Çankaya Üniversitesi Fen-Edebiyat Fakültesi,
Journal of Arts and Sciences Sayı: 4 / Aralık 2005

A study on tautomerism of dihydroxypyrimidines

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Abstract

Tautomerism of 4,6-dihydroxypyrimidine, 4-methoxy-pyrimidine-6-one, the monoanion of 4,6-dihydroxypyrimidine, 2,5-dihydroxypyrimidine, and 4,5-dihydroxypyrimidine have been examined in aqueous solution by means of semi-empirical AM1, PM3, PM5 and high level B3LYP/6-31G(d) and B3LYP/6-311++G(d,p) methods. The results obtained from the calculations are consistent with the available experimental data.

Keywords: *Pyrimidine; Tautomeric equilibrium; Conformation; AM1; PM3; PM5; B3LYP; IEFPCM; COSMO*

Özet

4,6-dihidroksipirimidin, 4-metoksi-6-pirimidin-6-on, 4,6-dihidroksipirimidinin monoanyonu, 2,5-dihidroksipirimidin ve 4,5-dihidroksipirimidine ait tatomerik dengeler yarı-ampirik AM1, PM3, PM5 ve yüksek seviyede B3LYP/6-31G(d) ve B3LYP/6-311++G(d,p) yöntemleri kullanarak incelenmiştir. Hesaplamalardan elde edilen sonuçlar mevcut deneysel veriler ile oldukça iyi uyum göstermiştir.

Anahtar kelimeler: pirimidin; tatomerik denge; konformasyon; AM1; PM3; PM5; B3LYP; IEFPCM; COSMO.

1. Introduction

Understanding tautomeric equilibria in heterocyclic molecules is of central importance in synthetic chemistry. Compounds with heterocyclic rings are also widely involved in biochemical processes. Tautomerism in nitrogen containing heterocycles has been investigated both experimentally [1-10] and theoretically [11-22]. The effect of the environment is of particular interest since the position of equilibrium is often

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sensitive to the solvent, and other intermolecular interactions. This has led to the use of quantum mechanical studies to predict the relative energies of such tautomers in aqueous solution. The accuracy of this type studies depends on both the relative energies of the isolated tautomers, estimated by quantum chemical calculations, and the solvent-solute interactions which are modelled by means of variety of methods such as Conductorlike Screening Model (COSMO) [23], Polarizable Continuum (PCM) [24].

As a continuation of our previous tautomerism studies [25] on important heterocyclic molecules, the tautomeric equilibrium positions for 4,6-dihydroxypyrimidine **1**, 4-Methoxy-pyrimidine-6-one **2**, the monoanion of 4,6-dihydroxypyrimidine **3**, 2,5-dihydroxypyrimidine **4**, and 4,5-dihydroxypyrimidine **5** have been examined. Pyrimidine and its derivatives are biologically important components of nucleic acids (DNA, RNA) and coenzymes. They can be the parent compound of many drugs, including the barbiturates. 4,6-Dihydroxypyrimidine, which is an important analogue of the main building blocks of DNA and bio-polymers, is used as an intermediate for the synthesis of pharmaceuticals. Uracil, which is 2,4-dihydroxypyrimidine, and its derivatives have been excluded from studying since they have been investigated extensively both experimentally [26-31] and theoretically [15-16, 20, 22, 32-33] because they are important nucleic acid constituents. Little work has been reported experimentally [34-43] on tautomerism of compounds **1-5**. No theoretical work on tautomerism of compounds **1-5** could be encountered in the literature.

Even though the semi empirical methods may not give good results for the tautomeric equilibrium studies, they were used due to their speed compared to Density Functional Theory (DFT) methods and obtain initial geometries for the latter calculations. DFT calculations are an invaluable tool to obtain information about the structure, relative stability and other properties of such tautomers, in the sense that physical properties of tautomers can be directly analysed by the results of the quantum chemical calculations. It is well known that the equilibrium between the tautomers is largely influenced by medium. Since theoretical treatments of solvent effects on tautomeric energies of heterocyclic systems are of general interest to organic chemists and the experimental works on tautomerism have been carried out generally in aqueous solution all calculations in the present study have been performed in water, using a relative permittivity of 78.4 corresponding to water, to reproduce the experimental tautomeric equilibrium in aqueous solution. Finally, the results obtained from the tautomeric equilibrium calculations have been compared with the experimental data.

