REGIO AND STEREOSPECIFITY OF SOLVENT PHOTOADDITION TO 5-FLUOROURACIL AND 1,3-DIMETHYL-5-FLUOROURACIL*

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Irradiation of 1,3-dimethyl-5-fluorouracil in methanol, ethanol, water and acetic acid, and 5-fluorouracil in water at $\lambda = 253 \cdot 7$ nm resulted in the formation of two addition products. Regiospecifity was in all cases the same with functionalization at position 6 while the stereochemistry of addition depended on the solvent. In water preferential *trans* addition proceeded while in acetic acid *cis* addition was predominant. Photoconversion of starting material was also twofold increased in acetic acid, compared to that in water.

Photochemical reactions of nucleic acids have been a subject of considerable interest[2,3]. The nature of photoadducts formed by irradiation of uracil and 1,3-dimethyluracil strongly depend on solvent and concentration. Reaction in water gave 6-hydroxy derivatives[4,5], in ethanol two types of adducts[6] were formed with functionalization at position 6, while in the case of tetrahydrofuran as solvent the regioselectivity mentioned above was lost and functionalization at positiion 5 and 6 was observed[7]. On the other hand, photoreactions of 5-halosubstituted uracils gave products which depended on the halogen. Koch and coworkers[8] have recently shown that photoreaction of 5-bromouracil undergoes ionic and free-radical pathways, while Matsuura and coworkers[9] found photoinduced coupling reaction with various amino acids. Photohydration of 5-fluorouracil and 1,3-dimethyl-5-fluorouracil gave 6-hydroxy products[10,11], and on the basis of the infrared spectra the *trans* position of fluorine and hydroxy substituents was suggested[11]. Burr and coworkers[5] have followed the phototransformation of 5-fluorouracil on the basis of the double bond UV-absorption disappearance.

In our continuing work on phototransformation of fluorosubstituted organic molecules[12] we found it interesting to study photoreactions of 5-fluorouracil and 1,3-dimethyl-5-fluorouracil in hydroxylic solvents, Scheme 1.

1,3-Dimethyl-5-fluorouracil (I, $R^1 = CH_3$) in water was irradiated at 32°C with $\lambda = 253 \cdot 7$ nm. After 6 h the solvent was removed under reduced pressure and the crude

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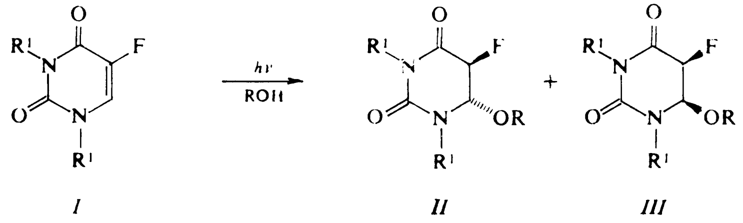
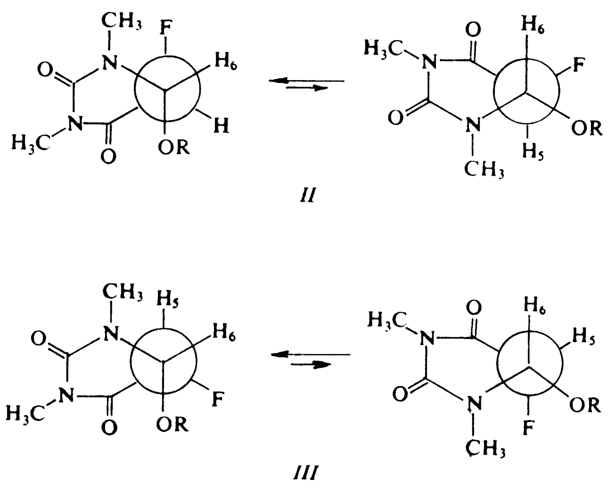
reaction mixture was analysed by ^{19}F NMR. The amount of starting material *I* was diminished by 34%, two doublet of doublets at −193·3 ppm and −206·5 ppm (in the ratio 19 : 81) appeared and 7% transformation to nonfluorinated derivatives was observed. 40 h irradiation resulted in complete disappearance of the starting material



