A semi-empirical study on structures of 5-substituted uracils

Ali Jameel Hameed

Department of Chemistry, College of Science, University of Basrah, Basrah, Iraq

Abstract

Semi-empirical calculations were carried out to study the structural and electronic properties of uracil and certain of its 5-substituted derivatives which include CF_3, NO_2 , F, Cl, Br,CH_3 and OCH_3. The optimized structures and electronic properties of the molecules have been investigated theoretically by AM1and PM3 semi-empirical methods. The Mulliken charges, total energies, heats of formation, position of HOMO and LUMO and the electrostatic potential of the molecules are obtained.

Keywords : 5-substituted uracils; semi-empirical AM1and PM3 methods.

Introduction

Uracil and certain of its 5-substituted derivatives have been the focus of enormous interest due to its involvement in a number of biochemically significant roles (i.e., composition of RNA and DNA) in all living systems [1-3] .

The 5-substituted uracils and their nucleoside and nucleotide counterparts function either as substrates, products or inhibitors of certain enzymes which catalyze the synthesis degradation or interconversion of pyrimidine compounds [4] . Certain naturally occurring uracil derivatives known to participate in intracellular mechanisms regulating pyrimidinine metabolism , while a number of synthetic 5-substituted uracils and nucleotide analogues have found use as chemotherapeutic, antiviral and antiherpes agents [5-6] .Some of physical and chemical properties of 5-substituted uracils have been investigated theoretically. The values of PKa were calculated for these compound [7]. The effect of hydrogen bonding on the acidity of C5- and C6-substituted uracils derivatives were investigated theoretically too [8].In this study, varying substituents at the 5-position of uracils ring were selected to show the effect of such structural change on the electronic properties of the molecules. The structural and electronic properties of 5-substituted uracils were investigated theoretically by performing semi-empirical molecular orbital calculations at the levels of AM1 and PM3 of the theory.

1. *Method of calculation*

All semi-empirical calculations were performed using the hyperchem modeling program version 6.0 [9] running on a windows XP workstation in Pentium IV PC . The 5-substituted uracils of this investigation were geometry optimized considering the semi-empirical molecular orbital theory at levels of Austin Model 1 (AM1) [10]and Parametric Method (PM3) [11] within the restricted Hartree-Fock (RHF) [12] formalism . The conjugate gradient (Polak-Ribiere) algorithm [13] was employed with the termination condition being an rms of less than 0.001 kcal mol^{-1}.

2. *Results and discussion*

The AM1 and PM3 geometry optimization yields planar uracil rings .Table 1 lists selected structural parameters for the molecules studied predicted by AM1 method. The values of bond lengths and angles predicted by AM1 and PM3 methods are very similar, so for the sake of clarity only the AM1 results are reported here. As shown in Table1, there are slight changes in the bond lengths and angles of 5-substituted molecules compared to the unsubstituted uracil molecule.Mulliken charges for the carbon, nitrogen and oxygen atoms were calculated for the optimized structures by semi-empirical molecular theory at levels of AM1 and PM3 calculations. The results are shown in Table 2.It can be seen from these Table

Table 1. Selected bond lengths and angles obtained from AM1 calculation for 5-substituted uracils
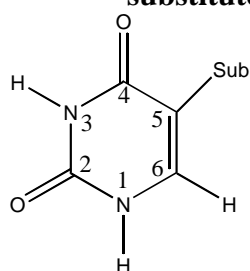
Sub.	H	CF3	NO$_2$	F	Cl	Br	CH$_3$	OCH$_3$
Bond lengths(Å)								
N1-C2	1.415	1.423	1.427	1.412	1.415	1.417	1.413	1.407
C2-N3	1.402	1.398	1.396	1.403	1.401	1.399	1.402	1.405
N3-C4	1.409	1.411	1.412	1.404	1.409	1.410	1.408	1.404
C4-C5	1.469	1.470	1.478	1.487	1.477	1.476	1.477	1.485
C5-C-6	1.359	1.369	1.382	1.372	1.367	1.368	1.363	1.364
C2=O	1.249	1.246	1.245	1.248	1.248	1.248	1.249	1.250
C4=O	1.242	1.238	1.235	1.238	1.239	1.239	1.242	1.238
C6-H	1.106	1.110	1.114	1.106	1.107	1.109	1.106	1.103
N1-H	0.994	0.996	0.998	0.995	0.995	0.995	0.994	0.993
N3-H	0.997	0.999	1.000	0.998	0.998	0.998	0.997	0.998
Bond angles(°)								
N1-C2-N3	118.2	117.9	117.8	118.2	118.0	117.8	118.1	118.3
C2-N3-C4	122.6	123.3	123.7	123.3	123.3	123.4	122.8	123.4
N3-C4-C5	116.3	115.7	115.1	115.5	115.6	116.0	116.5	115.1
C4-C5-C6	120.4	120.6	120.8	120.7	120.5	119.7	119.7	121.3
C5-C6-N1	121.8	121.8	121.3	121.1	121.6	122.2	122.1	120.8
C6-N1-C2	120.7	120.8	121.3	121.3	121.0	120.9	120.9	121.2