2. Method

The semi empirical calculations were carried out at the restricted Hartree-Fock level (RHF) by using AM1 [44] and PM3 [45] in the MOPAC2000 [46], and PM5 [47] methods in the MOPAC2002 [48] implemented on an Intel Pentium IV 3.2 GHz computer, using a relative permittivity of 78.4 corresponding to water, with up to 252, instead of default value 42, surface segment per atom (NSPA, which controls the number of segments) being able to get more accurate results for the COSMO [23] model being used to van der Waals radii. Initial estimates of the geometry of the all structures were obtained by Chem3D in ChemOffice [49] followed by full optimisation of all geometrical variables (bond lengths, bond angles, and dihedral angles), without any symmetry constraint. All structures were optimised to a gradient norm 0.1-0.5, using the eigenvector following method (EF). The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using the calculated entropies (see footnotes in Table 1-3).

DFT molecular orbital calculations were performed with GaussianW03 [50] package. Becke's three parameter exact exchange functional (B3) [51] combined with gradient corrected correlation functional of Le-Yang-Par (LYP) [52] of DFT methods have been employed to optimise the geometries of all tautomers by implementing the 6-31G(d) and 6-311++G(d,p) basis sets . For the optimised geometries, the frequencies were obtained from the second derivatives of the energy computed using analytically calculated first derivatives to establish the stationary points. All optimised structures were checked by analysis of harmonic vibrational frequencies. The optimised structures of all tautomers are at the stationary points corresponding to local minima without imaginary frequency. DFT energy evaluations were carried out at molecular geometries optimised at B3LYP levels. The thermo chemical analysis was carried out to obtain Gibbs free energy values of the individual tautomeric species for normal conditions (298.15 K and 1 atm.). To take into account the effects of solvent polarity IEFPCM [24], Integral Equation Formalism Polarizable Continuum Model, self consistent reaction field (SCRF) [53] method, which defines the cavity as the union of a series interlocking atomic spheres, was used.

The entropy, enthalpy and energy values for individual species are calculated by ab inito and DFT methods in Gaussian programme as follows [54],

Table I: *The AM1 calculated thermodynamic properties of hydroxypyrimidines in aqueous solution (e = 78.4)*

