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Tautomerism of 5-Fluoro-4-hydroxy-2-methoxypyrimidine. Conditions for Stabilization of the Zwitterionic Tautomer

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Abstract—5-Fluoro-4-hydroxy-2-methoxypyrimidine exists in a solution as two oxo tautomers with the conjugated and isolated double bonds in the ring. The latter tautomer has a zwitterionic structure, and it dominates in water and trifluoroethanol. 5-Fluoro-4-hydroxy-2-methoxypyrimidine in acidic medium gives rise to an equilibrium mixture of two protonated forms at a ratio of about ~1 : 1. The zwitterionic structure of 4-hydroxypyrimidines is stabilized if the solvent is capable for specific solvation via hydrogen bonding.

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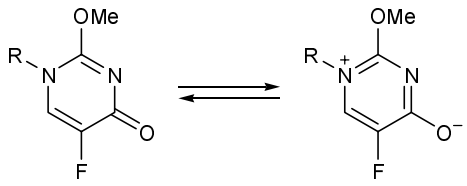
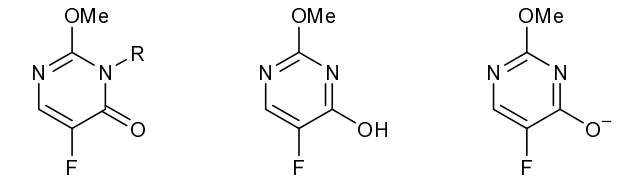
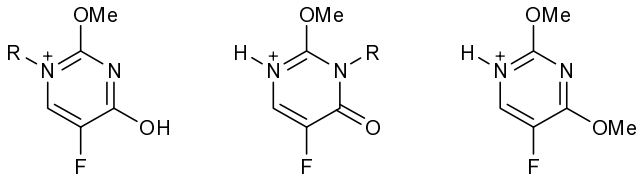
5-Fluoro-4-hydroxy-2-methoxypyrimidine is a compound interesting from the practical viewpoint; it is an intermediate product in the preparation of antitumor drug Ftorafur [1] and antimicrobial agent Mycocitin [2]. 5-Fluoro-4-hydroxy-2-methoxypyrimidine is potentially tautomeric, and it can exist in solution as a mixture of *para*- and *ortho*-quinoid forms **I** and **II** (R = H). The fraction of hydroxy tautomer **III** is likely to be small, as was found for other compounds of the 4-hydroxypyrimidine series [3]. Tautomers **I** and **II** may formally be regarded as cyclic amides (1*H* and 3*H*, respectively). Our interest in the amide–amide tautomerism of 5-fluoro-4-hydroxy-2-methoxypyrimidine originates from the results of our preceding study [3], where we showed that the *para*-quinoid tautomer of 4-hydroxypyrimidines has zwitterionic structure and presumed that just zwitterionic structure is responsible for the lower stability of this tautomer even in aqueous medium despite synergistic solvation effect. The presence of an amino or alkylsulfanyl group in the 2-position of the pyrimidine ring increases the fraction of the *para*-quinoid tautomer, presumably due to partial charge delocalization. On the other hand, introduction of the above groups reduces the gas-phase energy difference between the *ortho*- and *para*-quinoid forms (ΔE_{o-p}) by only 0.6–2 kcal/mol (the ΔE_{o-p} value for the analogs having no substituent in position *2* is 7–11.5 kcal/mol) [4]. According to the PM3 calculations performed by A.V. Moskvin, the difference in the energies of formation of the *ortho*- and *para*-quinoid tautomers of 5-fluoro-4-hydroxypyrimidine is equal to



Ia **Ib**



II **III** **IV**



V **VI** **VII**

R = H, Me.

7.6 kcal/mol, while introduction of a methoxy group into the molecule reduces this value by 0.5 kcal/mol.

Methoxy group is a good hydrogen bond acceptor and simultaneously a strong electron donor; therefore, it is expected to considerably increase the fraction of tautomer **I**, though its effect in an inert medium is comparable with those produced by amino and methylsulfanyl groups. The effect of protic solvents on the amide–amide equilibrium is difficult to predict, for the energy contribution of specific solvation due to hydrogen bonding with participation of the nitrogen and oxygen atoms may exceed the contributions of the above factors. On the other hand, there are systems capable of specifically solvating zwitterionic species but characterized by a lower dielectric constant than that of water; such systems could favor stabilization of the *para*-quinoid tautomer. It was interesting to verify our concepts using 5-fluoro-4-hydroxy-2-methoxypyrimidine as an example, for the conclusions drawn on this basis may be extended to the whole series of 4-hydroxypyrimidines. The state of the tautomeric equilibrium under study is weakly influenced by the presence or absence of a fluorine atom in the 5-position [3, 5].

The amide–amide equilibrium N^1–H $\rightleftharpoons$ N^3–H of 5-fluoro-4-hydroxy-2-methoxypyrimidine was studied by comparing their UV and ^{1}H and ^{13}C NMR spectra with those of the corresponding *N*- and *O*-methyl derivatives (Tables 1, 2). Table 3 contains the results of calculation of the tautomeric composition, depending on the solvent system and temperature; these data demonstrate a satisfactory agreement between the two methods. Table 4 lists the fractions of *para*-quinoid tautomers in equilibrium mixtures of 5-fluoro-4-hydroxypyrimidine derivatives with different substituents in the 2-position.