SCHEME 1

and only a signal at −206·5 ppm was observed. The product was isolated by preparative TLC and high resolution mass spectral measurement shows a $C_9H_9FN_2O_3$ composition which indicates the addition of water. The product observed after 6 h irradiation, but decomposed by a longer reaction, was isolated by preparative TLC from a mixture obtained by 8 h irradiation and has the same composition as the product isolated before. The mass spectra of both products show very similar fragmentation which suggested that the products must be very similar. Both products show a doublet splitting of 48 Hz in the ^{19}F NMR, spectrum characteristic of a F, H geminal coupling which indicates the addition of a hydroxy group to position 6, while the minor product *II*, $R = H$, $R^1 = CH_3$ formed by 6 h irradiation shows a larger splitting (7 Hz) with neighbouring hydrogen than the main product (*III*, $R = H$, $R^1 = CH_3$, 2 Hz). The coupling constants between hydrogens at position 5 and 6 are the same for both products. On the basis of the differences in NMR spectra mentioned, it is very difficult to establish the preference of *cis* or *trans* addition of water to the double bond. Robins and coworkers[13] have synthesized (±)-*cis*-5-fluoro-6-methoxy-5,6-dihydrouracil and (±)-*cis*-5-fluoro-6-methoxy-1-methyl-5,6-dihydrouracil and the structure was proven by single crystal X-ray analysis[14]. The comparison of NMR data of products *II* and *III* with the literature[13] enabled us to establish that the minor product *II* formed by 6 h irradiation resulted from *cis* and the major product *III* from *trans* addition of water, Scheme 2.

The effect of a solvent on the course of photoreaction of uracil stimulated us to investigate reactions of 1,3-dimethyl-5-fluorouracil in methanol, ethanol, and acetic acid (Table I). In all the cases the regioselectivity was the same, while the stereochemistry was changed to the preferential *cis* addition in the case of acetic acid. Conversion of the starting material is nearly the same in the case of water and alcohol and is doubled in acetic acid. The amount of 5-fluorouracil was diminished



II

III

SCHEME 2

to a half by 5 h irradiation in water and the amount of the product formed by *cis*--addition of water was also diminished compared to the dimethyl derivative. Adducts formed in water, methanol, and ethanol from 1,3-dimethyl-5-fluorouracil were separated and characterized by their spectroscopic data, while adducts formed in acetic acid were very unstable and decomposed during the separation. Their presence was established on the basis of ^{19}F NMR data (*II*: $\delta_F = -194$ (dd), $^2J_{FH_5} = 48$ Hz, $^3J_{FH_6} = 7$ Hz; *III*: $\delta_F = -207$ (dd), $^2J_{FH_5} = 48$ Hz, $^3J_{FH_6} = 2$ Hz) which are very similar to those of other adducts collected in Table II. Adducts

TABLE I

The effect of solvent on photoaddition to 5-fluorouracil (*I*, $R^1 = H$) and 1,3-dimethyl-5-fluorouracil (*I*, $R^1 = CH_3$) 6 h irradiation of 2·78 . 10^{-2}M solution of *I* at $\lambda = 253·7$ nm and 32°C; light intensity 8·89 . 10^{15} photons $ml^{-1} s^{-1}$. The reaction mixture was analysed by ^{19}F NMR spectroscopy

R^1	ROH	Conversion of *I*, %	Yield *II* + *III*, %	Ratio *II* : *III*
CH_3	H_2O	34	27	19 : 81
CH_3	CH_3OH	37	28	54 : 46
CH_3	C_2H_5OH	30	17	55 : 45
CH_3	CH_3COOH	78	41	68 : 32
H	H_2O	52	34	12 : 88

formed by reaction of 5-fluorouracil in water are also very unstable and their presence was established on the basis of ^{19}F NMR spectra (*II*: $\delta_F = -191{\cdot}6$ (dd), $^2J_{FH_5} = 48$ Hz, $^3J_{FH_6} = 7$ Hz; *III*: $\delta_F = -205$ (dd), $^2J_{FH_5} = 48$ Hz, $^3J_{FH_6} = 2$ Hz) and their transformation to 5-fluorouracil on heating of the reaction mixture[10]. In all cases solvents were saturated with oxygen before irradiation. Under the conditions mentioned the formation of dimers was not detected.