Compound	ΔH_f[a] (kcal/mol)	ΔS[b] (cal/mol K)	ΔG_f[c] (kcal/mol)	Relative stability (kcal/mol)	Mol fractions of conformers	Mol fractions of tautomers
1a	-63.76	77.67	-86.91	16.79		N_{1a} = 0.00
1b	-73.24	78.55	-96.65	7.05		N_{1b} = 0.00
1c	-70.55	79.17	-94.14	9.56		N_{1c} = 0.00
1d	-62.11	80.03	-85.96	17.74		N_{1d} = 0.00
1e	-78.75	78.63	-101.93	1.77		N_{1e} = 0.05
1f	-80.97	76.20	-103.70	0.00		N_{1f} = 0.95
2as	-61.98	89.07	-88.52	2.31	N_{2as} = 0.64	N_{2a} = 0.02
2at	-61.64	89.05	-88.18	2.65	N_{2at} = 0.36	
2bs	-65.11	86.31	-90.83	0.00	N_{2bs} = 0.67	N_{2b} = 0.98
2bt	-64.59	86.62	-90.40	0.43	N_{2bt} = 0.33	
2cs	-53.81	88.79	-80.27	10.56	N_{2cs} = 0.99	N_{2c} = 0.00
2ct	-51.91	86.86	-77.79	13.04	N_{2ct} = 0.01	
2ds	-55.81	86.91	-81.71	9.12	N_{2ds} = 0.82	N_{2d} = 0.00
2dt	-54.97	86.74	-80.82	10.01	N_{2dt} = 0.18	
3a	-163.54	78.04	-186.80	9.55		N_{3a} = 0.00
3b	-173.31	77.31	196.35	0.00		N_{3b} = 1.00
3c	-167.45	77.90	-190.66	5.69		N_{3c} = 0.00
4a	-66.74	80.25	-90.65	0.00		N_{4a} = 1.00
4b	-58.95	76.48	-81.74	8.91		N_{4b} = 0.00
4c	-57.61	80.99	-81.75	8.90		N_{4c} = 0.00
4d	-58.45	80.92	-82.56	8.09		N_{4d} = 0.00
4e	-43.66	81.93	-68.08	22.57		N_{4e} = 0.00
4f	-52.73	80.38	-76.68	13.97		N_{4f} = 0.00
5a	-61.98	80.52	9.18	9.18		N_{5a} = 0.00
5b	-65.83	80.52	5.33	5.33		N_{5b} = 0.00
5c	-63.66	81.08	7.33	7.33		N_{5c} = 0.00
5d	-55.10	80.77	15.98	15.98		N_{5d} = 0.00
5e	-71.13	80.62	0.00	0.00		N_{5e} = 0.90
5f	-69.69	80.81	1.38	1.38		N_{5f} = 0.09
5g	-43.04	80.61	28.09	28.09		N_{5g} = 0.00
5h	-50.22	80.55	20.93	20.93		N_{5h} = 0.00
5i	-68.88	78.12	2.99	2.99		N_{5i} = 0.01
5j	-43.46	80.61	27.67	27.67		N_{5j} = 0.00

[a] ΔH_f; heat of formation estimated from MOPAC
[b] ΔS entropy estimated from MOPAC
[c] ΔG_f; Gibbs free energy calculated from $\Delta G_f = \Delta H_f - T\Delta S$

Table II: *The PM3 calculated thermodynamic properties of hydroxypyrimidines in aqueous solution (e= 78.4)*

Compound	ΔH_f[a] (kcal/mol)	ΔS[b] (cal/mol K)	ΔG_f[c] (kcal/mol)	Relative stability (kcal/mol)	Mol fractions of conformers	Mol fractions or tautomers
1a	-78.32	79.12	-101.90	15.62		N_{1a} = 0.00
1b	-86.92	79.42	-100.59	6.93		N_{1b} = 0.00
1c	-87.60	80.04	-111.45	6.07		N_{1c} = 0.00
1d	-79.07	80.30	-103.00	14.52		N_{1d} = 0.00
1e	-93.48	80.68	-117.52	0.00		N_{1e} = 0.57
1f	-94.55	76.52	-117.35	0.17		N_{1f} = 0.43
2as	-77.74	88.78	-104.20	1.68	N_{2as} = 0.51	N_{2a} = 0.05
2at	-77.74	88.72	-104.18	1.70	N_{2at} = 0.49	
2bs	-76.44	87.84	-102.62	3.26	N_{2bs} = 0.00	N_{2b} = 0.95
2bt	-79.83	87.41	-105.88	0.00	N_{2bt} = 1.00	
2cs	-69.09	90.08	-95.93	9.95	N_{2cs} = 0.04	N_{2c} = 0.00
2ct	-70.89	90.12	-97.75	8.13	N_{2ct} = 0.96	
2ds	-67.91	88.48	-94.28	11.60	N_{2ds} = 0.01	N_{2d} = 0.00
2dt	-71.00	88.38	-97.34	8.54	N_{2dt} = 0.99	
3a	-185.28	79.46	-208.96	7.24		N_{3a} = 0.00
3b	-192.68	78.09	-215.95	0.25		N_{3b} = 0.40
3c	-192.41	79.84	-216.20	0.00		N_{3c} = 0.60
4a	-83.15	81.59	-107.46	0.00		N_{4a} = 1.00
4b	-79.96	76.90	-102.88	4.58		N_{4b} = 0.00
4c	-75.40	82.61	-100.02	7.44		N_{4c} = 0.00
4d	-74.27	81.75	-98.63	8.83		N_{4d} = 0.00
4e	-65.34	81.97	-89.77	17.69		N_{4e} = 0.00
4f	-72.53	82.43	-97.09	10.37		N_{4f} = 0.00
5a	-72.03	81.68	-96.37	11.16		N_{5a} = 0.00
5b	-78.67	79.71	-102.42	5.11		N_{5b} = 0.00
5c	-80.48	80.42	-104.45	3.08		N_{5c} = 0.01
5d	-69.54	79.82	-93.33	14.20		N_{5d} = 0.00
5e	-81.20	80.41	-105.16	2.37		N_{5e} = 0.01
5f	-83.52	80.40	-107.48	0.05		N_{5f} = 0.47
5g	-59.96	82.27	-84.48	23.05		N_{5g} = 0.00
5h	-65.57	80.72	-89.62	17.91		N_{5h} = 0.00
5i	-84.18	78.35	-107.53	0.00		N_{5i} = 0.51
5j	-69.01	79.89	-92.82	14.71		N_{5j} = 0.00

