100946-60-9; (Z)-**4a**, 99894-21-0; (E)-**4a**, 101052-88-4; (Z)-**4b**, 99946-18-6; (E)-**4b**, 101052-96-4; (Z)-**4c**, 99946-19-7; (E)-**4c**, 101052-90-8; (Z)-4c', 101052-92-0; (Z)-5a, 99946-17-5; (E)-**5a**, 101052-89-5; (Z)-**5b**, 99894-22-1; (Z)-**5c**, 99894-23-2; (E)-**5c**, 101052-91-9; (Z)-**5c'**, 101052-93-1; (Z)-**6a**, 100946-61-0; (E)-**6a**, 100946-62-1; (Z)-**6c**, 100946-63-2; **7a**, 99894-24-3; **7b**, 99894-25-4; **7c**, 99894-26-5; **7c'**, 101052-94-2; **8a**, 99946-20-0; **8b**, 99946-21-1; **8c**, 99946-22-2; **8c'**, 101052-95-3; **9c**, 100946-64-3; **10c**, 101052-97-5; **13c**, 99946-16-4; (1S)-*d*-10-camphorsulfonyl chloride, 21286-54-4; cyclopentadiene, 542-92-7.

Supplementary Material Available: Tables of crystal data for compounds **9c** and **10c** (6 pages). Ordering information is given on any current masthead page.

Mechanism and Stereochemistry of the Fluorination of Uracil and Cytosine Using Fluorine and Acetyl Hypofluorite

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The products of the reaction of CH_3COOF and F_2 with uracil and cytosine dissolved in acetic acid and water were studied by using ^{18}F as a tracer. Apart from 5-fluorouracil (**2**) and the 5,5-difluoro adducts **5a** and **5b**, the ^1H NMR spectra of the crude reaction mixture showed the presence of two geometric isomers of both 5-fluoro-6-acetoxy-5,6-dihydrouracil (**3a, 4a**) and 5-fluoro-6-hydroxy-5,6-dihydrouracil (**3b, 4b**). In the fluorination of cytosine, corresponding products were observed with the exception of the acetoxy adducts. For both reagents and for both substrates a radical-cation mechanism is proposed. The observed conversions of the acetoxy adducts of uracil are explained by an acylimine (iii) as an intermediary.

In 1957 Wang[1] proposed that in the reaction of N_1-substituted uracils with bromine in aqueous systems, 5-bromo-6-hydroxy-5,6-dihydrouracils were initially formed. Analogous intermediaries were reported for the iodination of N_1-substituted uracils.[2,3] In contrast, uracil itself yields no monohalogenated adduct upon chlorination,[4] bromination,[5] or iodination.[3] Only the 5,5-dihalo-6-hydroxy-5,6-dihydrouracils were found to be stable. Apart from this the 5,6-dihydrocytosine adducts have been reported to be less stable than those of uracil.[6]

This is in accord with our findings that in the synthesis of [^{18}F]-5-fluorocytosine only the 5,5-difluorinated by-product **10a** was found[7] and no monofluorinated adducts as in the fluorination of uracil.[8-10] Interestingly for the monohalogenation with Cl, Br, and I all adducts were found to exist in the trans form,[3,5,11] while for **3a** and **3**, R = CH_3 also only one geometric isomer was obtained but which appeared to have the cis configuration.[9,10,12]

In the reaction of F_2 with uracil, Vine et al.[9] found **3a** to be a stable compound, while Cech et al.[13] obtained **3a** as a very unstable intermediary. The latter author proposed an initial addition of F_2 to uracil and a subsequent displacement of fluorine at C_6 by an acetoxy group.[13] Shiue et al.[14] proposed that the initial step in the reaction of F_2 with uracil in CH_3COOH is the formation of CH_3COOF, followed by a stereospecific syn addition[15] of this compound across the C_5 and C_6 double bond to give **3a**. However, we have recently shown that for reactions with F_2 in CH_3COOH, CH_3COOF is hardly formed.[16]

In view of the above-mentioned conflicting results regarding the reaction of F_2 with uracil and other aspects of interest such as the exclusive cis addition and the different chemical stability of the fluoro adduct **3a** from that of cytosine,[7] we have restudied the addition of F_2 to uracil—using either acetic acid or water as solvent—in comparison to the addition of CH_3COOF. Similar studies were performed with cytosine. Because of the limited solubility of uracil and in order to simplify the detection of the UV-insensitive intermediaries, these experiments were carried out on 5–30 μmol scale using ^{18}F as a tracer.