Further we have investigated the effect of irradiation time on product composition. In all cases experiments were repeated several times and the crude reaction mixtures were analysed by ^{19}F NMR. In Fig. 1 the course of photohydration of 5-fluorouracil and 1,3-dimethyl-5-fluorouracil is presented. It can be seen that products formed in *trans*-addition of water are more stable than *cis* adducts. Photoconversion of 1,3-dimethyl-5-fluorouracil with solvents follows first order kinetics in the first 5 h and data are presented in Fig. 2. The effect of the solvent on decomposition of 1,3-dimethyl-5-fluorouracil to nonfluorinated products is presented in Fig. 3 and shows that starting material and photoadducts are much more unstable in the acetic acid than in water. The effect of irradiation time on the ratio of *cis* : *trans* addition products for 1,3-dimethyl-5-fluorouracil in various solvents is presented in Fig. 4. It can be seen that the difference between the stability of both products is most pronounced in acetic acid. Fig. 5, shows the effect of light intensity on the ratio of *cis* : *trans* adducts in acetic acid, while in Fig. 6, the effect of light intensity on photoconversion of 1,3-dimethyl-5-fluorouracil in acetic acid is presented.

Finally, we studied the quantum yields of the photoconversion of 1,3-dimethyl-5-fluorouracil in hydroxylic solvents at the light intensity of $3{\cdot}61 \cdot 10^{15}$ photons ml^{-1} s^{-1} and found that quantum yields for photoconversion and the formation of adducts are very unreproducible on the time of irradiation, which may be ascribed to a change of reaction conditions, *e.g.* elimination of hydrogen fluoride. The only

TABLE II

NMR Data for *II* and *III*

Value	R					
	H	CH_3	CH_3CH_2	H	CH_3	CH_3CH_2
δ_F	−193·3	−193·5	−196·13	−206·5	−207·5	−207·75
δ_{H_5}	4·77	4·8	4·74	5·16	5·16	5·16
δ_{H_6}	5	4·53	4·53	5·16	4·74	4·86
$^2J_{FH_5}$	48	48	48	48	48	48
$^3J_{FH_6}$	7	7	7	2	2	2
$^3J_{H_5H_6}$	3	3	3	3	3	3

reproducible data have been observed in acetic acid, where quantum yields for photoconversion are between 0·08 ± 0·01 after 2 h irraditation and 0·075 ± 0·003 after 6 h irradiation (corrections for light transmission were taken into account).

EXPERIMENTAL

IR spectra were recorded using a Perkin Elmer 727 B instrument and ^1H and ^{19}F NMR spectra on a Jeol JNM PS 100 spectrometer from C^2HCl_3 solution, with $(CH_3)_4Si$ or CCl_3F as internal reference. Mass spectra and high resolution measurements were taken on a CEC 21-110 spectrometer. TLC separations were carried out on a Merck PSC Fertigplatten Silicagel F254. Melting points were determined on a Kofler microscope and were uncorrected. Irradiation was carried out in a Rayonet photochemical chamber reactor, model RPR 100, with RPR 253·7 lamps and quantum yields were measured using one RPR 253·7 lamp, using additional cuvette for measurements of transmitted light. Light intensities were measured using a ferrioxalate actinometer.