[a] ΔH_f; heat of formation estimated from MOPAC
[b] ΔS entropy estimated from MOPAC
[c] ΔG_f; Gibbs free energy calculated from $\Delta G_{f=} \Delta H_{f-} T\Delta S$

Table III: *The PM5 calculated thermodynamic properties of hydroxypyrimidines in aqueous solution (e = 78.4)*

Compound	ΔH_f[a] (kcal/mol)	ΔS[b] (cal/mol K)	ΔG_f[c] (kcal/mol)	Relative stability (kcal/mol)	Mol fractions of conformers	Mol fractions of tautomers
1a	-70.74	78.86	-94.24	18.94		N_{1a} = 0.00
1b	-82.34	79.50	-106.03	7.15		N_{1b} = 0.00
1c	-79.29	80.53	-103.29	9.89		N_{1c} = 0.00
1d	-69.91	82.13	-94.38	18.80		N_{1d} = 0.00
1e	-85.72	76.87	-108.63	4.55		N_{1e} = 0.00
1f	-90.22	77.06	-113.18	0.00		N_{1f} = 1.00
2as	-69.41	84.17	-94.49	5.45	N_{2as} = 0.01	N_{2a} = 0.02
2at	-70.73	90.01	-97.55	2.39	N_{2at} = 0.99	
2bs	-73.29	87.84	-99.47	0.47	N_{2bs} = 0.31	N_{2b} = 0.98
2bt	-73.76	87.86	-99.94	0.00	N_{2bt} = 0.69	
2cs	-61.00	86.11	-86.66	13.28	N_{2cs} = 0.67	N_{2c} = 0.00
2ct	-59.82	88.66	-86.24	13.70	N_{2ct} = 0.33	
2ds	-61.78	88.13	-88.04	11.90	N_{2ds} = 0.39	N_{2d} = 0.00
2dt	-62.03	88.16	-88.30	11.64	N_{2dt} = 0.61	
3a	-183.09	79.08	-206.66	11.90		N_{3a} = 0.00
3b	-195.29	78.08	-218.56	0.00		N_{3b} = 1.00
3c	-189.01	78.75	-212.48	6.08		N_{3c} = 0.00
4a	-76.30	80.97	-100.43	0.00		N_{4a} = 1.00
4b	-71.53	77.60	-94.65	5.78		N_{4b} = 0.00
4c	-64.88	77.68	-88.03	12.40		N_{4c} = 0.00
4d	-64.06	82.46	-88.63	11.80		N_{4d} = 0.00
4e	-49.92	83.70	-74.86	25.57		N_{4e} = 0.00
4f	-62.73	81.71	-87.08	13.35		N_{4f} = 0.00
5a	-66.50	81.48	-90.78	13.66		N_{5a} = 0.00
5b	-71.96	76.98	-94.90	9.54		N_{5b} = 0.00
5c	-71.13	77.70	-94.28	10.16		N_{5c} = 0.00
5d	-61.58	77.23	-84.59	19.85		N_{5d} = 0.00
5e	-78.86	81.89	-103.26	1.18		N_{5e} = 0.11
5f	-79.20	80.95	-103.32	1.12		N_{5f} = 0.12
5g	-48.36	81.94	-72.78	31.66		N_{5g} = 0.00
5h	-55.87	82.19	-80.36	24.08		N_{5h} = 0.00
5i	-80.92	78.93	-104.44	0.00		N_{5i} = 0.77
5j	-52.89	81.79	-77.66	26.78		N_{5j} = 0.00