Results

The products from the reaction of F_2 and CD_3COOF with uracil are given in Figure 1. In order to eliminate a possible HF-catalyzed hydrolysis of the acetate group, gaseous CH_3COOF[17] was also used because in this case F^-

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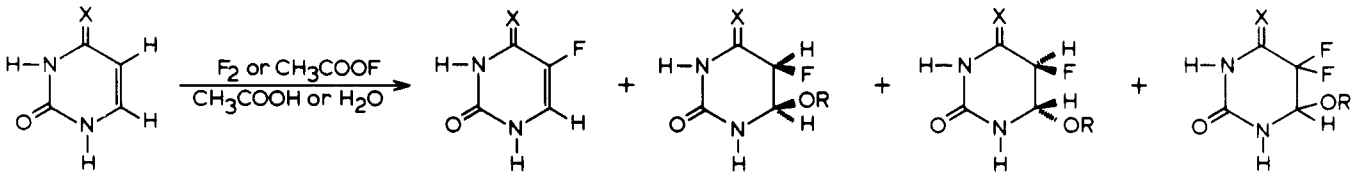

	X
1	O
6	NH

	X
2	O
7	NH

	X	R
3a	O	Ac
b	O	H
8a	NH	Ac
b	NH	H

	X	R
4a	O	Ac
b	O	H
9a	NH	Ac
b	NH	H

	X	R
5a	O	Ac
b	O	H
10a	NH	Ac
b	NH	H

Figure 1. Fluoro products formed from the reactions of F_2 and CH_3COOF with uracil (1) and cytosine (6) dissolved in acetic acid and/or water.

Table I. Characteristics of the [^{18}F]Fluorouracil Compounds

compnd	R_f value	R_t value (min)	^{1}H NMR δ H_5	δ H_6	$J_{5F,5H}$ (Hz)	$J_{5H,6H}$ (Hz)	$J_{5F,6H}$ (Hz)
1	0.45	17	5.89 (d)	7.54 (d)		7.7	
2	0.63	19		7.61 (d)			5.4
3a	0.77		5.48 (dd)	6.29 (dd)	45.0	4.3	2.2
4a	0.77		4.97 (dd)	6.11 (dd)	45.6	2.9	8.1
3b	0.56	8	5.30 (dd)	5.33 (dd)	46.7	4.0	2.2
4b	0.56	8	4.90 (dd)	5.27 (dd)	46.7	4.3	7.7
5a	0.87			6.21 (dd)			2.0, 6.8
5b	0.79	25		5.22 (dd)			2.9, 5.9

Table II. Radiochemical Yields (%) of the [^{18}F]Fluorouracil Compounds Formed under Various Reaction Conditions

reaction	2	3a + 4a	3b + 4b	5a/5b[a]
[^{18}F]F_2 (A)	5-7	15-20	6-8	1-2 (**5a**)
[^{18}F]F_2 (B)	3-5		20-25	1 (**5b**)
gaseous [^{18}F]CH_3COOF (A)	8-10	25-30	5-6	1-3 (**5a**)
gaseous [^{18}F]CH_3COOF (B)	5-8		32-37	1-2 (**5b**)
[^{18}F]CD_3COOF (C)	7-10	25-30	1-2	2-3 (**5a**)
[^{18}F]CD_3COOF (D)	4-6	14-16	19-21	1-2 (**5a** + **5b**)
[^{18}F]CD_3COOF (E)	4-6	9-11	24-26	1-2 (**5a** + **5b**)
[^{18}F]CD_3COOF (F)	3-5	5-7	29-31	1 (**5a** + **5b**)

[a] Yields determined after conversion of **5a** into **5b**.

ions adhere to the column. Barely any difference is observed between the reactions with F_2, CD_3COOF, or gaseous CH_3COOF (Table II). In all cases, TLC analysis showed that apart from 5-fluorouracil (**2**), two other compounds were obtained, dependent upon the solvent used. The ^{1}H NMR spectra of the crude reaction mixture revealed that these compounds were the geometric isomers of both the 6-acetoxy and the 6-hydroxyuracil adducts **3a**, **4a** and **3b**, **4b**, respectively, with a ratio **3**/**4** of about 10. A typical example of a NMR spectrum is given in Figure 2. In acetic acid the acetoxy compounds **3a** and **4a** were the main products whereas in water the corresponding hydroxy compounds **3b** and **4b** were formed predominantly (Table II and Figure 2). Besides, very small amounts of the difluorinated products **5a** and **5b** were also found. The acetoxy compounds **3a** and **4a** were found to be stable in CD_3COOD solution. This means that neither **3a** nor **4a** is the source for the direct formation of the small amounts of 5-fluorouracil (**2**), a conclusion that is confirmed by the observation that **2** was also found when only D_2O was used as the solvent (Table II).