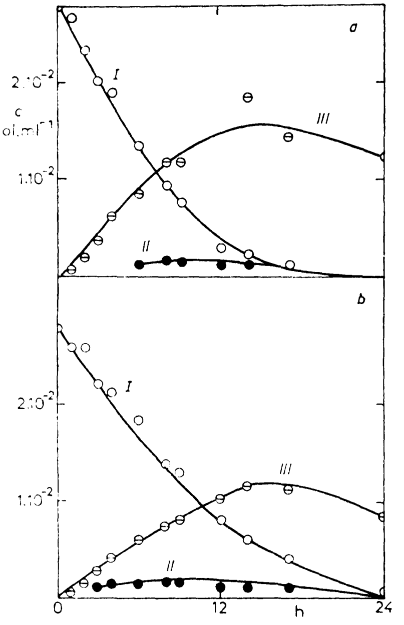


FIG. 1

Time dependence for photohydration at λ = 253·7 nm and 32°C; initial concentration 2·78 . 10^{-2} mol l^{-1} (saturated with O_2), light intensity 8·89 . 10^{15} photons ml^{-1} s^{-1}. *a* 5-fluorouracil (*I*, R^1 = H), *b* 1,3-dimethyl-5-fluorouracil (*I*, R^1 = CH_3)

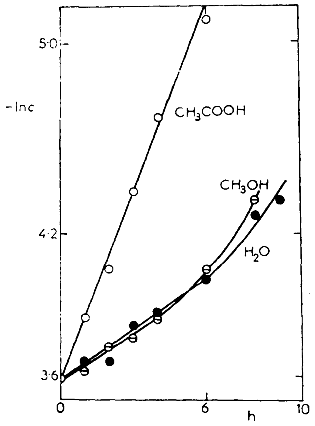


FIG. 2

Photoconversion of 1,3-dimethyl-5-fluorouracil (c = 2·78 . 10^{-2} mol l^{-1}, λ = 253·7 nm) in H_2O (k 1·93 . 10^{-5} s^{-1}) in CH_3OH (k 1·8 . 10^{-5} s^{-1}) and in CH_3COOH (k 7·32 . . 10^{-5} s^{-1}) at 32°C and light intensity 8·89 . . 10^{15} photons ml^{-1} . s^{-1}

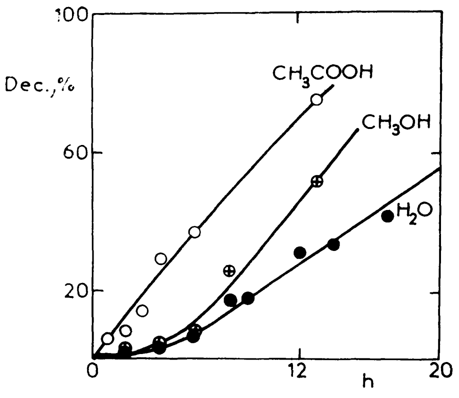


FIG. 3

The effect of solvent on decomposition of 1,3-dimethyl-5-fluorouracil to nonfluorinated products. $\lambda = 253{\cdot}7$ nm, c $2{\cdot}78 \,.\, 10^{-2}$ mol l^{-1}, T 32°C and light intensity $8{\cdot}89 \,.\, 10^{15}$ photons ml^{-1} s^{-1}

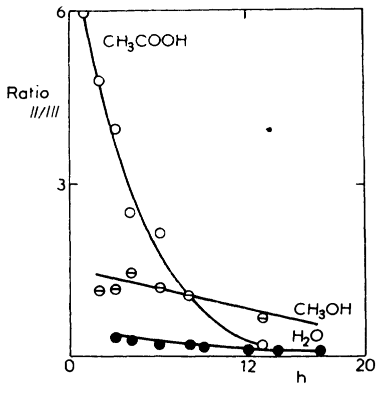


FIG. 4

The effect of irradiation time on ratio of *cis* : *trans* addition products for 1,3-dimethyl-5-fluorouracil photolysis (c $2{\cdot}78 \,.\, 10^{-2}$ mol . l^{-1}, $T = 32$°C, $\lambda = 253{\cdot}7$ nm, light intensity $8{\cdot}89 \,.\, 10^{15}$ photons ml^{-1} s^{-1}