[a] ΔH_f; heat of formation estimated from MOPAC
[b] ΔS entropy estimated from MOPAC
[c] ΔG_f; Gibbs free energy calculated from $\Delta G_f = \Delta H_f - T\Delta S$

Table IV: *The B3LYP/6-31G (d) // B3LYP/6-31G(d) calculated energy values of hydroxypyrimidines in aqueous solution (ε= 78.4)*

Compound	B3LYP/6-31G(d)// B3LYP/6-31G(d)					
	E[a] in Hartree	Relative stability kcal/mol	G[b] in Hartree	Relative stability kcal/mol	Mol fractions of conformers	Mol fractions of tautomers
1a	-414.813378	4.92	-414.759676	4.56		N_{1a} = 0.00
1b	-414.821224	0.00	-414.766937	0.00		N_{1b} = 0.61
1c	-414.808894	7.74	-414.755251	7.33		N_{1c} = 0.00
1d	-414.790321	19.39	-414.736845	18.88		N_{1d} = 0.00
1e	-414.814158	4.43	-414.759690	4.55		N_{1e} = 0.00
1f	-414.820899	0.20	-414.766504	0.27		N_{1f} = 0.39
2as	-454.098199	12.17	-454.017845	11.60	N_{2as} = 0.00	N_{2a} = 0.00
2at	-454.106573	6.91	-454.025250	6.95	N_{2at} = 1.00	
2bs	-454.117587	0.00	-454.036331	0.00	N_{2bs} = 0.73	N_{2b} = 0.99
2bt	-454.117406	0.11	-454.035389	0.59	N_{2bt} = 0.27	
2cs	-454.087868	18.65	-454.006905	18.47	N_{2cs} = 1.00	N_{2c} = 0.00
2ct	-454.081010	22.95	-454.001782	21.68	N_{2ct} = 0.00	
2ds	-454.110373	4.53	-454.032072	2.67	N_{2ds} = 0.97	N_{2d} = 0.01
2dt	-454.108215	5.88	-454.028804	4.72	N_{2dt} = 0.03	
3a	-414.331471	6.05	-414.289401	5.79		N_{3a} = 0.00
3b	-414.341107	0.00	-414.298625	0.00		N_{3b} = 1.00
3c	-414.332289	5.53	-414.289900	5.48		N_{3c} = 0.00
4a	-414.798120	0.00	-414.745094	0.00		N_{4a} = 0.99
4b	-414.786269	7.44	-414.732066	8.18		N_{4b} = 0.00
4c	-414.779888	11.44	-414.727433	11.08		N_{4c} = 0.00
4d	-414.794386	2.34	-414.741464	2.78		N_{4d} = 0.01
4e	-414.758092	25.12	-414.706133	24.45		N_{4e} = 0.00
4f	-414.777832	12.73	-414.724834	12.71		N_{4f} = 0.00
5a	-414.794261	6.22	-414.740845	5.73		N_{5a} = 0.00
5b	-414.787974	10.17	-414.734849	9.49		N_{5b} = 0.00
5c	-414.785056	12.00	-414.731648	11.50		N_{5c} = 0.00
5d	-414.775796	17.81	-414.722179	17.44		N_{5d} = 0.00
5e	-414.804181	0.00	-414.749979	0.00		N_{5e} = 1.00
5f	-414.798007	3.87	-414.744018	3.74		N_{5f} = 0.00
5g	-414.760122	27.65	-414.706962	26.99		N_{5g} = 0.00
5h	-414.764615	24.83	-414.712291	23.65		N_{5h} = 0.00
5i	-414.792899	7.08	-414.738440	7.24		N_{5i} = 0.00
5j	-414.737180	42.04	-414.684594	41.03		N_{5j} = 0.00