From solvent mixture experiments (Table II) it can be concluded that independent of the fluorinating agent an intermediary is formed that reacts with the solvent mixture

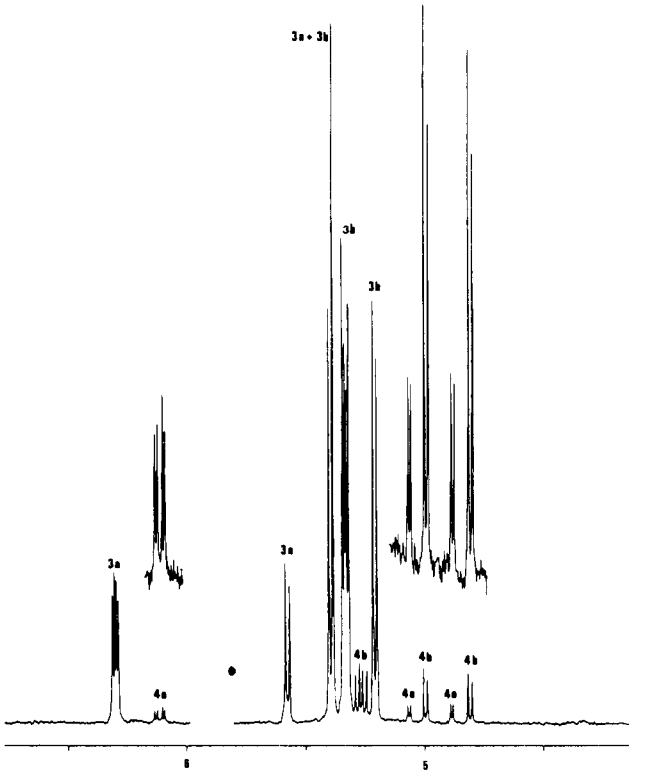

Figure 2. Part of the ^{1}H NMR spectrum of the crude reaction mixture formed by the reaction of F_2 with uracil (1) in a D_2O/CD_3COOD mixture.

but preferentially with water; the sum of the yields of **3a**, **4a** and **3b**, **4b** remains almost constant. The small amounts of **3b** and **4b** found in CD_3COOD are probably caused by reaction with traces of water; formation of **3b** and **4b** could be eliminated when acetic anhydride was added before reaction.

The results of similar experiments with cytosine are given in Tables III and IV and Figure 1. Again, little difference was found between the reactions of F_2 and CH_3COOF/CD_3COOF. ^{1}H NMR analysis showed the formation of 5-fluorocytosine (**7**), the difluorocytosine

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Table III. Characteristics of the [^{18}F]Fluorocytosine Compounds

compnd	R_f value	R_t value (min)	^{1}H NMR δ H_5	δ H_6	$J_{5F,5H}$ (Hz)	$J_{5H,6H}$ (Hz)	$J_{5F,6H}$ (Hz)
6	0.30	10	6.24 (d)	7.75 (d)		7.0	
7	0.45	15		7.72 (d)			5.3
8b			5.30 (dd)	5.34 (dd)	46.6	4.1	2.3
9b			4.90 (dd)	5.28 (dd)	46.7	4.2	8.0
10a	0.82			6.22 (dd)			2.5, 6.6
10b	0.80	24		5.22 (dd)			2.8, 5.8

Table IV. Radiochemical Yields (%) of the [^{18}F]Fluorocytosine Compounds Formed under Various Reaction Conditions

reaction	7	8b + 9b[a]	10a/10b[b]
[^{18}F]F_2 (A)	20–25	3	8–12 (**10a**)
[^{18}F]F_2 (B)	7–9	15	2–3 (**10b**)
gaseous [^{18}F]CH_3COOF (A)	24–29	3	12–17 (**10a**)
gaseous [^{18}F]CH_3COOF (B)	7–9	15	2–3 (**10b**)
[^{18}F]CD_3COOF (C)	16–20	1	10–15 (**10a**)
[^{18}F]CD_3COOF (D)	10–13	10	6–9 (**10a** + **10b**)

[a] Only observed in solution; the yields are estimated by comparison of NMR integration with that of 7. [b] Yields determined after conversion of **10a** into **10b**.

adducts **10a** and **10b**, and the two geometric 6-hydroxy isomers **8b** and **9b** (ratio 8/9 = 8); the acetoxy compounds **8a** and **9a** were not observed.

By ^{1}H NMR analysis it appeared that both geometric isomers **8b** and **9b** are stable in solution. However, TLC and HPLC analysis using ^{18}F as a tracer showed that, in contrast to **3b** and **4b**, **8b** and **9b** are destroyed through interactions with silica. Performing the reactions with gaseous CH_3COOF or F_2 in water, we observed that as with uracil, a certain amount (7–9%) of 5-fluorocytosine (**7**) is formed directly. However, in acetic acid this amount is strongly enhanced (20–25%), indicating that the formation of 5-fluorocytosine in acetic acid is the result of two reaction pathways.

Elimination and Substitution at C_6 in Compounds 3a, 4a, 5a, and 10a. When CH_3COOF was bubbled through uracil in a D_2O/CD_3COOD mixture, both solvents were incorporated, leading to **3a**, **4a** and **3b**, **4b**. However, when D_2O was added 3 min after the reaction of gaseous CH_3COOF with uracil in CD_3COOD, no **3b** and **4b** (only 5% due to the traces of water) were found, indicating that once formed, **3a** and **4a** are stable against substitution or hydrolysis by water.