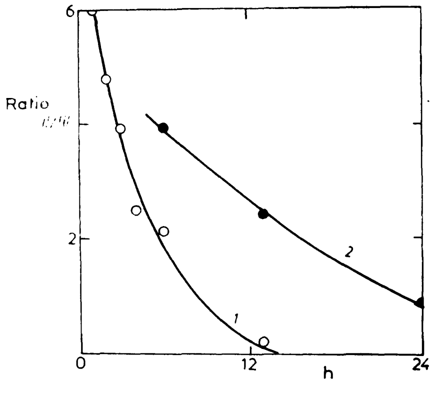


FIG. 5

The effect of light intensity on ratio of *cis* : *trans* addition products in CH_3COOH. $\lambda = 253{\cdot}7$ nm, initial concentration of 1,3-dimethyl-5-fluorouracil, *1* $2{\cdot}78 \,.\, 10^{-2}$ mol l^{-1} light intensity $8{\cdot}89 \,.\, 10^{15}$ photons ml^{-1} s^{-1}, *2*, $3{\cdot}61 \,.\, 10^{15}$ photons ml^{-1} s^{-1}

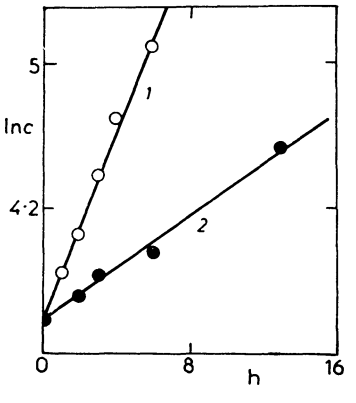


FIG. 6

The effect of light intensity on photoconversion of 1,3-dimethyl-5-fluorouracil in CH_3.COOH (c $2{\cdot}78 \,.\, 10^{-2}$ mol l^{-1}, $\lambda = 253{\cdot}7$ nm, T 32°C); light intensity $8{\cdot}89 \,.\, 10^{15}$ photons ml^{-1} s^{-1}, *1* (k $7{\cdot}32 \,.\, 10^{-5}$ s^{-1}), $3{\cdot}61 \,.\, 10^{15}$ photons ml^{-1} s^{-1}, *2* (k $1{\cdot}98 \,.\, 10^{-5}$ s^{-1})

5-Fluorouracil, 1,3-dimethyl-5-fluorouracil and solvents were purified before irradiation[15]. All the solutions were saturated with oxygen before irradiation.

5-Fluorouracil and 1,3-Dimethyl-5-fluorouracil Phototransformations in Hydroxylic Solvents

18 ml of $2{\cdot}78 \,.\, 10^{-2}$M oxygen saturated solution of 5-fluorouracil or 1,3-dimethyl-5-fluorouracil in selected solvent was irradiated in a RPR chamber photoreactor, model 100 with RPR 253·7 lamps at a light intensity of $8{\cdot}89 \,.\, 10^{15}$ photons $\text{ml}^{-1}\ \text{s}^{-1}$, determined with ferrioxalate actinometer at 32°C, for 1—24 h. The solvent was evaporated under reduced pressure, internal reference (octafluoronaphthalene or trifluoromethylbenzene) was added and the reaction mixture was was analysed by ^{19}F NMR spectroscopy. The data are presented in the scheme and in the figures.

Photoreaction of 1,3-Dimethyl-5-fluorouracil in Water

2 mmol of *I* ($R^1 = CH_3$) were dissolved in 72 ml of water and irradiated at $\lambda = 253{\cdot}7$ nm and 32°C for 8 h, the solvent was evaporated *in vacuo*, the mixture was separated by preparative TLC (SiO_2, $CHCl_3$—CH_3OH 9 : 1) and 21 mg (6%) of oily product *II*, decomposing on heating, was isolated. Under these conditions, the starting material and product *III* were not separated. Product *III* was isolated by TLC (60 mg, 17%) as solid crystals, melting point 150—153°C (decomposition), from the experiment, where the above mentioned solution was irradiated for 40 h, with no starting material and product *II* observed. NMR data for product *II* and *III* are listed in the Table II.

(±)-trans-5-*Fluoro*-6-*hydroxy*-5,6-*dihydro*-1,3-*dimethyluracil* (II, $R = C_2H_5$, $R^1 = CH_3$): exact mass, calculated for $C_6H_9FN_2O_3$ 176·0597, found 176·0600; mass spectrum, *m*/*z* 176 ($M^{+\bullet}$, 49), 158 (11), 156 (19), 119 (10), 91 (43), 74 (11), 73 (20), 71 (11), 62 (34), 61 (10), 60 (33,) 58 (100), 57 (16), 56 (18), 55 (15), 43 (39), 42 (70).