The *N*-methyl derivatives simulating amide tautomers **I** and **II** are characterized by essentially different UV and NMR spectra. The ^{13}C NMR spectra of vinylogous amide **I** (R = Me) are consistent with structure **Ib** (R = Me), at least in polar media. In the ^{13}C NMR spectrum of neutral compound **I** (R = Me) the chemical shifts of the *N*-methyl carbon atom and C^2 are very similar to those in the spectrum of its cation **V** (R = Me), and the chemical shifts of C^2 and C^6 coincide with those typical of aromatic cation **VII**. On the other hand, the chemical shift of C^4 in **I** (R = Me) fully coincides with $\delta(C^4)$ of ambident anion **IV** in which the main part of the negative charge is undoubtedly localized on the oxygen atom [6]. The chemical shifts of C^4 in cations **V** (R = Me) and **VII** (δ_C 165.7 ppm)

Table 1. UV spectra of 5-fluoro-4-hydroxy-2-methoxypyrimidine, its *N*-methyl derivatives, and 5-fluoro-2,4-dimethoxypyrimidine

Solvent[a]	λ_{max}, nm	$\varepsilon \times 10^{-3}$, l mol^{-1} cm^{-1}
5-Fluoro-4-hydroxy-2-methoxypyrimidine		
0.005 N hydrochloric acid	261	6.9
0.005 N hydrochloric acid[b]	262	6.3
0.1 N NaOH	270	6.9
4 M $H_2N(CH_2)_2COOH$, pH 3.2	259.5	7.3
1 M $H_2N(CH_2)_5COOH$, pH 4.0	260	7.0
MeOH	271	6.65
Dioxane	274	7.4
Dioxane–MeOH, 1:2	274	6.9
Dioxane–malonodinitrile, 1:1.9	273	5.4
DMSO	275	6.8
DMSO–*t*-BuOH, 1:1	275	6.8
DMSO–H_2O, 1:4	265.5	6.7
DMSO–H_2O, 1:1	271	6.65
DMSO–H_2O–NH_4ClO_4, 5.6:5.6:1	265.5	6.7
DMSO–H_2O– $Me_4N \cdot 0.5H_2SO_4$, 9.2:9.2:1	274	6.65
DMSO–H_2O–HCOOH, 5.1:5.1:1	272.5	6.7
DMSO–H_2O–AcOH, 4.9:4.9:1	273.5	6.7
DMSO–CF_3CH_2OH, 1:1	271	6.65
DMSO–CF_3CH_2OH, 1:3	264, 271 sh	6.85
MeCN	274	6.8
MeCN–CF_3CH_2OH, 1:1	263	6.8
MeCN–malonodinitrile, 3.8:1	274	5.4
MeCN–malonodinitrile, 1.9:1	271	5.2
CF_3CH_2OH	260	6.8
CCl_3CH_2OH	265	5.05
CF_3CH_2OH[c]	259, 226	4.6, 6.9
CF_3CH_2OH[d]	277, 233	5.5, 10.1
5-Fluoro-2-methoxy-3-methylpyrimidin-4(3*H*)-one		
H_2O, pH 6.2	274. 5	7.35
MeOH	275	7.4
Dioxane	274	7.1
Dioxane–MeOH, 1:2	275	7.4
Dioxane–malonodinitrile, 1:1.9	273.5	6.2
DMSO	276	7.1
DMSO–H_2O, 1:4	275	7.1
DMSO–H_2O, 1:1	276	7.0

Table 1. (Contd.)

Solvent[a]	λ_{max}, nm	$\varepsilon \times 10^{-3}$, l mol^{-1} cm^{-1}
DMSO–H_2O–NH_4ClO_4, 5.6:5.6:1	276	6.9
MeCN	274	7.1
MeCN–malonodinitrile, 3.8:1	275	6.3
MeCN–malonodinitrile, 1.9:1	280, 274	5.9, 6.1
CF_3CH_2OH	273.5	8.05
CCl_3CH_2OH	281.5, 277	6.7, 6.55
CF_3CH_2OH[e]	268.5, 226	3.9, 5.8
CF_3CH_2OH[f]	293–295, 240	8.9, 5.7
5-Fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one		
H_2O, pH 6.2	261, 226	8.9, 7.8
MeOH	260, 229	8.7, 7.2
Dioxane	258, 230	7.7, 8.1
Dioxane–MeOH, 1:2	259	8.8
Dioxane–malonodinitrile, 1:1.9	260	6.55
DMSO	262	7.5
DMSO–H_2O, 1:4	261	8.0
DMSO–H_2O, 1:1	261	8.2
DMSO–H_2O–NH_4ClO_4, 5.6:5.6:1	261	7.95
MeCN	258, 230	7.7, 8.1
MeCN–malonodinitrile, 3.8:1	260, 230	6.8, 6.4
MeCN–malonodinitrile, 1.9:1	260.5, 235	6.55, 6.1
CF_3CH_2OH	261, 223.5	8.9, 7.4
CCl_3CH_2OH	262	7.5
CF_3CH_2OH[g]	243	10.3
CF_3CH_2OH[h]	233.5	22.5
5-Fluoro-2,4-dimethoxypyrimidine		
H_2O, pH 6.2	269	6.5
MeOH	270	7.2
Dioxane	267	6.6
MeCN	269	6.1

[a] For mixed solvent systems, molar ratios are given.
[b] The spectrum was recorded at 85°C; otherwise, at room temperature.
[c] Data for 5-fluoro-4-hydroxypyrimidine.
[d] Data for 5-fluoro-4-hydroxy-2-methylsulfanylpyrimidine.
[e] Data for 5-fluoro-3-methylpyrimidin-4(3*H*)-one.
[f] Data for 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one.
[g] Data for 5-fluoro-1-methylpyrimidin-4(1*H*)-one.
[h] Data for 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one.

