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Electrophilic Fluorination of 6-Methyl- and 1,3,6-Trimethyluracils in Water

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Abstract—The reaction of 4-chloromethyl-1-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) with 6-methyl- and 1,3,6-trimethyluracil in water has been studied. According to the kinetic data, the fluorination follows a bimolecular mechanism with intermediate formation of cationic σ-complexes.

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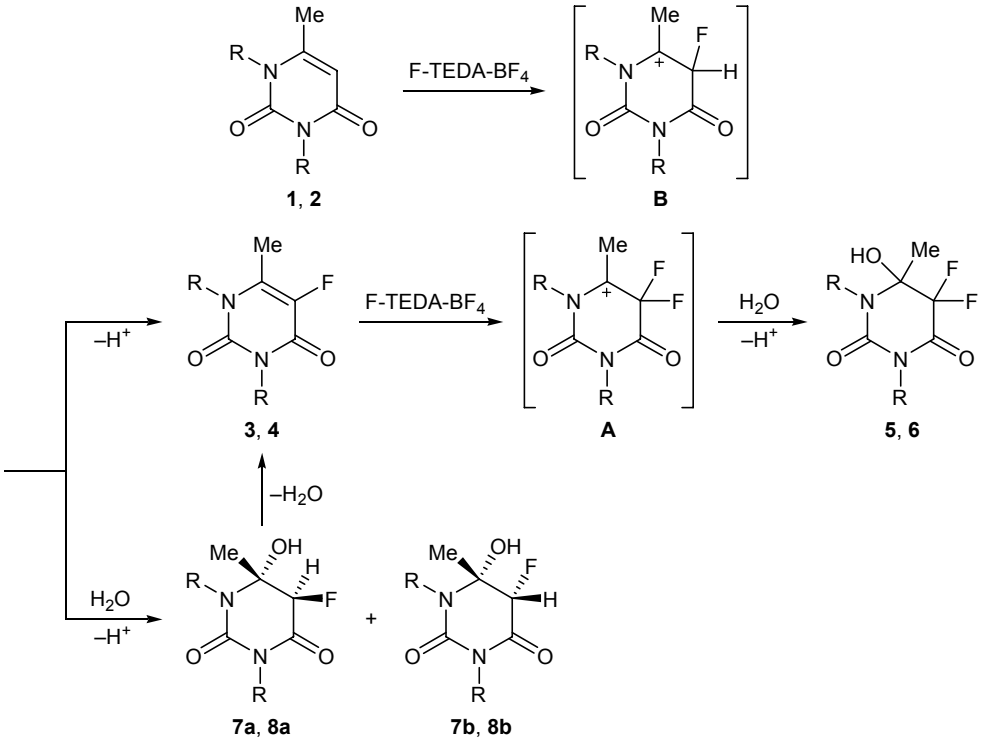
Uracil derivatives exhibit antiviral activity, while 6-methyluracil is used in medicine as anti-inflammatory, anabolic, and anti-catabolic drug [1]. Introduction of fluorine atoms into organic molecules usually enhances their therapeutic properties [2]. Schuman et al. [3] patented a procedure for the synthesis of 5-fluoro-6-methyluracil by fluorination of 6-methyluracil with gaseous fluorine in water. Cech et al. [4] later obtained 5-fluoro-6-methyluracil by the action of fluorine on 6-methyluracil in acetic acid, and the authors noted that no 5-fluoro-6-methyluracil was formed when acetic acid was replaced by water. Elemental fluorine was widely used to synthesize a number of other fluorinated uracils (see, e.g., [4, 5]). In addition, such fluorinating agents as OF_2 [6], AcOF [7, 8], CF_3OF [9, 10], XeF_2 [11], and $CsSO_4F$ [12] were used. All these compounds, as well as elemental fluorine, cannot be regarded as environmentally safe [13]. Gaseous fluorine is very aggressive toward many materials, toxic, and dangerous in handling, OF reagents are toxic and insufficiently stable, while XeF_2 is toxic and expensive.