In the reaction of CD_3COOF with uracil in acetic acid, **3a** and **4a** appeared to be completely converted into 5-fluorouracil (**2**) after evaporation of the solvent and redissolution in CD_3COOD. In contrast, in the reactions with F_2 or gaseous CH_3COOF, **3a** and **4a** remained present after repeated evaporation of the acetic acid and redissolution in CD_3COOD, while the yield of 5-fluorouracil was only slightly enhanced. But when after removal of the acetic acid D_2O was added instead of CD_3COOD, **3a** and **4a** appeared to be completely converted into **3b** and **4b**! This means that after evaporation of the solvent (CD_3COOD), **3a** and **4a** are converted into an intermediary that reacts with D_2O very efficiently. It is of note that evaporation of D_2O followed by the addition of CD_3COOD produced no change, which means that **3b** and **4b** are stable toward elimination or substitution at C_6.

When NH_4OAc, NaOAc, KF, or cytosine dissolved in CD_3COOD was added to the reaction mixtures of F_2 and gaseous CH_3COOF with uracil, even after 3 h no change was found in the TLC or ^{1}H NMR analyses. However, after evaporation of CD_3COOD and redissolution in CD_3COOD or D_2O, the main product was 5-fluorouracil. Therefore, these salts must have an influence on **3a** and **4a** after evaporation of CD_3COOD. The latter result explains why after evaporation of the solvent in the case of the F_2 reaction the yield of 5-fluorouracil was slightly enhanced (presence of a small amount of F^-), and why 5-fluorouracil was obtained as the main product in the case of the CD_3COOF reaction (the presence of ND_4OOCCD_3 is necessary for the production of CD_3COOF in CD_3COOD).

Finally, it appeared that the acetoxy adducts **5a** and **10a** remained present after repeated evaporation and readdition of CD_3COOD, but that they gave the hydroxy adducts **5b** and **10b**, respectively, upon redissolution in D_2O, which again indicates the formation of a reactive intermediary.

Proposed Reaction Sequence for the Reaction of F_2 and CH_3COOF with Uracil and Cytosine. For CH_3COOF and F_2 an electrophilic behavior has been concluded from the reaction with certain aromatic compounds[18] and for CH_3COOF also from the high degree of regiospecificity upon the reaction with triacetylglucal.[19]

The concept of electrophilic fluorination has been the subject of considerable debate and controversy,[18b,20-25] since the process appears to require the removal of a pair of electrons from fluorine, the most electronegative element. Nowadays, the term "electrophilic fluorination" is also used for Sn_2 reactions on fluorine attached to a good leaving group, so that a deficiency of electrons around the fluorine atom does not develop.[25] But, of course, reaction pathways are dependent upon the substrate, the temperature, the solvent, and the concentration of the reactants. As an example, the products from the reaction of CF_3OF with simple alkenes have shown to be consistent with a free radical addition,[24] whereas for other substrates Hesse[22] reports that the reaction is initiated by nucleophilic attack of the π-electron system upon the F atom to afford initially an α-fluorinated carbocation. In general, this initial α-fluorocation is an extremely unstable species and may collapse rapidly from a tight ion pair into cis addition products or may undergo deprotonation. Furthermore, for substrates, which afford relatively stable carbocations, like pyrimidines, the incorporation of external nucleophiles can take place. So, assuming the 7% of 5-fluorouracil (**2**) and 5-fluorocytosine (**7**) is formed from deprotonation of the α-fluorocation, according to this reaction sequence the "standard" products of an electrophilic reaction are obtained upon reaction of F_2 and CH_3COOF with uracil and cytosine. However, the fact that for both F_2 and CH_3CO-

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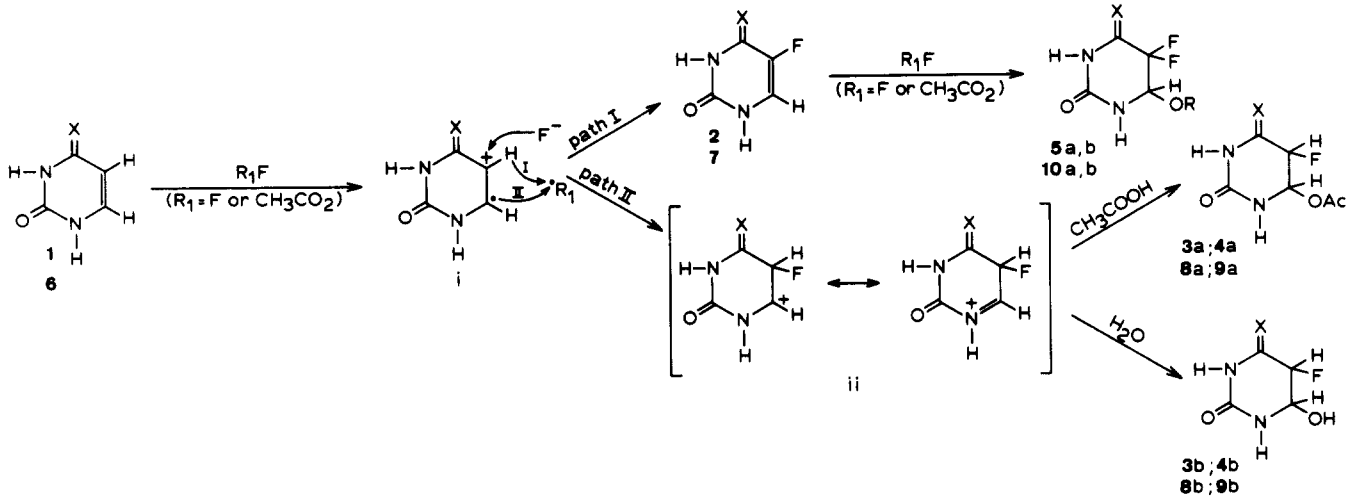

Figure 3. Proposed reaction mechanism for the reactions of F_2 and CH_3COOF with uracil (1) and cytosine (6).