also approach $\delta(C^4)$ of **IV** (δ_C 167.3 ppm). The bond between C^4 and the oxygen atom in molecule **VII** can be only ordinary. Finally, the coupling constants $J(F^5–C^4)$ in the spectra of **I**, **V** (R = Me), and **VII** are similar (15.1 Hz), but they differ from $J(F^5–C^4)$ > 20 Hz which is observed for sructures with double-bonded C^4 and oxygen atoms (Table 2). We can conclude that a neutral molecule of vinylogous amide **I** (R = Me) includes both cationic and anionic fragments, i.e., it has zwitterionic structure **Ib** (R = Me). The contribution of dipolar structure to isomer **II** (R = Me) is small, presumably due to restricted area for electron circulation. The tautomeric composition was calculated using the chemical shift of C^4, taking into account that this parameter of 4-hydroxypyrimidines is most sensitive to the nature of the functional center (change of the latter in tautomers **Ib** and **II** is equivalent to change in hybridization [3]).

The positions of the long-wave absorption maxima in the electron spectra of *N*-methyl derivatives corresponding to tautomers **I** and **II** differ by 15 nm. If the absorption maximum is located within that interval, we can speak about solvent effect on the state of the tautomeric equilibrium. Thus, tautomer **II** predominates in acetonitrile, while trifluoroethanol favors tautomer **I**. The position of the absorption maximum in mixtures of the above solvents is linearly related to the mole fraction of trifluoroethanol (c_{TFE}):

$$\lambda_{max}\ (nm) = 272.85 - 15.69 c_{TFE}\ (mol\ \%);\ r = 0.96.$$

The fraction of the 1*H* tautomer (R_{1H}) was calculated by the formula

$$R_{1H} = (D - D_{3\text{-Me}})/(D_{1\text{-Me}} - D_{3\text{-Me}}),$$

where D, $D_{3\text{-Me}}$, and $D_{1\text{-Me}}$ are, respectively, the optical densities of solutions of a tautomeric compound and its 3- and 1-methyl derivatives at an analytical wavelength; the latter was selected in such a way that the D value for the binary tautomeric mixture be within the range between $D_{1\text{-Me}}$ and $D_{3\text{-Me}}$.

In the ^{13}C NMR spectra of 5-fluoro-4-hydroxy-2-methoxypyrimidine and 2-amino-5-fluoro-4-hydroxypyrimidine, the signals from C^2 and C^5 are narrow, while the C^4 and C^6 signals are broadened, regardless of the solvent nature. The broadened signals become narrow at elevated temperature (80°C) or on addition of an acid or base at room temperature (Table 2). The corresponding *O*- and *N*-methyl derivatives give narrow signals from all carbon atoms. Broadening of

Table 2. ^{1}H and ^{13}C NMR spectra of 2-substituted 5-fluoro-4-hydroxypyrimidines, their *N*-methyl derivatives, and 5-fluoro-2,4-dimethoxypyrimidine

Solvent	Signal	Chemical shifts δ, δ_C, ppm						Coupling constants *J*,[a] Hz		
		C^2	C^4	C^5	C^6 or 6-H	NH or NMe	OMe	F^5–C^4	F^5–C^6	F^5–6-H
5-Fluoro-4-hydroxy-2-methoxypyrimidine										
D_2O	H	–	–	–	7.80	–	3.95	–	–	3.0
	C	156.2	164.1[b]	146.0	131.8[b]	–	56.6	–[b]	–[b]	–
D_2O[c]	H	–	–	–	7.78	–	3.96	–	–	3.94
	C	155.9	163.1	146.0	131.9	–	56.5	21.1	30.2	–
CD_3OD	H	–	–	–	7.79	–	3.98	–	–	3.21
	C	156.2	161.0[b]	147.9	135.2[b]	–	56.2	–[b]	–[b]	–
DMSO-d_6	H	–	–	–	7.85	12.87	3.85	–	–	3.3
	C	154.2	156.9[b]	146.5	134.6[b]	–	55.2	20.0	–[b]	–
D_2O–DMSO-d_6, 1 : 1[d]	H	–	–	–	7.78	–	3.81	–	–	4.0
	C	155.1	158.6	146.9	134.5	–	56.1	21.0	19.0	–
NaOD–D_2O	H	–	–	–	7.70	–	3.79	–	–	2.64
	C	161.9	167.5	147.6	138.4	–	55.1	16.0	24.8	–
DCl–D_2O	H	–	–	–	8.18	–	4.22	–	–	4.0
	C	156.05	161.8	143.6	129.2	–	59.4	20.4	34.0	–
Dioxane-d_8	H	–	–	–	7.84	11.3[b]	4.09	–	–	–
	C	154.2	156.0	148.0	135.7	–	55.1	22.8	27.0	–
5-Fluoro-2-methoxy-3-methylpyrimidin-4(3*H*)-one										
D_2O	H	–	–	–	7.81	3.43	4.02	–	–	–
	C	154.2	159.1	146.3	135.8	29.5	57.0	24.9	22.8	–
D_2O[b]	H	–	–	–	7.81	3.42	4.03	–	–	–
	C	154.4	158.7	146.2	135.7	29.3	57.0	24.9	22.6	–
CD_3OD	H	–	–	–	7.79	3.46	4.06	–	–	2.00
	C	154.8	158.5	147.5	135.8	29.1	56.9	24.9	21.8	–
DMSO-d_6	C	–	–	–	7.90	3.31	3.95	–	–	1.98
	C	153.2	155.6	145.8	134.1	28.4	56.1	25.9	21.8	–
D_2O–DMSO-d_6, 1 : 1[d]	H	–	–	–	7.80	3.27	3.90	–	–	2.6
	C	154.0	156.9	146.3	135.2	29.3	57.0	25.0	11.0	–
DCl–D_2O	H	–	–	–	8.00	3.47	4.37	–	–	3.3
D_2SO_4–D_2O	H	–	–	–	7.97	3.51	4.26	–	–	2.6
	C	154.9	157.5	145.5	130.1	29.7	59.2	22.6	30.2	–
Dioxane-d_8	H	–	–	–	7.85	3.55	4.17	–	–	1.98
	C	153.8	156.1	147.0	133.7	28.1	55.8	26.4	21.8	–
5-Fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one										
D_2O	H	–	–	–	7.84	3.51	3.99	–	–	4.62
	C	156.15	167.3	144.7	131.7	38.4	57.2	14.5	35.3	–

