Hydroxymethylation of 1,3-Dimethyluracil and Its Derivatives induced by a Photoredox System of Eu^{III}/Eu^{II} in MeOH

Akito Ishida,* Susumu Toki, and Setsuo Takamuku

The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

Irradiation of a methanol solution of $EuCl_3$ and 1,3-dimethyluracil through a Pyrex filter induced a regioselective hydroxymethylation with high efficiency, probably *via* an electron-transfer mechanism.

Recently, we have investigated a photoredox system of Eu^{III}/Eu^{II} in alcohol in the presence of organic substrates in order to apply such a redox system of metal ions to organic photochemical reactions.[1] On illumination of a methanol solution of $EuCl_3$ (λ >300 nm), oxidation of methanol occurs along with formation of the Eu^{II} ion.[2,3] Thereafter, Eu^{II} becomes the main light-absorbing species and promotes

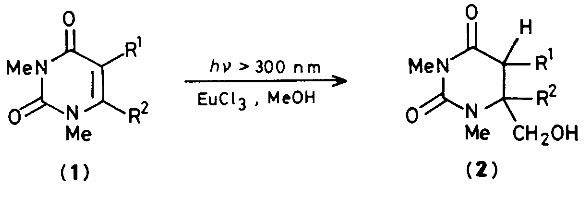
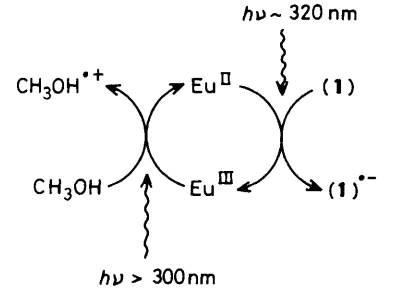


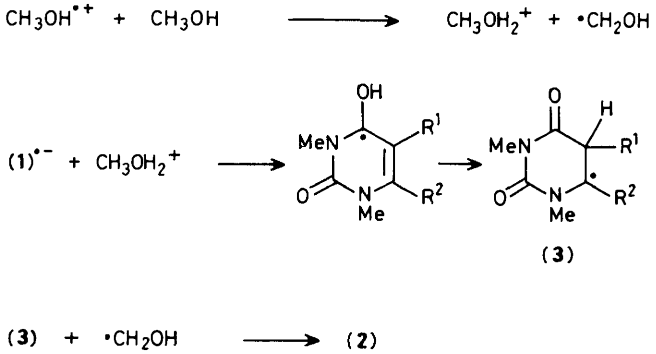
Table 1. Photolysis of (**1**) in methanol.[a]

	R^1	R^2	Concentration of (**1**)/mmol dm^{-3}	Irradiation time/h	% Conversion	% Yield of (**2**)[b]
(**1a**)	H	H	20	3	100	84
			100	6	89	98
			200	8	66	95
(**1b**)	CH_3	H	100	5	88	91
(**1c**)	F	H	100	5	64	78
(**1d**)	Cl	H	50	5	71	57
				12	100	32 (35)[c]
(**1e**)	H	CH_3	100	5	8	40

[a] Methanol solutions of (**1**) were irradiated in the presence of $EuCl_3$ (10 mmol dm^{-3}) by a high-pressure mercury lamp through a Pyrex filter with a merry-go-round apparatus under Ar at running water temperature. Products were determined by g.l.c. (OV-17, 1 m, flame-ionisation detector). [b] Yields of (**2**) are based on the amount of (**1**) consumed. [c] Yield of (**2a**): a dechlorinated product of (**2d**) found on prolonged irradiation.



Scheme 1. Initial reactions induced by a Eu^{III}/Eu^{II} photoredox system.



Scheme 2. Subsequent reactions of the photoredox system of Eu^{III}/Eu^{II} in MeOH to give compound (**2**).

hydrogen evolution. On addition of α-methylstyrene to this system, the formation of a dihydrodimer of α-methylstyrene and a 2 : 1 methanol adduct becomes predominant instead of hydrogen formation, and a radical mechanism where a hydrogen atom and a hydroxymethyl radical react with α-methylstyrene has been proposed.[1]

In the present study, we found that when 1,3-dimethyluracil and its derivatives were used as substrate, a regioselective hydroxymethylation took place with high efficiency probably *via* an electron-transfer mechanism. The photochemical reactivity of uracil and its derivatives towards alcohol is a subject of significant interest to investigators studying the photo-induced cross-linking of uracil and amino acid.[4,5]

A methanol solution of $EuCl_3$ (5 mmol dm^{-3}) and 1,3-dimethyluracil (**1a**) (0.1 mol dm^{-3}) was irradiated with a high-pressure mercury lamp through a Pyrex filter under argon. The product was isolated by column chromatography on silica-gel using benzene–acetone (4 : 1, v/v) and identified as 1,3-dimethyl-6-hydroxymethyl-5,6-dihydrouracil (**2a**) on the basis of its spectral data.† The results of the photolysis of 1,3-dimethyluracil and its derivatives (**1a**—**e**) are shown in Table 1.†