OF the same products in nearly the same amounts are obtained is rather surprising. Upon reaction with other compounds F_2 often leads to charry products,[18a,26] while we have observed a great difference in reaction products from the reaction of F_2 or CH_3COOF with cyclohexene in acetic acid.[16] Therefore, although it may only seem to be of theoretical interest in this special case, we would like to discuss the concept of a radical cation mechanism as a more general concept, because we think that this mechanism may give more insight in the substrate and solvent dependency of the fluorinating reagents F_2 and CH_3COOF.

The concept of a radical-cation mechanism is not new in fluorine chemistry. It has been shown that XeF_2 reacts this way,[27] while for the anodic fluorination,[28] kinetic evidence[29] favored a mechanism wherein a complex between the radical cation and the nucleophile is formed, followed by a second one-electron oxidation.

In the case of a one-electron oxidation, the polarity of the solvent plays a big role, as does the oxidation potential of the substrate. Apart from this, electron transfer is often preceded by the formation of a charge-transfer complex between the substrate and the reagent.[30] We propose, that in solvents that do not allow the creation of an ionic pair, the formation of such a charge-transfer complex only leads to what is called "molecule assisted homolysis",[31] whereafter radical reactions follow. This we observed for the reaction of CH_3COOF with cyclohexene in CH_2Cl_2.[16] In polar solvents such as acetic acid which do allow this ionic pair formation, three possiblities exist. Firstly, the oxidation potential of the substrate is too high; the main reaction is hydrogen abstraction.[32] Secondly, the F^- ion in the formed radical-cation–fluoride complex and the resulting acetoxy radical immediately recombine with the radical cation leading to a "normal" addition product.[16] This concept can be regarded as an alternative for the tight ion pair mechanism.[22] Finally, the formed radical-cation–fluoride complex can undergo a second one-electron oxidation when a more stabilized cation can be formed. In the latter case the F atom seems to execute a real electrophilic substitution.

It is clear that this concept also fits with electrophilic behavior because in compounds containing polarized double bonds, a one-electron oxidation occurs at that carbon atom that carries the highest electron density.[30]

With these facts in mind, we suggest for F_2 and CH_3COOF a slight modification of the reaction sequence as proposed for CF_3OF[22] and which differs from the postulated reaction sequences of Cech et al.[13] and Shiue et al.[14] for the reaction of F_2 with uracil (Figure 3). We suggest the same reaction sequence for cytosine, whereby the product yields differ because of the instability of the intermediaries **8a** and **9a**.

A one-electron oxidation is carried out by F_2 or CH_3COOF affording the radical cation i, a F^- ion complexed with i and a F· or CH_3COO· radical (Figure 3). Consequently, F^- is incorporated while the F· or CH_3COO· radicals abstract—in a minor reaction—the hydrogen atom at C_5, resulting in the direct formation of some 7% of 5-fluorouracil (**2**) or 5-fluorocytosine (**7**) (path I, Figure 3). However, the main reaction of the F· or CH_3COO· radicals is the second one-electron oxidation at C_6, affording the α-stabilized cationic intermediary ii. Intermediary ii reacts with the nucleophilic solvents giving mainly **3a** or **3b** and **8a** or **8b**, respectively. In CH_3COOH/H_2O mixtures **3b** and **8b** are formed to a greater extent, H_2O being the better nucleophile.

In analogy with the differences in stability between the hydroxy adducts **8b**, **9b** and **3b**, **4b**, the acetoxy adducts **8a** and **9a** are less stable than **3a**, **4a** and undergo proton (H_5) abstraction (Figure 4) already in solution at room temperature. That cytosine itself acts as base could be demonstrated by its addition to **3a**, **4a** followed by evaporation: only 5-fluorouracil (**2**) resulted. About 12–15% 5-fluorocytosine (**7**) is thus formed through path II (Figure 3) via cytosine-catalyzed acetic acid elimination from **8a**, **9a** (Figure 4).

