol) afforded **4a** (13.5 mg, 7%) together with recovered 6-CDMU (147 mg, 73.5%). **4a**: mp 102—103 °C (from methanol–H_2O, ethanol or benzene-hexane).

Similarly, photolysis of 6-IDMU (100 mg) in benzene (100 ml)[5] (4 h) afforded **4a** quantitatively. **4a**: mp 102—103 °C (from methanol). NMR ($CDCl_3$) δ: 3.22 (3H, s, 1N-CH_3), 3.41 (3H, s, 3N-CH_3), 5.70 (1H, s, 5-H), 7.26—7.55 (5H, m, aromatic).

Photolysis of 3d in Xylene (2d)——A solution of **3d** (2.5 mg) in **2d** (5 ml) was irradiated for 10 h. No detectable **4d** was formed.

Photolysis of 3d[^{14}C] in the Presence of 1——A solution of **3d**[^{14}C] (1.89 mg, 18640 dpm), prepared from 5-BDMU[2-C^{14}] by the above procedure, and **1** (2.50 mg) in **2d** (3.5 mg) was irradiated in a degassed sealed tube (Pyrex) for 10 h. The reaction mixture was evaporated *in vacuo*, and the residue was subjected to TLC using ether–hexane (1 : 1) as a developing solvent to afford **3d** (2.73 mg) and **4d** (0.27 mg), respectively. The radioactivity of **3d** was 14333 dpm, and that of **4d** was 104 dpm. This indicates that the ammount of **3d** derived from **3d**[^{14}C] is 1.45 mg and that arising from **1** is 1.28 mg, whereas the amount of **4d** derived from **1** is 0.263 mg, and that of **4d** from **3d**[^{14}C] is at most 0.007 mg. Taking into consideration that crude **4d** used for the radioactivity measurement was obtained directly from TLC plate and not further purified, it can be said that **3d** did not substantially isomerize to **4d** under the above conditions.

Phosphorescence Emission Measurements——A solution of **1** (2.6×10^{-2} mM), **2d** (2×10^{-1} mM), and TFA (1×10^{-1} M) in hexane solution was prepared, and **1**-H^+ and **2d** were excited at 300 nm and at 275 nm, respectively. The phosphorescence emissions of **2d** between 350—500 nm (with an emission maximum at 402 nm) were measured at liquid nitrogen temperature.

MO Calculations——MO calculations were performed on an NEC 16-bit personal computer (9801E) using the geometries of 1,3-dimethyluracil optimized by CNDO/2[22] (for **6** and **6**-H^+), 1,3-dimethyl-5-fluorouracil calculated by the *ab initio* method[23] (for 5-CDMU and 5-CDMU-H^+), and anisole determined by the *ab initio* (STO-3G) calculation.[24] Bond distances used are C–Cl = 1.69 Å[25] and H–O^+ (carbonyl) = 1.0 Å.

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$$\Delta E = -\frac{Q_r Q_s}{R_{rs}\varepsilon} + n\left(\sum_{a}^{\text{occ.}} \sum_{b}^{\text{unocc.}} + \sum_{b}^{\text{occ.}} \sum_{a}^{\text{unocc.}}\right)\frac{(c_{ra}c_{sb} \cdot \Delta\beta)^2}{E_a - E_b} \qquad (1)$$

Q_r and Q_s, the total charges on atoms r and s; R_{rs}, the distance between the atoms r and s; ε, the local dielectric constant; c_{ra} and c_{sb}, the coefficients of atomic orbital r in the molecular orbital a and of atomic orbital s in molecular orbital b; E_a and E_b, the energies of molecular orbitals a and b; n, the number of electrons; $\Delta\beta$, the resonance integral.

This equation can be simplified to Eq. 2 on the bases of the frontier orbital theory.

$$\Delta E = -\frac{Q_r Q_s}{R_{rs}\varepsilon} + n\frac{(c_r c_s \Delta\beta)^2}{E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}} \qquad (2)$$

According to Eq. 2, the perturbation energies for the LUMO–LUMO interactions between the excited **6** (at C-6) and **2c** (at C-5, *meta*-position) and that of the excited **6**-H$^+$ and **2c** were estimated as 0.122 and 1.311 eV, respectively, by using the following values; $R_{rs}=2.3$ Å, $\Delta\beta=3.8$ eV, $\varepsilon=2.4$ reported for toluene,[26] and $n=1$.

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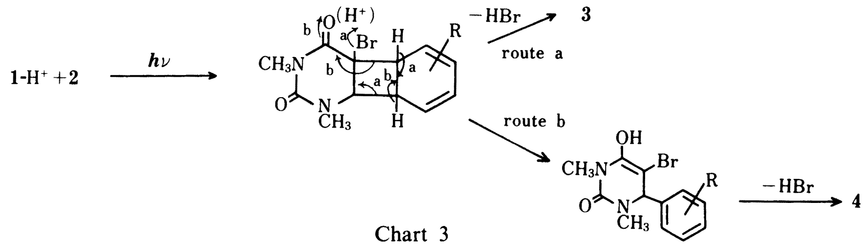

Chart 3

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