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Effect of the microhydration on the tautomerism in the anticarcinogenic drug 5-fluorouracil and relationships with other 5-haloderivatives

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HIGHLIGHTS

- The six tautomers of 5-FU were determined and optimized at different levels.
- The first hydration shell 5-FU-$(H_2O)_{10}$ was calculated in the five most stable tautomers.
- The hydration causes a reordering of the stability order of the tautomers.
- The CP corrected interaction and formation energies were calculated.

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ABSTRACT

The 5-fluorouracil (in short 5-FU) mutagenicity was investigated in the isolated state and in the hydrated form through an exhaustive quantum-chemical analysis. The most optimum tautomers of 5-FU were optimized and analyzed. Six of them were related to those of uracils molecule, with the same stability order. The effect of the halogen substitution in position 5 on the uracil ring in the stability of the different tautomers was analyzed. Solvent effects were considered using a variable number (1–10) of explicit water molecules surrounding 5-FU in order to simulate the first hydration shell. More than 100 cluster structures with water were analyzed. A comparative analysis in the different tautomers of the hydration effect on the molecular structure and energetics was carried out. For cases where literature data are available, the computed values were in good agreement with previous experimental and theoretical studies. Depending on the nature of the tautomers, cyclic, distributed, or clustered structures were formed. The deformation and interaction counterpoise (CP)-corrected energies between 5-FU and water molecules were determined. The maximum interaction was found in the *enol* form T2. The microhydrated environment stabilized remarkably the *enol* forms T3 and T5 (present in the corresponding nucleoside) more than the canonical *keto* T1, although this one continues being the most stable. Several relationships with 5-XU derivatives (X = F, Cl, Br, I) between the relative energy of tautomer T2 and the geometric parameters/atomic charges were underlined.

1. Introduction

Data of the World Health Organization show that cancer is now among the three main causes of death in the world. Lung cancer accounts for about 13% of all new cancers and around 28% of all cancer deaths. Current treatment options include surgery, radiation therapy, and chemotherapy alone or in combination. One important possible treatment uses 5-fluorouracil (5-FU), which has a long history of use as a chemotherepatic agent [1]. It affects the synthesis and repair of DNA and RNA processing in Cancer Cells [2], and effectively blocks the replication of DNA viruses. It is also used as antibacterial and antiviral drug [3,4]. For targeted delivery of 5-FU, a controlled release of 5-FU can effectively inhibit tumor growth and metastases [5,6]. Despite its side effects, clinical studies on patients have shown that 5-FU is of some benefit as a chemotherapeutic drug [7]. This has increased the interest for more experimental and theoretical investigations on 5-FU. For all above, the present research undertakes the study of this anticancer drug.

The geometrical parameters of 5-FU have been discussed many times both experimentally and theoretically [8–11]. Also from the spectroscopy point of view, its vibrational spectra have been analyzed recently by us [12,13] and other authors [11,14–18], especially by Raman spectroscopy [15,19–24]. In these spectra the frequency assignment was supported by DFT computations and accurate scaling procedures [25]. Although many studies have been carried out on 5-FU, however, its mutagenicity and the hydration influence on it has not been reported yet.

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The existence of tautomeric equilibrium in nucleobases under physiological conditions has not only biomedical interest, but also opens interesting biotechnological applications. A large amount of work has been performed using both theoretical [10,26–30] and experimental approaches [31,32]. Much of the interest is due to the fact that tautomers induce alterations in the normal base pairing, leading to the possibility of spontaneous mutations in the DNA or RNA helices. Tautomerism in nucleic acid bases and their derivatives has a role in mutagenesis of DNA [33]. The process is intimately connected with the energetics of the chemical bonds. The occurrence of the rare tautomeric forms might lead to a point mutation developing during DNA replications. When incorporated into double-helical DNA, halogenated bases produce specific mutations that appear to arise from their occasional mis-pairing with guanine during genetic replication. Similarly, 5-FU residues in messenger RNAs produce coding errors, apparently by mis-pairing with guanine during translation processes. Also the biological functions of nucleic acids are dependent on their interactions with the surrounding water. Therefore, the aim of this study is to report the hydration effect of the tautomerism of this medicinally important anticancer agent, using the MP2 and B3LYP quantum chemical methods.