[a] sum of electronic and thermal energy

[b] sum of electronic and thermal free energy

Table V: *The B3LYP/6-311++G(d,p) // B3LYP/6-311++G(d,p) calculated energy values of hydroxypyrimidines in aqueous solution (e = 78.4)*

Compound	B3LYP/6-311++G(d,p)// B3LYP/6-311++G(d,p)					
	E[a] in Hartree	Relative stability kcal/mol	G[b] in Hartree	Relative stability kcal/mol	Mol fractions of conformers	Mol fractions of tautomers
1a	-414.948327	6.66	-414.898083	4.69		$N_{1a} = 0.00$
1b	-414.957069	1.16	-414.903674	1.18		$N_{1b} = 0.12$
1c	-414.946542	7.78	-414.893694	7.44		$N_{1c} = 0.00$
1d	-414.920936	23.85	-414.868247	23.41		$N_{1d} = 0.00$
1e	-414.944276	9.20	-414.892372	8.27		$N_{1e} = 0.00$
1f	-414.958942	0.00	-414.905556	0.00		$N_{1f} = 0.88$
2as	-454.238222	11.15	-454.158991	10.70	$N_{2as} = 0.00$	$N_{2a} = 0.00$
2at	-454.246785	5.78	-454.166776	5.81	$N_{2at} = 1.00$	
2bs	-454.255953	0.03	-454.176036	0.00	$N_{2bs} = 0.67$	$N_{2b} = 1.00$
2bt	-454.255995	0.00	-454.175376	0.41	$N_{2bt} = 0.33$	
2cs	-454.221678	21.54	-454.141959	21.38	$N_{2cs} = 1.00$	$N_{2c} = 0.00$
2ct	-454.214994	25.73	-454.136489	24.82	$N_{2ct} = 0.00$	
2ds	-454.247835	5.12	-454.168191	4.92	$N_{2ds} = 0.90$	$N_{2d} = 0.00$
2dt	-454.246025	6.26	-454.166076	6.25	$N_{2dt} = 0.10$	
3a	-414.480876	6.64	-414.439527	6.45		$N_{3a} = 0.00$
3b	-414.491461	0.00	-414.449809	0.00		$N_{3b} = 1.00$
3c	-414.474935	10.37	-414.433251	10.39		$N_{3c} = 0.00$
4a	-414.934363	0.00	-414.882243	0.00		$N_{4a} = 0.99$
4b	-414.925435	5.60	-414.872089	6.37		$N_{4b} = 0.00$
4c	-414.909266	15.75	-414.857878	15.29		$N_{4c} = 0.00$
4d	-414.929445	3.09	-414.877319	3.09		$N_{4d} = 0.01$
4e	-414.888312	28.90	-414.836035	29.00		$N_{4e} = 0.00$
4f	-414.777832	98.22	-414.724834	98.78		$N_{4f} = 0.00$
5a	-414.929522	6.55	-414.876835	6.12		$N_{5a} = 0.00$
5b	-414.916678	14.61	-414.864752	13.70		$N_{5b} = 0.00$
5c	-414.915312	15.47	-414.863142	14.70		$N_{5c} = 0.00$
5d	-414.904819	22.05	-414.852174	21.59		$N_{5d} = 0.00$
5e	-414.939961	0.00	-414.886584	0.00		$N_{5e} = 0.98$
5f	-414.935970	2.50	-414.882755	2.40		$N_{5f} = 0.02$
5g	-414.889686	31.55	-414.837422	30.85		$N_{5g} = 0.00$
5h	-414.894021	28.83	-414.846320	25.27		$N_{5h} = 0.00$
5i	-414.932661	4.58	-414.879000	4.76		$N_{5i} = 0.00$
5j	-414.872609	42.26	-414.820736	41.32		$N_{5j} = 0.00$