(±)-cis-5-*Fluoro*-6-*hydroxy*-5,6-*dihydro*-1,3-*dimethyluracil* (III, R = H, $R^1 = CH_3$): exact mass, calculated for $C_6H_9FN_2O_3$ 176·0597, found 176·0590; mass spectrum, *m*/*z* 176 ($M^{+\bullet}$, 70), 158 (35), 119 (18), 102 (15), 101 (15), 91 (60), 74 (20), 73 (35), 62 (50), 61 (15), 60 (75), 58 (90), 56 (26), 45 (19), 43 (30), 42 (100).

Photoreaction of 1,3-Dimethyl-5-fluorouracil (*I*) in Methanol

Products *II* and *III* were isolated from the reaction mixtures under the above mentioned conditions, after 24 h and 40 h irradiation, respectively.

(±)-trans-5-*Fluoro*-6-*methoxy*-5,6-*dihydro*-1,3-*dimethyluracil* (*II*, $R = R^1 = CH_3$): 32 mg (8%) of oily product, decomposing on heating. NMR data are in Table II. Exact mass, calculated for $C_7H_{11}FN_2O_3$ 190·0754, found 190·0760; mass spectrum, *m*/*z* 190 ($M^{+\bullet}$, 27), 159 (25), 119 (20), 117 (21), 105 (18), 102 (33), 90 (16), 86 (22), 75 (32), 74 (59), 73 (19), 72 (12), 61 (11), 60 (27), 58 (18), 56 (16), 45 (12), 43 (37), 42 (100).

(±)-cis-5-*Fluoro*-6-*methoxy*-5,6-*dihydro*-1,3-*dimethyluracil* (*III*, $R = R^1 = CH_3$): 108 mg (28%) of solid product, melting point 135—138°C (decomposition). NMR data are in the Table II. Exact mass, calculated for $C_7H_{11}FN_2O_3$ 190·0754, found 190·0750; mass spectrum, *m*/*e* 190 ($M^{+\bullet}$, 43), 159 (48), 105 (27), 102 (72), 90 (22), 76 (28), 74 (100), 73 (27), 72 (15), 62 (13), 61 (14), 60 (37), 58 (15), 56 (23), 43 (18), 42 (59).

Photoreaction of 1,3-Dimethyl-5-fluorouracil (*I*) in Ethanol

Products *II* and *III* were isolated from the reaction mixture obtained after 24 h irradiation under the conditions mentioned above, by preparative TLC.

(±)-trans-5-*Fluoro*-6-*ethoxy*-5,6-*dihydro*-1,3-*dimethyluracil* (*II*, $R = C_2H_3$, $R^1 = CH_3$): 15 mg (4%) of oily product, decomposing on heating. NMR data are in Table II. Exact mass, calculated for $C_8H_{13}FN_2O_3$ 204·0910, found 204·0905; mass spectrum, *m*/*z* 204 ($M^{+\bullet}$, 100), 159 (86), 119 (27), 103 (43), 102 (92), 91 (24), 88 (11), 75 (32), 74 (62), 73 (27), 62 (32), 62 (32), 60 (30), 59 (12), 58 (38), 56 (14), 55 (12), 47 (38), 43 (51), 42 (89).

(±)-cis-5-*Fluoro*-6-*ethoxy*-5,6-*dihydro*-1,3-*dimethyluracil* (*III*, $R = C_2H_5$, $R' = CH_3$): 35 mg (9%) of waxy product, decomposed on heating. NMR data are in Table II. Exact mass, calculated for $C_8H_{13}FN_2O_3$ 204·0910, found 204·0915; mass spectrum, *m*/*z* 204 ($M^{+\bullet}$, 33), 184 (13), 167 (12), 159 (71), 156 (15), 119 (19), 102 (100), 99 (31), 91 (13), 90 (15), 82 (15), 74 (71), 73 (21), 71 (13), 69 (17), 62 (27), 60 (31), 58 (33), 56 (19), 55 (15), 43 (23), 42 (88).

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