Table 2 . Mulliken atomic charges(in units of electron charge) of 5-substituted uracils by AM1 and PM3 calculations

Sub.	Method	C-2	C-4	C-5	C-6	N-1	N-3	O-2	O-4
CF_3	AM1	0.395	0.375	-0.353	0.121	-0.304	-0.362	-0.339	-0.296
	PM3	0.207	0.329	-0.379	0.012	0.116	-0.007	-0.364	-0.321
NO_2	AM1	0.394	0.373	-0.331	0.141	-0.296	-0.364	-0.328	-0.268
	PM3	0.205	0.333	-0.610	0.054	0.131	-0.012	-0.354	-0.296
F	AM1	0.394	0.342	-0.075	-0.002	-0.306	-0.361	-0.351	-0.301
	PM3	0.204	0.289	-0.096	-0.115	0.110	-0.004	-0.378	-0.323
Cl	AM1	0.394	0.362	-0.245	0.049	-0.310	-0.363	-0.353	-0.306
	PM3	0.206	0.303	-0.321	-0.078	0.107	-0.004	-0.382	-0.336
Br	AM1	0.394	0.368	-0.354	0.079	-0.310	-0.363	-0.351	-0.306
	PM3	0.208	0.319	-0.328	-0.038	0.100	-0.010	-0.380	-0.327
H	AM1	0.397	0.353	-0.300	0.048	-0.319	-0.365	-0.361	-0.323
	PM3	0.208	0.298	-0.277	-0.065	0.090	-0.011	-0.387	-0.352
CH_3	AM1	0.393	0.355	-0.231	0.035	-0.315	-0.365	-0.363	-0.331
	PM3	0.204	0.303	-0.227	-0.090	0.094	-0.013	-0.385	-0.350
OCH_3	AM1	0.394	0.365	-0.077	-0.064	-0.309	-0.365	-0.365	-0.299
	PM3	0.200	0.300	-0.046	-0.208	0.107	-0.016	-0.383	-0.323

that C-5, C-6, O-2, O-4 atoms indicate significant charge change as a function of substituent. For the two methods, the C-2 and C-4 atoms which form bonds with oxygen and nitrogen atoms have positive excess charge, while the C-5 atom has negative excess charge. As AM1 method , the C-6 atom which binds with nitrogen and hydrogen atoms has a slight negative charge for F and OCH_3 substituents and positive charge for CF_3, NO_2, Cl, Br, H and CH_3 substituents. In contrast by PM3 method, it possess a negative charge for F, Cl, Br, H, CH_3 and OCH_3 substituents and a positive charge for CF_3 and NO_2 substituents. The N-1 and N-3 atoms have negative excess charge by AM1 method, while by PM3 method the N-1atom has positive charge and N-3 atom has a slight negative charge. The O-2 and O-4 atoms indicated negative excess charge by the two methods. The examination of oxygen atoms charges values by AM1 and PM3 methods indicated that O-2 atom have the largest values of negative charges. The magnitudes of negative charges on O-2 vary from-0.328 to -0.365 electron charge whereas the magnitudes on O-4 vary from -0.268 to -0.331 electron charge by AM1 method. The corresponding quantities of negative charges on O-2 vary from -0.354 to-0.387 electron charge while on O-4 vary from-0.296 to-0.352 electron charge by PM3 method. This means that double bonded O-2 atom is more reactive than O-4 atom. This suggestion is in agreement with fact that 2-carbonyl group of thymine making hydrogen bonding with hydroxyl groups of certain small base molecules in DNA [5]. The Mulliken charges of carbon and oxygen atoms that calculated by PM3 method are in agreement with assignments of C-13 and O-17 NMR chemical shifts for these atoms[14,15]. The optimized total energies and semi-empirical heats of formation of the molecules studied are given in Table 3.