In recent time, NF reagents, in particular 4-chloromethyl-1-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4), have been widely used as a source of fluorine for mild and selective fluorination of organic compounds [13–18]. This reagent is quite reactive and soluble in water and is a moderate oxidant. Lal et al. [19] were the first to use F-TEDA-BF_4 to fluorinate pyrimidine bases, uracil and thymine. According to the authors, the reaction of uracil with F-TEDA-BF_4 in water afforded 5-fluorouracil in 82% yield. However, Rangwala et al. [20] under analogous conditions obtained labeled 5-fluoro-(2-^{13}C)uracil in a much lower yield.

With a view to developing an efficient environmentally acceptable procedure for the synthesis of fluorinated uracil derivatives, in this work we examined the reactions of 6-methyluracil (**1**) and 1,3,6-trimethyluracil (**2**) with F-TEDA-BF_4 in water. The reactions with **1** and **2** at 80°C (3 h) afforded, respectively, 5-fluoro-6-methyluracil (**3**) and 5-fluoro-1,3,6-trimethyluracil (**4**) together with 5,5-difluoro-6-hydroxy-6-methylhexahydropyrimidine-2,4-dione (**5**) and 5,5-difluoro-6-hydroxy-1,3,6-trimethylhexahydropyrimidine-2,4-dione (**6**). The formation of compounds **5** and **6** may be rationalized by reaction of intermediate cationic σ-complexes **A** with water (see table, Scheme 1). Presumably, the primary intermediate is σ-complex **B** which is capable of either losing a proton to give compound **3** or **4** or reacting with water to produce stereoisomeric hydroxy compounds **7** or **8**. The latter were detected in the reaction mixture by ^{1}H and ^{19}F NMR spectroscopy when the reaction was carried out at lower temperature (40°C; see table). Compounds **7** and **8** readily undergo dehydration; therefore, we failed to isolate them in the pure state and record their mass spectra.

Presumably, the *gauche* effect in the attack of complex **B** by water molecule favors formation of *cis* isomers **7b** and **8b** (cf. [7, 8]). According to the ^{1}H and ^{19}F NMR data, compound **8b** (in a mixture of fluorination products) in water at 40°C is gradually converted into 5-fluoro-1,3,6-trimethyluracil (**4**).

Scheme 1.



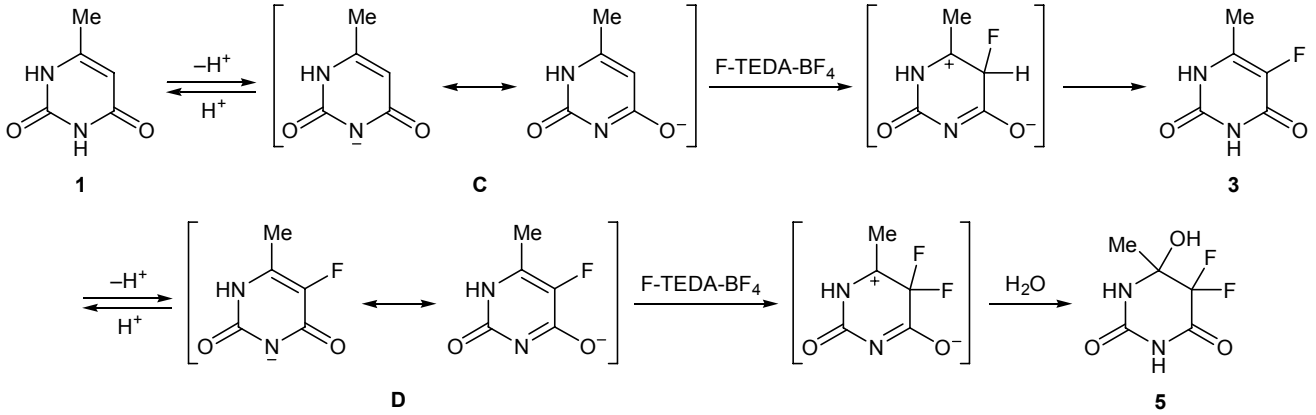
1, **3**, **5**, **7**, R = H; **2**, **4**, **6**, **8**, R = Me.