Table 2. (Contd.)

Solvent	Signal	Chemical shifts δ, δ_C, ppm						Coupling constants *J*, [a] Hz		
		C^2	C^4	C^5	C^6 or 6-H	NH or NMe	OMe	F^5–C^4	F^5–C^6	F^5–6-H
D_2O[c]	H	–	–	–	7.78	3.51	4.01	–	–	5.28
	C	156.05	166.8	144.8	131.3	38.2	57.2	15.1	34.5	–
CD_3OD	H	–	–	–	7.92	3.54	4.06	–	–	5.28
	C	156.65	167.0	146.1	131.3	38.2	57.3	15.6	36.3	–
DMSO-d_6	H	–	–	–	8.05	3.38	3.87	–	–	5.97
	C	154.4	162.6	144.5	129.3	37.2	56.0	15.1	37.7	–
D_2O–DMSO-d_6, 1 : 1[d]	H	–	–	–	7.89	3.35	3.85	–	–	5.3
	C	155.3	164.4	145.0	130.5	38.1	57.0	15.8	35.8	–
DCl–D_2O	H	–	–	–	8.43	3.72	4.20	–	–	4.6
D_2SO_4–D_2O	H	–	–	–	8.27	3.74	4.19	–	–	4.6
	C	155.9	165.7	142.6	135.3	39.4	58.4	15.1	37.7	–
Dioxane-d_8	H	–	–	–	7.58	3.55	4.15	–	–	5.28
	C	[e]	[e]	[e]	127.5	36.2	55.9	[e]	36.8	–
5-Fluoro-2,4-dimethoxypyrimidine										
D_2O	H	–	–	–	8.11	–	4.03, 3.93[f]	–	–	
	C	160.6	161	143.6	143.1	–	56.0, 55.4[f]	12.5	21.8	–
CD_3OD	H	–	–	–	8.18	–	4.09, 3.98[f]	–	–	2.64
	C	161.4	161.2	143.9	143.9	–	56.0, 55.2[f]	11.4	20.8	–
DMSO-d_6	H	–	–	–	8.37	–	3.97, 3.86[f]	–	–	3.30
	C	159.9	159.4	142.6	143.5	–	55.0, 54.4[f]	12.5	21.0	–
DCl–D_2O	H	–	–	–	8.46	–	4.29, 4.23[f]	–	–	3.80
	C	156.2	165.0	141.1	132.2	–	58.5, 57.7[f]	15.1	37.7	–
Dioxane-d_8	H	–	–	–	8.34	–	4.20, 4.09[f]	–	–	2.64
	C	160.9	160.4	143.7	143.4	–	55.0, 54.3[f]	11.4	21.1	–
2-Amino-5-fluoro-4-hydroxypyrimidine										
DMSO-d_6	H	–	–	–	7.63	11.34	6.49[g]	–	–	4.08
	C	153.1	156.3[b]	143.2	137.5[b]	–	–	–[b]	–[b]	–
2-Butylamino-5-fluoro-3-methylpyrimidin-4(3*H*)-one										
DMSO-d_6	H	–	–	–	7.73	3.24	7.05[h]	–	–	2.40
	C	151.4	155.4	142.3	136.8	30.8	[i]	25.1	19.8	–

Table 2. (Contd.)

Solvent	Signal	Chemical shifts δ, δ_C, ppm						Coupling constants *J*, [a] Hz		
		C^2	C^4	C^5	C^6 or 6-H	NH or NMe	OMe	F^5–C^4	F^5–C^6	F^5–6-H
2-Butylamino-5-fluoro-1-methylpyrimidin-4(1*H*)-one										
DMSO-d_6	H	–	–	–	7.78	3.29	6.97	–	–	6.50
	C	152.1	162.6	142.7	128.6	37.8	[j]	15.0	35.9	–
5-Fluoro-2-chloro-4-hydroxypyrimidine										
DMSO-d_6	H	–	–	–	8.14	12.65[b]	–	–	–	–
	C	145.5	157.6	148.8	138.35	–	–	22.6	22.6	–
CD_3OD	C	146.1	159.2	151.1	138.25	–	–	22.0	22.6	–

[a] $^1J(C^5–F)$ = 232–257 Hz.
[b] Broadened signal.
[c] The spectrum was recorded at 80°C; otherwise, at room temperature.
[d] Molar ratio.
[e] The compound is poorly soluble.
[f] The lower value was assigned to the 4-OMe group.
[g] NH_2.
[h] NHBu.
[i] Bu: δ_C 13.8, 19.7, 28.0 ppm.

some signals in the ^{13}C NMR spectra of 4-hydroxypyrimidines having an electron-donor substituent in position *2* was discussed by us previously; it results from reduction of the rate of the tautomer exchange process (N^1–H ⇌ N^3–H) at room temperature [3]. It should be noted that all signals in the spectrum of 2-chloro-5-fluoro-4-hydroxypyrimidine are narrow (Table 2).