Table 3. Total energies and Heats of formation (in kcal/mol) for 5-substituted uracils by AM1 and PM3 calculations

Sub.	Total energy		Heat of formation	
	AM1	PM3	AM1	PM3
CF_3	-73618.42	-66248.92	-205.82	-223.33
NO_2	-56556.47	-50249.07	-44.89	-72.97
F	-48267.51	-43180.09	-93.94	-107.40
Cl	-45702.10	-40334.21	-57.28	-72.29
Br	-45230.18	-41177.73	-46.16	-56.85
H	-37401.48	-33385.59	-54.00	-67.79
CH_3	-40995.62	-36837.59	-61.30	-76.67
OCH_3	-48369.14	-43594.74	-85.68	-101.75

The total energy in a molecular orbital calculation is the net result of electronic kinetic energies and the interactions between all electrons and atomic cores in the system. The more stable geometry of a molecule has a minimal total energy [16] . From AM1 and PM3 calculations, it is obtained that the smallest value of total energy to CF_3 substituent. The unsubstituted molecule has the largest total energy. Computation of the relative energies of the molecules with respect to unsubstituted molecules gave the values 36216.9, 19155.0, 10866.0, 8300.6, 7828.7, 3594.1 and 10967.7 kcal/mol for CF_3, NO_2 , F, Cl, Br,CH_3 and OCH_3 substituents respectively by AM1 method. For the PM3 method, the values obtained were 32863.3, 16863.5, 9794.5, 6948.6, 7792.1, 3452.0 and 10209.2 kcal/mol for CF_3, NO_2 , F, Cl, Br,CH_3 and OCH_3 substituents respectively. On the other hand the heats of formation of all molecules are exothermic by both methods. The values of the heats of formation are varying which can be attributed to a function of substituent . The highest occupied and the lowest unoccupied molecular orbital (HOMO and LUMO respectively) energies and the energies band gaps (LUMO-HOMO energy difference, ΔE) values are given in Table 4 for both methods. Substitution on uracil ring with donor or acceptor substituents affect HOMO and LUMO energies and lead to decreased LUMO-HOMO gaps compare to unsubstituted uracil molecule. For the two methods, HOMO energies increased with donor substituents and decreased with strong acceptor CF_3 and NO_2 substituents. LUMO energies decreased with acceptor substituents, while they increased by AM1 method or slightly decreased by PM3 method with donor substituents. According to these results, in any excitation process 5-substituted with CF_3, NO_2 , F, Cl, Br,CH_3 and OCH_3 uracil need less by (ca 0.052,0.342, 0.498, 0.498, 0.514, 0.324 and 0.651 eV respectively) energy than that unsubstituted uracil with AM1culculations, whereas for PM3 calculations they need less by (ca 0.081, 0.194, 0.289, 0.611, 0.260, 0.195 and 0.432 eV respectively) energy than that for unsubstituted uracil.Three-dimensional pictures of electrostatic potential (ESP) of uracil and 5-NO_2, 5-F, 5-OCH_3 substituents molecules by AM1 method are shown in Fig.1. Green colors indicate positive ESP regions and red colors indicate negative ESP regions. As shown in the Table 2, for both methods AM1 and PM3 the negative charges of N-1atom are largest than O-4 atom, while negative charges of N-3 atom are largest than O-2 atom . The pictures of ESP have indicated that most negative ESP regions located at the oxygen lone pair sites. In other word, protonation and hydrogen bonding favorably occurs at these sites.

Table 4.The MO energies of HOMO, LUMO levels and ΔE (in eV) for the 5-substituted molecules