[a] sum of electronic and thermal energy

[b] sum of electronic and thermal free energy

$E_0 = E_{elec}$ + ZPE sum of electronic and zero-point energies

$E = E_0 + E_{vib} + E_{rot} + E_{trans}$ sum of electronic and thermal energies

H= E + RT sum of electronic and thermal enthalpies

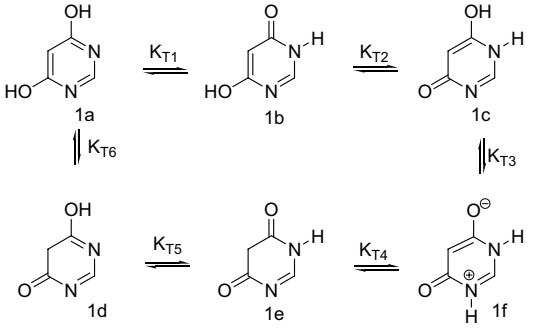
G= H –TS sum of electronic and thermal free energies.

Where, T= 298.15 K

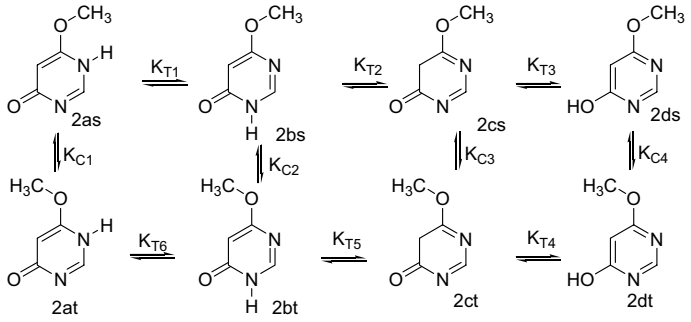
The zero-point energy and thermal energy corrections are calculated first by programme, followed by the estimated energy of the system taking them into account. The output also contains the corrections to and the final predicted values for the enthalpy and Gibbs energy. All values are in Hartrees.

3. Results and Discussion

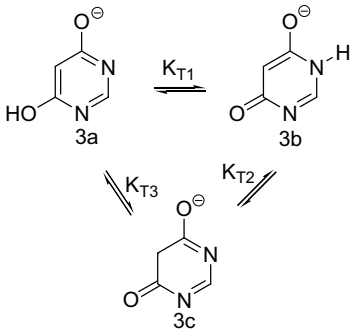
The AM1, PM3, PM5, B3LYP/6-31G(d), and B3LYP/6-311++G(d,p) calculated energy values and mole fractions are given in Tables 1-5 for the individual tautomeric forms as presented in Schemes 1-5.



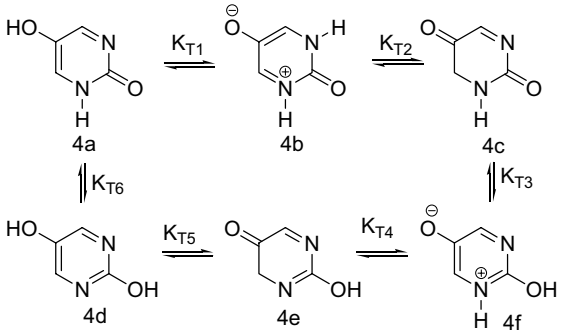
Scheme 1 Tautomers of 4,6-dihydroxypyrimidine