5-FU as analog of uracil, may exist in various tautomeric forms differing from each other by the position of the proton which may be bounded to either ring nitrogen atoms or oxygen atoms. It is well known that the heterocyclic tautomerism depends on the environment [30]. Examination of the experimental data strongly suggests that the dioxo-tautomers of uracil and 5-FU are the only stable ones in the solid state. From the biological point of view, the tautomerism of purine and pyrimidine bases is better understood if the calculations are carried out in solution. Thus, the aim of this work was to investigate this tautomerism in 5-FU under hydration conditions and to estimate the substituent effect on the tautomerization process. We have previously calculated the effect of the water molecules on this process in uracil [34a] and 5-bromouracil [27] molecules as well as we have reported the results in thymidine [34b] obtained in the same fashion. Other authors have investigated the effect of a microhydrated environment on the tautomerism of several nucleic acid bases, using only one or two water molecules explicitly [30,32,35,36], 10–15 water molecules [37], or PCM [38]. However, many questions about the hydration effect on the tautomerism have not been treated yet. The present paper tries to answer them, and for this purpose the tautomerism of uracil and 5-FU is studied with 10 explicit water molecules for the first time. We restrict this discussion to tautomerization and hydration energies only. Application of the B3LYP method to the tautomeric forms in water solution might provide useful information about its significance as a mechanism of mutation in nucleic acids.

Table 1
Calculated gas-phase relative energies (kcal/mol) of uracil and 5-FU tautomers.

Method	ΔE + ZPE							ΔG						
	T1	T2	T3	T4	T5	T6	T9	T1	T2	T3	T4	T5	T6	T9
Uracil														
B3LYP/6-31+G** [10]	0[a]	11.09	11.95	12.78	19.55	21.39		0	11.2	12.02	13.02	19.28	20.89	–
B3LYP/6-311++G(3df,pd)	0[b]	11.12	11.53	12.89	18.89	20.34	–	0[l]	11.25	11.61	13.12	18.86	20.33	–
B3LYP/DGDZVP	0[c]	11.68	12.76	14.47	20.12	21.63	–	0[m]	11.83	12.87	14.74	20.12	21.63	–
MP2/6-31G**	0[d]	10.88	12.33	11.42	19.22	21.59	–	0[n]	11.06	12.46	11.73	19.2	21.62	–
MP2/6-31+G** [10]	0[e]	10.36	11.62	10.42	18.73	21.69		0	10.47	11.7	10.66	18.46	21.19	–
CCSD/6-31G**, ref. [68]	0	11.19	12.88	12.39	19.62	22.6	–							
Experimental, ref. [69]	0			19 ± 6	22 ±1		–							
5-FU														
B3LYP/6-31+G** [10]	0[f]	9.18	12.6	14.28	17.09	20.35		0	9.39	12.6	14.35	16.91	19.8	
B3LYP/6-311++G(3df,pd)	0[g]	9.21	12.27	11.59[k]	16.41	19.72	100.3	0[o]	9.36	12.33	11.84	16.43	19.69	98.84
B3LYP/DGDZVP	0[h]	9.83	13.46	13.2	17.76	20.78	102.7	0[p]	10.01	13.55	13.48	17.79	20.78	101.5
MP2/6-31G**	0[i]	9.08	13.21	10.43	17.05	21.31	105.7	0[q]	9.29	13.33	10.76	17.08	21.33	105.1
MP2/6-31+G** [10]	0[j]	8.31	12.48	11.83	16.43	20.88		0	8.52	12.48	11.9	16.25	20.33	
5-ClU														
B3LYP/6-311++G(3df,pd)	0	9.63	12	11,76	17.16	17,86	94.81	0	9.77	12.06	12.01	17.16	17.87	94.35
B3LYP/DGDZVP	0	10.13	13.14	13.24	18.49	19.28	101.7	0	10.29	13.23	13.52	18.5	19.3	101.2
5-BrU														
B3LYP/6-311++G(3df,pd)	0	9.72	11.92	11.79	17.24	17.51	92.72	0	9.85	11.99	12.03	17.24	17.53	92.22
B3LYP/DGDZVP	0	10.24	13.06	13.29	18.57	18.71	95.80	0	10.4	13.15	13.57	18.57	18.74	95.32
MP2/6-31G**	0	9.61	13.08	10.85	17.71	18.66	99.95	0	9.79	13.19	11.16	17.71	18.71	99.61
5-IU														
B3LYP/DGDZVP	0	10.46	13.09	13.57	18.74	18.82	90.04	0	10.62	13.19	13.84	18.74	18.86	89.54

[§] AU = 627.5095 kcal/mol.
[a] Total energy (+ZPE) −414.847362 AU (atomic units)[§].
[b] −414.888816 AU.
[c] −414.790386 AU.
[d] −413.578145 AU.
[e] −413.688525 AU.
[f] −514.073225 AU.
[g] −514.157999 AU.
[h] −514.045618 AU.
[i] −512.583646 AU.
[j] −512.692759 AU.
[k] In tautomer T4b is 13.86 kcal/mol.
[l] −414.919244 AU.
[m] −414.820894 AU.
[n] −512.615586 AU.
[o] −514.189730 AU.
[p] −514.077457 AU.
[q] −512.615586 AU.