Sub.	AM1			PM3		
	HOMO	LUMO	ΔE	HOMO	LUMO	ΔE
CF_3	-10.646	-1.045	9.601	-10.368	-1.249	9.119
NO_2	-10.881	-1.570	9.311	-10.686	-1.679	9.006
F	-9.811	-0.656	9.155	-9.752	-0.840	8.911
Cl	-9.757	-0.601	9.155	-9.322	-0.733	8.589
Br	-9.806	-0.667	9.139	-9.685	-0.745	8.940
H	-9.971	-0.318	9.653	-9.710	-0.510	9.200
CH_3	-9.608	-0.278	9.329	-9.531	-0.526	9.005
OCH_3	-9.283	-0.281	9.002	-9.292	-0.525	8.768
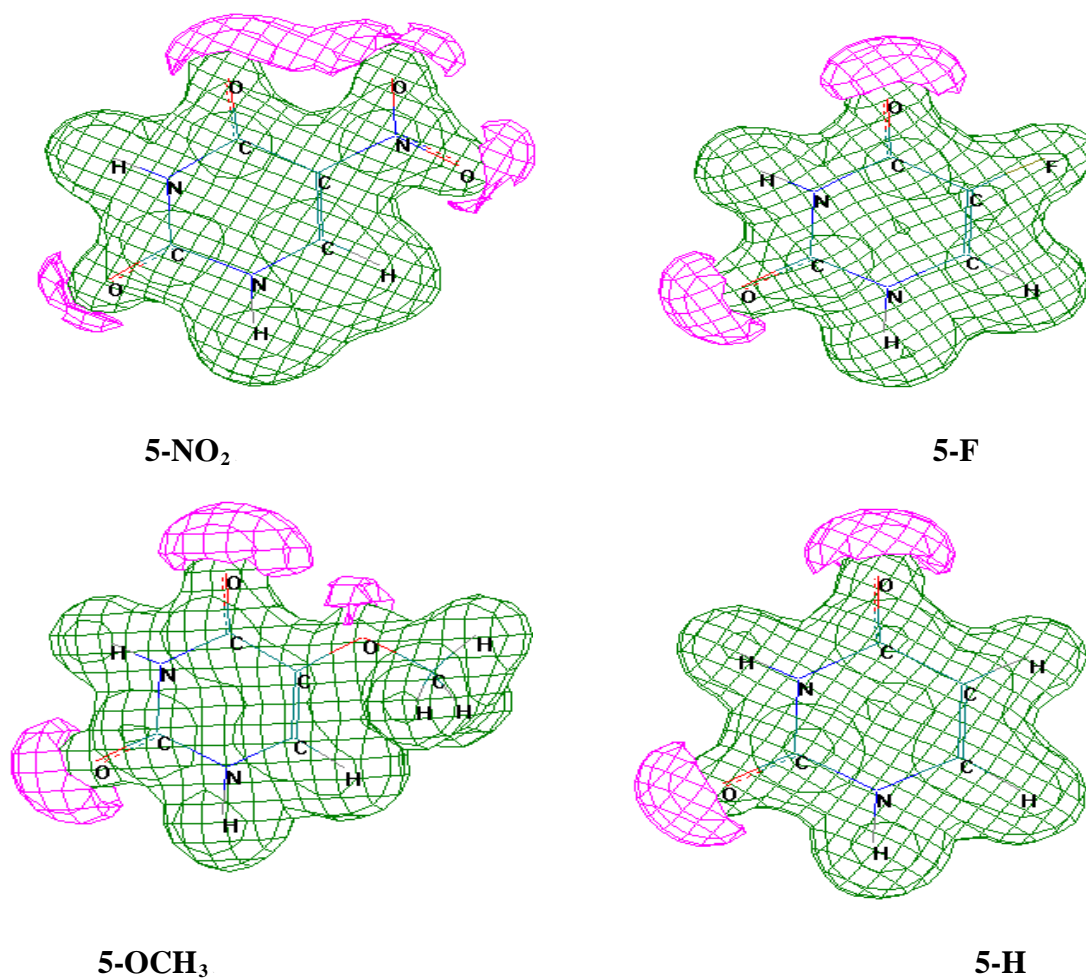
5-NO₂   **5-F**

5-OCH₃   **5-H**
Fig.1.Three-dimensional pictures of electrostatic potential of uracil substituted with 5-NO₂,5-F,5-OCH₃ groups by AMI method .

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دراسة شبه تجريبية لمركبات اليوراسيل المعوضة في الموقع-5

طه خلا شدي

أجريت حسابات شبه تجريبية لدراسة الصفات التركيبية والالكترونية لبعض مركبات اليوراسيل المعوضة في ذرة الكاربون رقم 5 بالمعوضات $CF_3, NO_2 , F, Cl, Br,CH_3,OCH_3$. تم الحصول من هذه الحسابات نظرياً على التراكيب المحسنة والصفات الالكترونية بالاعتماد على طريقتي الـ AM1 و PM3 شبه التجريبيتان . سجلت كذلك باستخدام هذه الحسابات شحن موليكان ,الطاقة الكلية,حرارات التكوين,مواقع أوطأ اوربتل ممتلىء وأوطأ اوربتال فارغ و سطوح الجهد الالكتروستاتيكي للجزيئات

Ali Jameel Hameed