The presence of a methoxy group in the molecule of 5-fluoro-4-hydroxypyrimidine considerably increases the fraction of tautomer **I** in proton-donor solvents (Tables 3, 4). Rise in temperature reduces the fraction of **I**, presumably due to weaker specific solvation of zwitterionic structure **Ib** (R = H) via hydrogen bonding. Addition of 3-aminopropionic or 6-aminohexanoic acid to an aqueous solution of 5-fluoro-4-hydroxy-2-methoxypyrimidine slightly increases the fraction of tautomer **I**; probably, this is the result of action of two opposite factors: enhanced synergistic solvation of zwitterionic species by functional groups of the amino acid and reduction of the overall solvating power of water due to its destructurization by the dissolved amino acid. A similar pattern was observed with 5-fluoro-4-hydroxy-2-methylsulfanylpyrimidine.

In dimethyl sulfoxide, as well as in acetonitrile and dioxane, the fraction of *para*-quinoid tautomer **I** is small (~20%). Dimethyl sulfoxide is a strong hydrogen bond acceptor but is capable of forming a hydrogen

Table 3. Ratios of the the 1*H* and 3*H* tautomers of 5-fluoro-4-hydroxy-2-methoxypyrimidine in solutions (%), determined from the UV spectra[a]

Solvent[b]	1*H*, %	3*H*, %
D_2O	62 (62)	38 (38)
D_2O[c]	52 (54)	48 (46)
CD_3OD	28 (29)	72 (71)
DMSO-d_6	20 (19)	80 (81)
DMSO-d_6–D_2O, 1:1[d]	21 (25)	79 (75)
DMSO–H_2O–NH_4ClO_4, 5.6:5.6:1[d]	42	58
DMSO–H_2O, 1:4[d]	31	69
Dioxane	16	84
Dioxane–MeOH, 1:2[d]	17	83
Dioxane–malonodinitrile, 1:1.9[d]	28	72
MeCN	19	81
MeCN–malonodinitrile, 3.8:1[d]	28	72
MeCN–malonodinitrile, 1.9:1[d]	30	70
CF_3CH_2OH	74	26
CCl_3CH_2OH	46	54

[a] In parentheses are given the tautomer ratios calculated from the ^{13}C NMR spectra.
[b] The UV spectra were recorded in the corresponding nondeuterated solvents.
[c] At 80°C; otherwise, at room temperature.
[d] Molar ratio.

Table 4. Fractions (%) of the *para*-quinoid 1*H* tautomer of 2-substituted 5-fluoro-4-hydroxypyrimidines in solutions

2-Substituent	H_2O (ε = 78.5)	CF_3CH_2OH (ε = 26.5)	MeOH (ε = 32.6)	DMSO (ε = 49)
H	30 [3]	29	7 [3]	5 [3]
SMe	42 [3]	49	18 [3]	17 [3]
OMe	62	74	29	19
NH_2	–	–	–	13

bond only with the cationic fragment of zwitterion **Ib**, and it very weakly solvates anions. Acetonitrile is a stronger acid but weaker base than DMSO; the ionic product of acetonitrile (10^{-31}) differs only slightly from the corresponding parameter of DMSO (10^{-30}) [7]. Dioxane exhibits only basic properties.

Addition of an equimolar amount of water (as proton-donor component) to a solution of 5-fluoro-4-hydroxy-2-methoxypyrimidine in DMSO only slightly increases the fraction of tautomer **I**, for most water molecules are likely to be bound by DMSO molecules. The concentration of tautomer **I** increases to an appreciable extent only when the amount of water reaches 4 equiv. The presence of 2 equiv of acetic or formic acid in an equimolar mixture of DMSO with H_2O does not change the position of the UV absorption maximum, whereas addition of the same amount of ammonium perchlorate induces a considerable blue shift of that maximum (Table 1), which corresponds to a two-fold increase in the fraction of tautomer **I**. No such effect is observed on addition of tetramethylammonium perchlorate. Presumably, the synergistic effect in the stabilization of tautomer **I** by the mixed solvate DMSO–H_2O–NH_4^+ results from formation of hydrogen bonds with both cationic and anionic fragments of zwitterionic species **Ib** (R = H). Ammonium ion is a strong acid and efficient hydrogen bond donor.