In contrast with **8a** and **9a**, **3a** and **4a** are stable in acetic acid solution in the presence of a weak base at room temperature. However, upon evaporation of the solvent, **3a** and **4a** give iii as intermediary (Figure 4), which can react with D_2O or CD_3COOD to give **3b**, **4b** and **3a**, **4a**, respectively, while in the presence of a base (NH_4OAc, KF, NaOAc, cytosine) iii undergoes proton (H_5) abstraction leading to 5-fluorouracil (**2**). The chemical behavior of iii follows that of acylimines: rearrangement to enamides in

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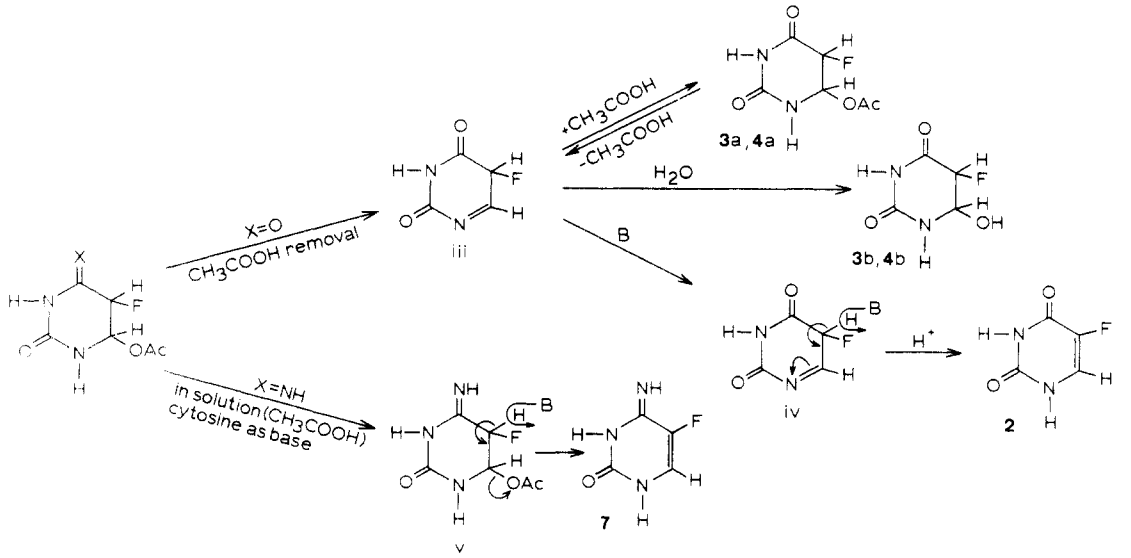

Figure 4. Chemical behavior of the 5F,6OAc adducts of uracil (**1**) and cytosine (**6**).

the presence of a base or formation of α-functionalized amino acids upon reaction with a nucleophile.[33] Only **3a** and **4a** can give iii upon evaporation because the acetoxy group in **3a**, **4a** is a better leaving group than the hydroxy group in **3b**, **4b**.

Compound **5a** is formed by the reaction of F_2 or CH_3COOF/CD_3COOF with 5-fluorouracil (**2**) produced during reaction, while **5a** can be converted into **5b** via an intermediary like iii. The reattack is most probably the reason why 5-fluorouracil is barely obtained in reactions using greater amounts of F_2.[9]

Another stable adduct in acetic acid is **10a**, due to the lack of H_5. It is formed by a reaction of CH_3COOF/CD_3COOF or F_2 with 5-fluorocytosine (**7**) produced during the reaction. As a consequence of the cytosine-catalyzed instability of **8a**, **9a**, 5-fluorocytosine (**7**) is formed in much greater quantities than 5-fluorouracil (**2**), and, therefore, the chance of the reattack resulting in **10a** is much higher. Finally, **10a** can be converted into **10b** through an intermediary like iii.

The Geometric Isomers 3a/4a, 3b/4b, and 8b/9b. The major acetoxy adduct (Figure 2) shows coupling constants which are in accord with the data found by Vine et al.,[9] who assumed it to be the cis isomer on the basis of the low $J_{5H,6H}$ coupling constant. The major hydroxy adduct **3b** shows coupling constants that are in accord with those found by Lozeron et al.[8] but for which the stereochemistry remained obscure. On chemical grounds it was assumed by them to be the trans isomer but was taken by Vine et al.[9] and Robins et al.[10] to be the cis isomer on the basis of the low $J_{5H,6H}$ coupling constant. However, from the $J_{5H,6H}$ coupling constant of the other acetoxy and hydroxy isomer (**4a** and **4b**) (Table I), the $J_{5H,6H}$ coupling constant appears to be a somewhat dubious basis to draw conclusions on the stereochemistry. A more reliable basis seems to be the $J_{5F,6H}$ coupling constant. This can be explained[34] by the fact that the phase shift of the Karplus relation for the vicinal H,H coupling, caused by electronegative substituents, is larger than the calculated substituent effects on the variation of $^3J_{FH}$. The $J_{5F,6H}$ values obtained for **3** and **4** can be compared with those found for **5a** and **5b**, products from the reaction of 5-fluorouracil (**2**) with CH_3COOF.[35]