Fluorination of 6-methyluracil (**1**) and 1,3,6-trimethyluracil (**2**) with F-TEDA-BF_4 in water

Compound no.	Temperature, °C	Molar ratio substrate–F-TEDA-BF_4	Reaction time, h	Yield,[a] %			
				3 or **4**	**5** or **6**	**7a** or **8a**	**7b** or **8b**
1	80	1:1	3	53	23	–	–
	80	1:1.5	3	24	63	–	–
	80	1:2	3	–	87	–	–
	80	1:3	3	–	100	–	–
	40	1:1.2	4	35	8	2	20
	40	1:2[b]	2	12	7	3	68
	20	1:1.2	20	21	4	2	31
	20	1:2	20	17	22	3	58
2	80	1:1	3	67	17	–	–
	80	1:1.5	3	51	48	–	–
	80	1:2	3	11	89	–	–
	80	1:3	3	–	100	–	–
	40	1:2[b]	2	8	6	7	75
	20	1:2	24	83	13	4	–

[a] Determined by averaging the ^1H and ^{19}F NMR data.
[b] Excess F-TEDA-BF_4 was removed by adding KI and $Na_2S_2O_3$ to the mixture.

Scheme 2.



The kinetics of the reaction of uracils **1** and **2** with F-TEDA-BF_4 in water conforms to the bimolecular mechanism (Scheme 1):

$$v = \partial[\text{F-TEDA-BF}_4]/\partial\tau = k[\text{Ur}][\text{F-TEDA-BF}_4],$$

where [Ur] is the concentration of **1** or **2**. The ln([Ur]/[F-TEDA-BF_4]) values are linearly related to the time τ (Fig. 1). The second-order rate constants for the fluorination of **1** and **2** [$k_{40°C} = (2.71 \pm 0.03) \times 10^{-3}$ and $(3.77 \pm 0.03) \times 10^{-3}$ L mol^{-1} s^{-1}, respectively] indicate higher reactivity of **2**, which may be due to donor effect of the methyl groups in positions *1* and *3*. The ratio of the fluorination rate constants of **2** and **1** weakly depends on the temperature. The calculated ratio $k_{40°C,\mathbf{2}}/k_{40°C,\mathbf{1}} = 1.39$ is close to that found by the competing reaction method at 70°C, ([**4**] + [**6**])/([**3**] + [**5**] + [**7**]) = 1.41. The reaction of **1** or **2** with F-TEDA-BF_4 is the rate-determining step. This follows from the higher rate of the bimolecular reaction of 5-fluoro-6-methyluracil (**3**) with F-TEDA-BF_4 [$k_{40°C} = (4.11 \pm 0.15) \times 10^{-3}$ L mol^{-1} s^{-1}]. The fluorination of 5-fluoro-6-methyluracil is also a bimolecular reaction (Fig. 2). The higher rate of fluorination of **3** may be rationalized assuming participation of its anionic form (Scheme 2). The presence of a fluorine atom in the 5-position should increase the acidity of **3**, and the reaction with anion **D** should be faster than with the neutral species. It should be noted that the acidity of 5-fluorouracil is appresiably higher than the acidity of uracil [21].

Thus, the use of F-TEDA-BF_4 as fluorinating agent and of water as solvent yields mono- and difluoro uracil derivatives in moderate and high yields, respectively. According to the kinetic data, the reactions follow the bimolecular mechanism with intermediate formation of cationic σ-complexes.