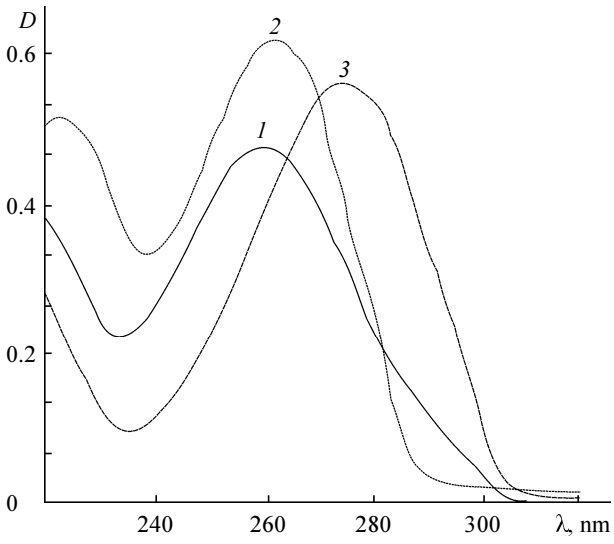
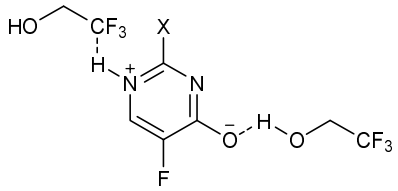


Fig. 1. UV spectra of solutions ($c = 7.33 \times 10^{-5}$ M) of (*1*) 5-fluoro-4-hydroxy-2-methoxypyrimidine, (*2*) 5-fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one, and (*3*) 5-fluoro-2-methoxy-3-methylpyrimidin-4(3*H*)-one in 2,2,2-trifluoroethanol.

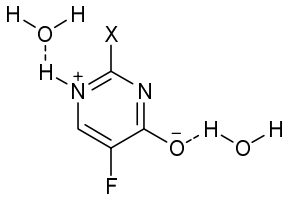
The state of the equilibrium **I** ⇄ **II** in an equimolar mixture of trifluoroethanol (TFE) with DMSO is approximately the same as in an analogous DMSO–H_2O mixture (Table 1). Being a stronger acid than water, TFE with DMSO forms strong complexes. In carbon tetrachloride, such complexes have a composition of 1:1 [8]. The equilibrium **I** ⇄ **II** sharply shifts to the left when DMSO is replaced by acetonitrile which binds TFE molecules to a lesser extent (the chemical shifts of the hydroxy proton in the ^{1}H NMR spectra of TFE in DMSO and acetonitrile are δ 7.96 and 5.45 ppm, respectively) [9]. The fraction of *para*-quinoid tautomer **I** in pure TFE is larger than in water, though the dielectric constant of TFE is lower by a factor of 3 than that of water (Table 4, Fig. 1). We also determined the concentration of the *para*-quinoid tautomers of two other compounds of the 5-fluoro-4-hydroxypyrimidine series. The results are presented in Fig. 2 and Table 4. It is seen that TFE approaches water in its ability to stabilize zwitterionic tautomers and that it sharply differs from methanol. Trifluoroethanol and water occupy the same place in the series corresponding to the strength of hydrogen bond formed with a carbonyl group, which is determined from the C=O stretching vibration frequencies in the IR spectra of aliphatic carbonyl compounds; these solvents are much superior to methanol but rank after 30% perchloric acid [10]. Trifluoroethanol is more viscous than ethanol (1.77 and 1.1 sP, respectively), which suggests its structurization in the liquid state. The IR spectra indicate self-association of TFE via hydrogen bonding with no difference between the O–H···O and O–H···F hydrogen bonds [11].

We believe that *para*-quinoid tautomer **I** is stabilized in TFE, as well as in water, due to synergistic effect of specific solvation via hydrogen bonding with dipolar molecules of the solvent. Presumably, the fluorine atoms in TFE are involved in formation of solvates like **A**. This follows from the facts that the fraction of tautomer **I** in trichloroethanol is considerably smaller and that the UV spectrum of tautomeric mixture strongly differs from the spectra in TFE and water (Tables 1, 3). Trichloroethanol and trifluoro-

ethanol are characterized by similar acidities (pK_a 12.2 and 12.4, respectively) [12], but chlorine atom is a much weaker hydrogen bond acceptor [13].



A



B

X = H, SMe, OMe.

Judging by the pK_a value (11.2 [14]), malonodinitrile approaches TFE in proton-donor ability, but this compound possesses no pronounced acceptor properties, and the fraction of tautomer **I** in solutions containing malonodinitrile* is almost the same as in methanol (Table 3). Presumably, the X group participates in stabilization of the *para*-quinoid tautomer via delocalization of the positive charge and formation of an additional hydrogen bond with the solvent, thus increasing the lifetime of solvates like **A** and **B** (Table 4).

Both 5-fluoro-4-hydroxypyrimidine and its *N*-methyl derivatives in acid medium give rise to cations of the same type by taking up proton at the nitrogen atom. This follows from the similarity of their UV and ^{13}C NMR spectra (in contrast to the spectra of the corresponding neutral species) [3]. An analogous pattern was observed previously for their analogs having no fluorine atom [15]. Contrastingly, 5-fluoro-4-hydroxy-2-methoxypyrimidine and its *N*-methyl derivatives **I** and **II** (R = Me) are characterized by different UV spectra in both acid and neutral media (Tables 1, 5; Fig. 3). As the acid concentration rises, the absorption maxima of the *N*-methyl derivatives simulating tautomers **I** and **II** shift in opposite directions, while the absorption maximum of 5-fluoro-4-hydroxy-2-methoxypyrimidine (which is a mixture of tautomers **I** and **II** in neutral medium) almost does not change its position. The data in Table 2 show that signals in the ^{13}C NMR spectra of both cationic species and neutral forms **I** and **II** (R = Me) differ appreciably. The maximal difference is observed for C^4 ($\Delta\delta_C$ = 8.2 ppm) and N–Me ($\Delta\delta_C$ = 10 ppm); the former value indicates