The characteristic features of this reaction are summarized as follows: (i) in all derivatives (**1a**—**e**), a regioselective hydroxymethylation occurs at the 6-position. (ii) The yields of (**2a**) and (**2b**) are very high, while the yields of halogenated derivatives (**2c**) and (**2d**) are rather low. In the case of (**1d**), further dechlorination of (**2d**) was observed which became a main path on prolonged irradiation. (iii) The reaction does not proceed in the absence of $EuCl_3$. The wavelength region of the effective light for this reaction is 300—350 nm. The absorption of the incident light occurs mainly by the Eu^{III} ion and also by the Eu^{II} ion once formed. (iv) A catalytic amount of $EuCl_3$ induces this reaction and the yield of (**2a**) based on $EuCl_3$ used goes up to over 1250%. (v) The yield of (**2b**) is very high also, although the 6-methyl derivative (**1e**) shows an extremely low reactivity and 92% of (**1e**) was recovered after 5 h irradiation.

In order to obtain an insight into this reaction, deuterium labelling experiments were carried out. When a [^{2}H]methanol solution (CH_3OD) of (**1a**) (0.1 mol dm^{-3}) and $EuCl_3$ (0.01 mol dm^{-3}) was irradiated to about 50% conversion, the incorporation of a deuterium atom in (**2a**) was observed by mass spectroscopy to be 99% and the deuterium was found preferentially at the 5-position of (**2a**) by n.m.r. spectroscopy (100%). On the other hand, the deuterium incorporation in the recovered (**1a**) was negligibly small (less than 3%). These facts suggest that an alcoholic proton selectively adds to the 5-position, preferably *via* the radical anion of (**1a**) (see Schemes 1 and 2) because such a high regioselectivity cannot be reasonably explained by a free radical addition to the C–C double bond of uracil derivatives.[6]

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† Satisfactory spectral data for all products were obtained. Compound (**2a**) was synthesized previously (ref. 4); viscous oil; found: M^+, 172.08604. $C_7H_{12}N_2O_3$ requires *m/z*, 172.0841; *m/z* 172 (M^+, 2%), 141 (81), 84 (81), 56 (6), 42 (100), and 28 (14); $\delta(^{13}C)$ ($CDCl_3$, $SiMe_4$, off-resonance) 27.04 (q, N-Me), 33.25 (t, C-CH_2), 35.25 (q, N-Me), 55.14 (d, N-CH-), 66.06 (t, CH_2OH), 153.0 (s, C=O), and 169.48 (s, C=O); $\delta(^1H)$ ($CDCl_3$, $SiMe_4$) 2.84 (m, 2H), 3.06 (s, 3H), 3.09 (s, 3H), 3.50 (m, 1H), 3.68 (m, 2H), and 4.28 (br s, 1H, this peak disappeared on shaking with D_2O). (**2b**); viscous oil; found: M^+, 186.10047. $C_8H_{14}N_2O_3$ requires *m/z*, 186.10035; *m/z* 186 (M^+, 1%), 155 (100), 98 (90), 57 (32), 42 (97), and 28 (23); $\delta(^{13}C)$($CDCl_3$, $SiMe_4$, off-resonance) 16.97 (q, C-CH_3), 27.51 (q, N-Me), 35.42 (d, C-CH-), 35.95 (q, N-Me), 37.93 (d, N-CH-), 62.19 (t, CH_2OH), 153.15 (s, C=O), and 173.39 (s, C=O); $\delta(^1H)$($CDCl_3$, $SiMe_4$) 1.33 (m, 3H), 2.82 (m, 1H), 3.09 (s, 3H), 3.11 (s, 3H), 3.36 (m, 1H), 3.66 (m, 2H), and 4.10 (br s, 1H, this peak disappeared on shaking with D_2O).

When (**1e**) was irradiated in [^{2}H]methanol in the presence of $EuCl_3$ for 40 h, about 50% incorporation of deuterium in the 5-position of the recovered (**1e**) was observed. No deuterium incorporation in (**1e**) was detected after 24 h in the dark. Therefore, the very low reactivity of (**1e**) can be explained by the fact that the radical of (**1e**) with added hydrogen [(**3**) see Scheme 2] does not readily recombine with a hydroxymethyl radical to give (**2e**) due to the steric hindrance of the 6-methyl group. The radical mainly undergoes deprotonation to give (**1e**) which causes the deuterium incorporation.

The formation of Eu^{II}, which is the key active species for the reduction of (**1**), was confirmed by the absorption spectra ($\lambda_{max.}$ 330 nm)[2] and also fluorescence spectra ($\lambda_{max.}$ 489 nm)[7] of the methanol solution of $EuCl_3$ after the irradiation. The fluoresence, which was considerably enhanced by the addition of 18-crown-6 ether as reported by Adachi *et al.*,[7] was found to be quenched by (**1**).

Dechlorination of (**2d**) induced by a prolonged irradiation may also proceed *via* the electron-transfer mechanism. Similar dehalogenation induced by one-electron reduction has been reported in 5-bromouracil[8] and 5-bromo-6-hydroxythymine.[9]

Kinetic details and reactions in other solvents such as ethanol, propan-2-ol, and tetrahydrofuran will be discussed elsewhere.

Received, 15th June 1985; Com. 895

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