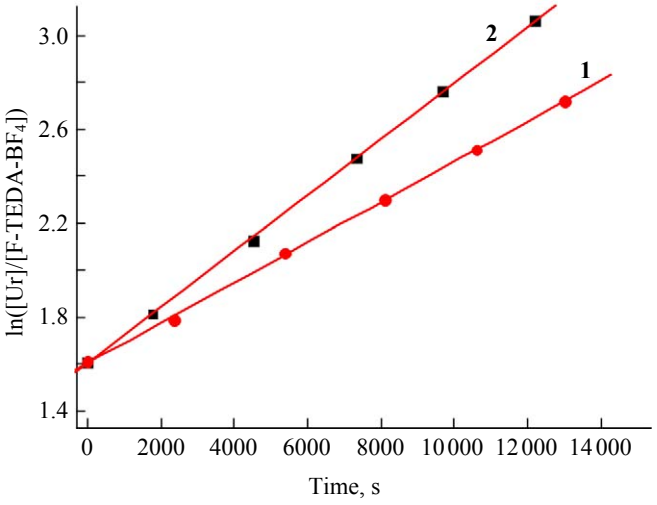


Fig. 1. Plot of ln([Ur]/[F-TEDA-BF_4]) versus time for uracils **1** and **2**.

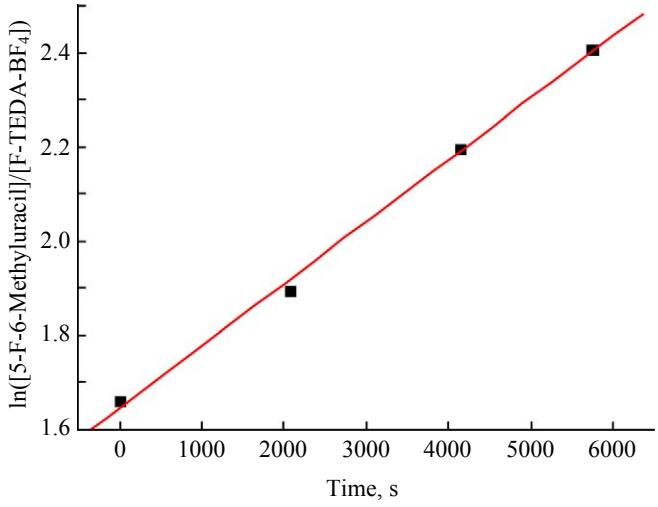


Fig. 2. Plot of ln([5-fluoro-6-methyluracil]/[F-TEDA-BF_4]) versus time.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AV-300 (300.1 MHz for ^1H, 75.5 MHz for ^{13}C, and 282.4 MHz for ^{19}F) and AV-400 spectrometers (100.6 MHz for ^{13}C). The chemical shifts were measured relative to the residual proton or carbon signal of the solvent ($CHCl_3$, δ 7.24 ppm, $CDCl_3$, δ_C 76.9 ppm; DMSO-d_5, δ 2.50 ppm, DMSO-d_6, δ_C 39.5 ppm) or added $CHCl_2CHCl_2$ (δ 5.94 ppm) or $PhCF_3$ (δ_F –63.73 ppm relative to $CFCl_3$). The high-resolution mass spectra were obtained on a Thermo Scientific instrument.

4-Chloromethyl-1-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4) was commercial product (>95%, Aldrich); DMSO-d_6 and $CDCl_3$ contained 99.8% of deuterium. 6-Methyl- and 1,3,6-trimethyluracils were synthesized as described in [22, 23].

Fluorination of 6-methyl- and 1,3,6-trimethyluracils 1 and 2 (*general procedure*). A solution of uracil **1** or **2** and F-TEDA-BF_4 in water was stirred under the conditions indicated in table, the solvent was purged off with a stream of air, the residue was dissolved in DMSO-d_6, and ^1H and ^{19}F NMR spectra were recorded. In some cases (see table), excess F-TEDA-BF_4 was removed by adding KI and $Na_2S_2O_3$ to the reaction mixture before purging with air.