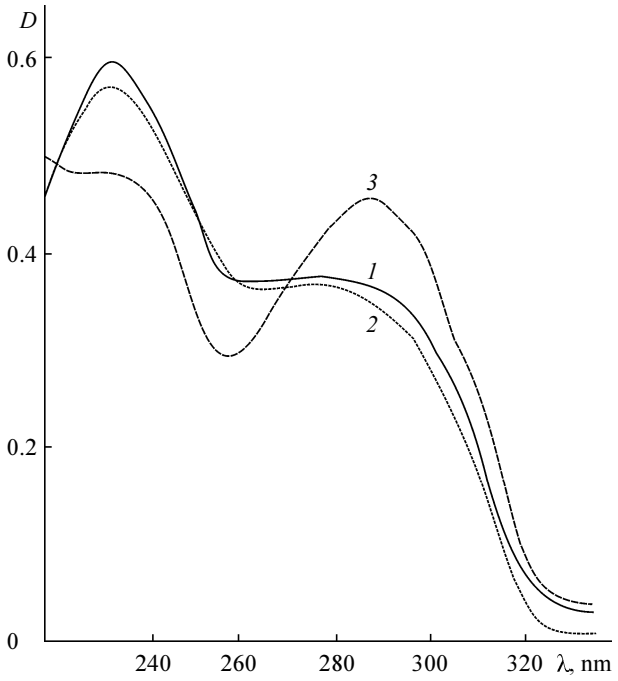


Fig. 2. UV spectra of solutions ($c = 4.75 \times 10^{-5}$ M) of 5-fluoro-4-hydroxy-2-methylsulfanylpyrimidine in (*1*) 0.005 N hydrochloric acid, (*2*) 2,2,2-trifluoroethanol, and (*3*) ethanol.

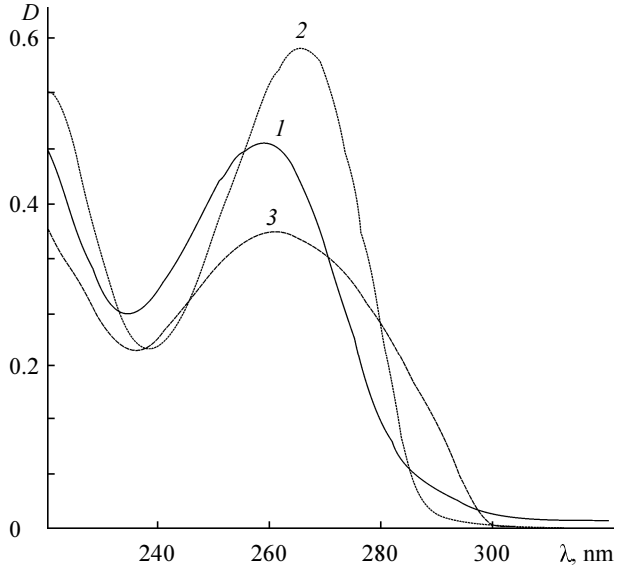


Fig. 3. UV spectra of solutions ($c = 7.33 \times 10^{-5}$ M) of (*1*) 5-fluoro-4-hydroxy-2-methoxypyrimidine, (*2*) 5-fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one, and (*3*) 5-fluoro-2-methoxy-3-methylpyrimidin-4(3*H*)-one in 6.25 N sulfuric acid, recorded in 1 min after dissolution.

* Insofar as malonodinitrile is a solid, it was used as solutions in acetonitrile and dioxane.

Table 5. Absorption maxima (λ, nm) in the UV spectra of 5-fluoro-4-hydroxy-2-methoxypyrimidine and its 1-methyl and 3-methyl derivatives in sulfuric acid

$[H_2SO_4]$, N	N–H	1-Me	3-Me
H_2O	261[a]	261	274.5
0.1	261	261	274.5
1	261	262	273.5
2	261	262	273
3	261	264	273
4	261	265	272
5	260	265	270
6.25	260	266	263
7.5	260	267	256
10.0	259	268	251.5, 222
12.7	257	269	251.5, 223

[a] In 0.005 N hydrochloric acid.

variation in the electron environment of the functional center. On the other hand, protonation does not change the chemical shift of the N–Me carbon atom in **II** (R = Me) but leads to deshielding of the methoxy carbon atom; protonation of **I** (R = Me) induces equally weak deshielding of carbon nuclei in both NMe and OMe groups (Table 2). The ^{13}C NMR spectrum of the cation derived from **I** (R = Me) resembles the spectrum of cation **VII**, and the positions of the C^4 and 2-OMe signals are similar. It should be emphasized that structure **VII** is nearly aromatic. The chemical shift of C^4 and the coupling constants $J(F^5–C^6)$, $J(F^5–C^4)$, and $J(F^5–H^6)$ in the spectrum of tautomeric 5-fluoro-4-hydroxy-2-methoxypyrimidine occupy an intermediate place between the corresponding parameters of cations **V** and **VI** (R = Me). Thus, the data of UV and NMR spectroscopy lead us to conclude that 5-fluoro-4-hydroxy-2-methoxypyrimidine in acid medium exists as a mixture of cations **V** and **VI** (R = H) formed by proton addition at the oxygen atom of tautomer **I** (R = H) and N^1 atom of tautomer **II** (R = H). Dynamic equilibrium between cations **V** and **VI** may be regarded as prototropic tautomerism involving interconversion of the corresponding neutral species. The fraction of cation **V** (R = H) in the binary mixture, calculated from three NMR parameters [chemical shift of C^4 and coupling constants $J(F^5–C^4)$ and $J(F^5–H^6)$] is 52±2%.