For 1-methyl-5-fluoro-6-methoxy-5,6-dihydrouracil a $J_{5H,6H}$ and a $J_{5F,6H}$ coupling constant of 4.0 and 2.2 Hz was found, respectively,[10] whereby single crystal X-ray analysis established the cis stereochemistry of this adduct.[12] Due to the lack of the corresponding trans adduct it could only be expected that the relative vicinal coupling magnitudes would be reversed in the trans compound.[10] Extrapolating the solid-state conformation of this cis methoxy adduct to our adducts found in solution, **3a**, **3b** and **8b** are tentatively assigned to the cis isomers and **4a**, **4b** and **9b** to the trans isomers, although in case of the hydroxy adducts **4b** and **9b** the $J_{5H,6H}$ coupling magnitude is not reversed. This assignment is supported by the large difference in the chemical shifts of H_5 between **3a**, **4a**, **3b** and **4b**, **8b** and **9b** (0.51, 0.40, and 0.40 ppm, respectively). Such a difference in chemical shift was also reported[11] for *cis*- and *trans*-1-methyl-5,6-dihydroxy-5,6-dihydrouracil (0.51 ppm) and is compatible to the change of the local magnetic field of a pseudoaxial position of H_5 in the cis compound to a pseudoequatorial position of H_5 in the trans compound. The observed low $J_{5H,6H}$ and $J_{5F,6H}$ coupling constants are compatible with the conformations 3′ and 4′ and not with the "ring flipped" conformers 3″ and 4″ (Figure 5). The preference for 3′ and 4′ is due to the favorable anomeric affect of an axial substituent at C_6 with N_1.[11] Because of the torsional strength of the amide bond, it is expected that the dihedral angle between the C_6–N_1 and C_5–C_4 bond (a measure for the "ring puckering") is less than the 60° which is normally found in cyclic compounds. Using Karplus relations, corrected for substituent effects,[34,36] it can be calculated from the $J_{5H,6H}$ and the $J_{5F,6H}$ coupling constants that this dihedral angle lies between 48 and 55°. In the cis compound the calculated "ring-puckering" is smaller than in the corresponding trans derivative. This can be explained by the fact that torsion of the C_5–C_6 bond in 3′ leads to a more favorable gauche interaction between the fluorine atom and the substituent at C_6.

In 4′ the pseudoaxial F atom has compensated its loss of gauche interaction with the oxygen atom of the C_6 substitutent with an interaction with the carbonyl group at C_4. This position also appears to be a more or less stabilizing one, as Byrd et al.[37] observed that their native

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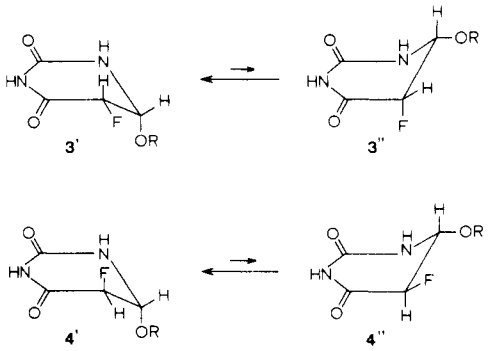

Figure 5.

5F-dUMP–enzyme complex, where the F atom was pseudoequatorial, underwent a conformational change upon denaturation to yield the F atom pseudoaxial.

In the chlorination, bromination, or iodination of pyrimidines, the exclusive trans addition was explained either by steric hindrance or by assuming a halonium-ion intermediary.[6] For fluorine the atomic radius is small, while the formation of a fluoronium atom has been proven to be highly questionable for this strongly electronegative element.[38] Therefore, bond formation of C_6 in intermediary ii (Figure 3) and iii (Figure 4) with solvent oxygen apparently proceeds with energetically favorable cisoid (gauche) stereochemistry[10] to produce mainly cis **3a**, **3b** and **8b**. Nevertheless, certain amounts of the corresponding trans compounds are formed. In this light it is surprising that fluorination of uracil with CF_3OF in CH_3OH gives the cis compound **3** (R = CH_3) exclusively.[10]

Conclusion

In this paper we have shown that the reaction of F_2 or CH_3COOF with uracil in acetic acid and water yields, among others, both geometric isomers of the 5F,6OAc or 5F,6OH adducts. On the basis of the observation that a part of the 5-fluoropyrimidines is directly formed and the fact that both F_2 and CH_3COOF led to the same "electrophilic substitution" products, which is rather unique, as an alternative of an electrophilic substitution a radical cation mechanism was suggested which, in this special case, for both F_2 and CH_3COOF leads to the same α-stabilized cationic intermediary ii. Furthermore, it was shown that the relative ease of formation of iii from **3a**, **4a** and the influence of the presence of a base, are most probably the origins of the conflicting reports of the stability of **3a**.[9,13] Finally, it was shown that cytosine follows the same reaction sequence, albeit leading to less stable addition products than uracil does.