5-Fluoro-6-methyluracil (3). A solution of 0.2 g (1.59 mmol) of 6-methyluracil (**1**) and 0.86 g (2.43 mmol) of F-TEDA-BF_4 in 8 mL of water was heated for 4 h at 80°C, and the mixture was evaporated under reduced pressure. The solid residue was washed with diethyl ether (2×10 mL) and acetonitrile (30 mL) and dried under reduced pressure. Yield 0.084 g (37%), white crystals, mp >300°C (decomp.); published data [3]; mp 313, 318°C (decomp.). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.04 d (3H, CH_3, J = 3.3 Hz), 10.8 br.s (1H, NH), 11.4 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 11.80 d (CH_3, J = 0.8 Hz), 136.73 d (C^6, J = 26.1 Hz), 137.06 d (C^5, J = 221.6 Hz), 149.57 s (C^2=O), 157.36 d (C^4=O, J = 25.9 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F –176.52 ppm, m. Mass spectrum: m/z 144.0331 $[M]^+$. $C_5H_5FN_2O_2$. Calculated: M 144.0330.

5-Fluoro-1,3,6-trimethyluracil (4). A solution of 0.05 g (0.32 mmol) of 1,3,6-trimethyluracil (**2**) and 0.23 g (0.65 mmol) of F-TEDA-BF_4 in 5 mL of water was kept for 25 h at room temperature. The mixture was extracted with diethyl ether (10×5 mL), the extract was dried over $MgSO_4$, the solvent was distilled off, and the residue was purified by silica gel column chromatography using ethyl acetate as eluent. Yield 0.024 g (44%), white crystals, mp 127–129°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.26 d (3H, 6-CH_3, J = 3.6 Hz), 3.35 s (3H, NCH_3), 3.38 d (3H, NCH_3, J = 0.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.96 d (6-CH_3, J = 2.6 Hz), 28.21 d (NCH_3, J = 1.4 Hz), 31.55 s (NCH_3), 136.10 d (C^6, J = 24.9 Hz), 137.97 d (C^5, J = 225.8 Hz), 150.55 s (C^2), 156.38 d (C^4, J = 26.2 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F –165.14 ppm, q.q (J = 3.6, 0.6 Hz). Found, %: C 48.90; H 5.26; F 11.20; N 16.29. Calculated, %: C 48.84; H 5.27; F 11.04; N 16.27. Mass spectrum: m/z 172.0645 $[M]^+$. $C_7H_9FN_2O_2$. Calculated: M 172.0643.

5,5-Difluoro-6-hydroxy-6-methylhexahydropyrimidine-2,4-dione (5). A solution of 0.2 g (1.59 mmol) of 6-methyluracil (**1**) and 1.685 g (4.76 mmol) of F-TEDA-BF_4 in 10 mL of water was heated for 3 h at 80°C. The mixture was evaporated to a volume of ~4 mL and extracted with diethyl ether (3×30 mL), the extract was dried over $MgSO_4$, and the solvent was distilled off. Yield 0.263 g (92%), white crystals, mp 194–196°C. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.42 d (3H, 6-CH_3, J = 1.5 Hz), 7.07 br.s (1H, OH), 8.80 br.m (1H, NH), 11.10 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 18.40 d (6-CH_3, J = 0.6 Hz), 78.94 d.d (C^6, J = 27.4, 26.4 Hz), 108.29 d.d (C^5, J = 255.4, 247.7 Hz), 150.84 s (C^2), 161.70 d.d (C^4, J = 31.5, 27.6 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: –116.35 d.q (J = 261.3, 1.5 Hz), –139.66 d.t (J = 261.3, 3.8 Hz). Found, %: C 33.66; H 3.56; F 21.46; N 15.75. $C_5H_6F_2N_2O_3$. Calculated, %: C 33.34; H 3.36; F 21.10; N 15.55.