In acid medium at room temperature, the compounds under study undergo demethylation at different rates to give the corresponding 5-fluorouracils. The ^1H NMR spectrum of 2,4-dimethoxy-5-fluoropyrimidinium cation (**VII**) in 15% aqueous DCl does not change during 24 h; cation **V** (R = Me) gives rise to 36% of 5-fluoro-1-methyluracil in 40 min [δ, ppm: 7.86 d (6-H), 3.33 s (1-Me)]; cation **VI** (R = Me) is converted into 42% of 5-fluoro-3-methyluracil in 10 min [δ, ppm: 7.67 d (6-H), 3.24 s (3-Me)]; and 36% of 5-fluorouracil [δ 7.70 ppm, d (6-H)] is formed in 30 min from 5-fluoro-4-hydroxy-2-methoxypyrimidine under the same conditions. Therefore, these cations can be arranged into the following series according to their stability under acidic conditions:

VII >> **V** (R = Me) ≥ **V** ⇌ **VI** (R = H) > **VI** (R = Me).

This series may be rationalized in terms of the different degrees of aromaticity of the pyrimidine ring in the cations [5, 16]. The rate of hydrolysis is related to the energy of dearomatization, which is necessary for the transformation of the ground state into transition state, the latter being nonaromatic [16]. Hydrolysis of the methoxy group in 2-methoxypyrimidine possessing a nearly aromatic pyrimidine ring requires heating in a boiling acid [17]. Among the examined species, cation **VII** is characterized by the greatest degree of aromaticity. Structure **V** (R = Me) is close to **VII** but differs considerably from **VI** (R = Me). Moreover, according to the ^{13}C NMR data, the carbon atom in the methoxy group of **VI** (R = Me) is deshielded to a greater extent than the corresponding carbon atom in cation **V** (R = Me). Elimination of the methoxy group in hydrochloric acid occurs more readily than in sulfuric acid, the acidities of the medium being equal. Apart from the difference in the nucleophile nature, the reason is that in the first case the reaction releases volatile methyl chloride (identified by ^1H NMR spectroscopy, δ 3.06 ppm [18]), while in the second case, methanol.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer operating at 300.13 and 75.47 MHz, respectively. While recording ^{13}C NMR spectra from dilute solutions, the number of scans reached 6000–7000. Samples were prepared at a concentration of 0.1–0.25 M (5-mm ampules). The UV spectra were measured on Beckman DU-650, SF-8, and SF-26 spectrophotometers.

Nondeuterated solvents were purified and distilled prior to use. The synthesis and properties of 5-fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one, 5-fluoro-3-

methyl-2-methoxypyrimidin-4(3*H*)-one, 2-butylamino-5-fluoro-1-methylpyrimidin-4(1*H*)-one, 2-butylamino-5-fluoro-3-methylpyrimidin-4(3*H*)-one, 5-fluoro-4-hydroxypyrimidine, and 5-fluoro-4-hydroxy-2-methylsulfanylpyrimidine were described in [3, 19].

5-Fluoro-4-hydroxy-2-methoxypyrimidine. A mixture of 5.6 g (0.035 mol) of 5-fluoro-2,4-dimethoxypyrimidine [20] in 38 ml of ethanol and 56 ml of a 2 N solution of potassium hydroxide was heated for 10 h at 95–100°C (until the initial pyrimidine disappeared according to the TLC data). The mixture was evaporated under reduced pressure to a volume of 60 ml, and hydrochloric acid was added on cooling to pH 4–5. The mixture was cooled to 0°C, and the precipitate was filtered off, washed with ice water, and dried. Yield 3.74 g (74%), colorless crystals, mp 205–206°C (from EtOH) [21]. Found, %: C 41.9; H 3.5; F 13.3; N 19.4. $C_5H_5FN_2O_2$. Calculated, %: C 41.7; H 3.5; F 13.2; N 19.4.

2-Amino-5-fluoro-4-hydroxypyrimidine was synthesized by a modified procedure [22]. Guanidine hydrochloride, 15 g (0.15 mol), was added to a solution prepared from 2.5 g of metallic sodium and 150 ml of anhydrous ethanol. The mixture was stirred for 15 min at room temperature, and the precipitate of sodium chloride was filtered off. 5-Fluoro-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione [23], 2.4 g (0.015 mol), was added to the filtrate, and the mixture was heated for 6 h at the boiling point on stirring under argon (until the initial pyrimidine disappeared according to the TLC data). Carbon dioxide was passed through the mixture, the solution was evaporated by half, and the precipitate of guanidinium carbonate was filtered off. The filtrate was evaporated under reduced pressure, the residue was dissolved in a minimal amount of water, and the solution was passed through a column charged with KU-2 cation exchanger. The column was eluted with water, and fractions absorbing in the UV region were collected and evaporated under reduced pressure. According to the TLC data, the product contained 1,3-dimethyluracil as an impurity; it was separated by column chromatography on silica gel 60 using methylene chloride–methanol (8:1) as eluent. Fractions containing the target product were combined and evaporated, and the residue was recrystallized twice from water. Yield 245 mg (13%), colorless crystals, mp 273–275°C; published data [24]: mp 271–274°C. Found, %: C 37.2; H 3.1; F 14.6; N 32.6. $C_4H_4FN_3O$. Calculated, %: C 37.2; H 3.1; F 14.7; N 32.6.

2-Chloro-5-fluoro-4-hydroxypyrimidine was synthesized by alkaline hydrolysis of 2,4-dichloro-5-fluoropyrimidine [25]. Yield 79%, mp 176–177°C (from anhydrous ethanol) [25].

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