Experimental Section

$[^{18}F]F_2$ was prepared by the $^{20}Ne(d\alpha)^{18}F$ reaction from ^{20}Ne containing 0.1% F_2 in a monel target.[39] $[^{18}F]CD_3COOF$ was prepared by bubbling $[^{8}F]F_2$ through 15 mL of CD_3COOD containing 0.36 mmol of ND_4OOCCD_3. Gaseous $[^{18}F]CH_3COOF$ was produced by passing $[^{18}F]F_2$ through a column of KOAc/HOAc.[17]

Thin-layer chromatography was performed on Merck precoated silica gel F-254 plates (thickness 0.3 mm). The organic phases of a 3:2:2 mixture (for cytosine) or a 4:1:2 mixture (for uracil) of ethyl acetate, *n*-propanol, and water (eluents A and B, respectively) were used as eluents. After development, the spots of uracil (**1**), **2**, cytosine (**6**), and **7** were visualized by UV light, and the chromatograms were wrapped in adhesive tape, cut into segments of 0.5 cm, and counted in a LKB compugamma counter. Reversed phase HPLC analysis of the products were performed on a 20-cm C18μ-bondapack column (eluent 0.1 M $NH_4H_2PO_4$, flow rate 0.5 mL/min). Peaks were detected by a radioactivity monitor and a UV detector (254 nm); fractions of 250 μL were collected and counted.

Separation of the ^{18}F-containing products was performed by column chromatography (20 cm) on silica gel (Merck 70-230 MESH; eluent A for cytosine; eluent B for uracil). Proton magnetic resonance spectra were measured on a Bruker WM-250 spectrometer. Chemical shifts are reported as δ values (ppm relative to tetramethylsilane); CD_3COOD was used as the solvent. Solvent removal was performed either by a rotary evaporator at 60 °C or by freeze-drying by using a Hg-diffusion pump. Yields are given as radiochemical yields based on $[^{18}F]F_2$. Therefore, the maximal theoretical yield is 50% for both $[^{18}F]F_2$ and $[^{18}F]CH_3COOF$.

Reaction of Fluorine and Acetyl Hypofluorite with Cytosine or Uracil. $[^{18}F]F_2$ (35 μmol) was bubbled through a solution of 8 mg (70 μmol) of cytosine or uracil in 15 mL of CD_3COOD or D_2O (conditions A and B). The same conditions were applied for the reaction with 30 μmol of gaseous $[^{18}F]CH_3COOF$.

From the 30 μmol of $[^{18}F]CD_3COOF$ prepared in 15 mL of CD_3COOD, 3 mL were added to 2 mg (about 20 μmol) of cytosine or uracil dissolved in 1 mL of CD_3COOD or in 1, 2, or 4 mL of D_2O, respectively (conditions C, D, E, and F).

Samples were taken from the deuterated solutions immediately after reaction (5 min) and analyzed by TLC and ^1H NMR. After removal of the CD_3COOD in vacuo, 2 mL of ultrapure water were added, and the samples were analyzed by reversed phase HPLC, TLC, and ^1H NMR (the last after evaporation of the H_2O and dissolution in CD_3COOD). For a separation of the products, the H_2O was removed in vacuo, and the residue was dissolved in 1.5 mL of eluents A or B. The radioactive peaks were collected after column chromatography, and samples were analyzed by TLC, reversed phase HPLC (after removal of the organic solvent and dissolution in H_2O), and ^1H NMR (after removal of the organic solvent and dissolution in CD_3COOD).

$[^{18}F]$-5-Fluorouracil (**2**) and $[^{18}F]$-5-fluorocytosine (**7**) were also identified by comparison of their ^1H NMR spectra and R_t and R_f values with those of authentic samples. The by products **5a** (**5b**) and **10a** (**10b**) were compared with the products obtained from the reaction of gaseous $[^{18}F]CH_3COOF$ with 5-fluorouracil and 5-fluorocytosine, respectively. The results are summarized in Tables I–IV.

Elimination and Exchange Experiments. The reaction mixtures obtained by bubbling $[^{18}F]F_2$ or gaseous $[^{18}F]CH_3COOF$ through the uracil/cytosine solutions were divided into several portions of 2 mL. One portion was used as a blank, to another 0.5 mL of D_2O was added, and to the others 1 mL of CD_3COOD solutions containing 70 μmol of NH_4OAc, NaOAc, KF, or cytosine was added. After 3 h, each solution was analyzed by TLC and ^1H NMR. The solvent was subsequently removed in vacuo, and either 2 mL of CD_3COOD were added and the resulting solutions analyzed by TLC and ^1H NMR or 2 mL of ultrapure water were added and the analysis was performed by TLC and reversed phase HPLC, followed by ^1H NMR analysis after removal of the water.

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Registry No. **1**, 66-22-8; **2**, 51-21-8; **3a**, 100814-55-9; **3b**, 93713-26-9; **4a**, 100814-58-2; **4b**, 93713-25-8; **5a**, 100814-61-7; **5b**, 55052-50-1; **6**, 71-30-7; **7**, 2022-85-7; **8a**, 100814-56-0; **8b**, 100814-57-1; **9a**, 100814-59-3; **9b**, 100814-60-6; **10a**, 100814-62-8; **10b**, 100814-63-9.

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