5,5-Difluoro-6-hydroxy-1,3,6-trimethylhexahydropyrimidine-2,4-dione (6). A solution of 0.1 g (0.65 mmol) of 1,3,6-trimethyluracil (**2**) and 0.69 g (1.95 mmol) of F-TEDA-BF_4 in 10 mL of water was stirred for 4 h at 80°C. The mixture was evaporated, the solid residue was dissolved in diethyl ether, the solution was filtered, and the filtrate was evaporated. Yield 0.131 g (97%), white crystals, mp 84–86°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.66 d.d (3H, 6-CH_3, J = 2.4, 0.9 Hz), 3.07 d (3H, NCH_3, J = 0.3 Hz), 3.23 d.d (3H, NCH_3, J = 0.9, 0.6 Hz), 3.66 br.s (1H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.39 t (6-CH_3, J = 1.9 Hz), 28.38 d (NCH_3, J = 1.1 Hz), 28.79 d (NCH_3, J = 1 Hz), 83.18 t (C^6, J = 26.5 Hz), 107.78 d.d (C^5, J = 251.6, 250.7 Hz), 151.48 s (C^2=O), 160.35 d.d (C^4=O, J = 30.9, 28.4 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm:

–116.93 d.m (J = 272.4 Hz), –129.79 d (J = 272.4 Hz). Mass spectrum: m/z 208.0652 $[M]^+$. $C_7H_{10}F_2N_2O_3$. Calculated: M 208.0654.

(5*R*,6*R*)- and (5*R*,6*S*)-5-Fluoro-6-hydroxy-6-methylhexahydropyrimidine-2,4-diones 7a and 7b and (5*R*,6*R*)- and (5*R*,6*S*)-5-fluoro-6-hydroxy-1,3,6-trimethylhexahydropyrimidine-2,4-diones 8a and 8b. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, **7a**: 1.36 d (CH_3, J = 2.2 Hz), 4.49 d (5-H, J = 48.1 Hz), 10.55 s (NH), 10.76 s (NH); **7b**: 1.40 s (CH_3), 5.18 d (5-H, J = 47.1 Hz), 8.31 s (NH), 10.34 s (NH); **8a**: 1.29 d (CH_3, J = 2.1 Hz), 2.84 s (NMe), 2.97 s (NMe), 4.98 d (5-H, J = 47.7 Hz); **8b**: 1.51 s (CH_3), 2.89 s (NMe), 2.96 s (NMe), 5.26 d (5-H, J = 46.5 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: **7a**: –192.4 d.d (J = 48.3, 2.5 Hz); **7b**: –213.7 d.t (J = 47.2, 2.7 Hz); **8a**: –202.98 d (J = 47.8 Hz); **8b**: –208.60 d (J = 46.6 Hz).

Kinetic study of the reaction of 6-methyluracil (1) with F-TEDA-BF$_4$. Preliminarily prepared solutions of compound **1** (c = 0.079 M) and F-TEDA-BF_4 (c = 0.0159 M) were kept for 60 min at 40°C and were then mixed together. The progress of the reaction was monitored by the concentration of F-TEDA-BF_4 (samples were withdrawn at definite time intervals), which was determined by iodometric titration [24]. The kinetic study of the fluorination of compounds **2** and **3** was performed in a similar way.

Competing fluorination of compounds 1 and 2 with F-TEDA-BF$_4$. Compounds **1** and **2**, 0.13 mmol each, were dissolved in 4 mL of water, 0.032 mmol of F-TEDA-BF_4 was added, and the mixture was kept for 3 h at 70°C. The solvent was removed by purging with a stream of air, the residue was dissolved in DMSO-d_6, and the ^{1}H and ^{19}F NMR spectra were recorded. The ratio of the fluorination products was determined from the ^{1}H and ^{19}F NMR signal intensities.

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