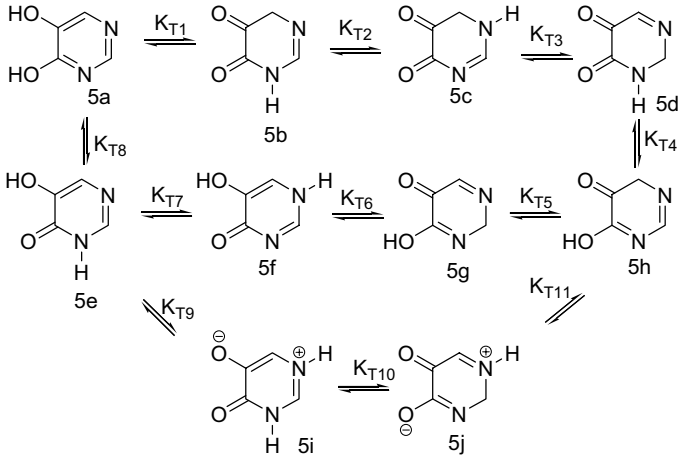
Scheme 2 Tautomers of 4-methoxy-pyrimidine-6-one



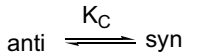
Scheme 3 Tautomers of the anion of 4,6-dihydroxypyrimidine



Scheme 4 Tautomers of 2,5-dihydroxypyrimidine



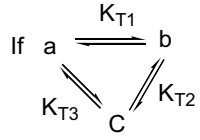
Scheme 5 Tautomers of 4,5-dihydroxypyrimidine



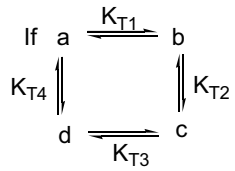
$N_{t(anti)} = 1 / [1 + K_C]$
$N_{s(syn)} = K_C / [1 + K_C]$ (1)

$K = e^{(-\delta\Delta G / RT)}$ $R = 1.987x10^{-3}$ kcal/mol and T = 298 Kº.

$N_a = 1 / [1 + K_T]$
$N_b = K_T / [1 + K_T]$ (2)



$N_a = 1 / [1 + K_{T1} + K_{T3}]$
$N_b = K_{T1} / [1 + K_{T1} + K_{T3}]$
$N_c = K_{T3} / [1 + K_{T1} + K_{T3}]$ (3)



$N_a = 1 /A$
$N_b = K_{T1} /A$
$N_c = K_{T1}K_{T2} /A$
$N_d = K_{T1}K_{T2}K_{T3} /A$
$A = 1 + K_{T1} + K_{T1}K_{T2} + K_{T1}K_{T2}K_{T3}$ (4)

The mole fractions for the tautomers and conformers have been estimated by using the following equations.

Where N_t, N_s, N_a, N_b, N_c, and N_d are the mole fractions of the individual conformers and/or tautomers. $\Delta G_{f(s)}$, $\Delta G_{f(t)}$, $\Delta G_{f(a)}$, $\Delta G_{f(b)}$, and $\Delta G_{f(c)}$, and $\Delta G_{f(d)}$ are the free energies of the *syn* and *anti* conformers and/or tautomers.

As it is well known that the results obtained by means of quantum chemical calculations such as both semi empirical and ab initio methods depend on the methods used. To be able to obtain more accurate result which is comparable to experimental data the higher basis sets should be employed in ab initio and DFT calculations. But this will lead to the higher cost in time. So high level B3LYP/6-311++G(d,p) even B3LYP/6-31G(d) basis sets are enough to use in prediction the relative stabilities of the heterocycles tautomers. It is also possible to use semi empirical methods such as AM1, PM3 and PM5 to estimate the tautomeric equilibria between heterocyclic systems if the parameters used in AM1, PM3, and PM5 are suitable for this type of systems.

3.1 4,6-Dihydroxypyrimidine (**1**)

4,6-Dihydroxypyrimidine **1** could exist in six tautomeric forms: these include the dihydroxy form **1a**, hydroxy-oxo forms **1b-1d**, dioxo form **1e**, and betaine form **1f**. 4,6-

Dihydroxypyrimidine **1** was tentatively shown by IR to exist in the hydroxy-oxo form **1b** [34]. The UV comparison of **1** with O- and *N*-allyl models for the forms supported that **1** exists in aqueous solution as a mixture of two tautomers **1e** and **1c**, with the dioxo form **1e** predominating over the hydroxy-oxo structure **1c** [35]. Russian workers [36] initially claimed from UV and NMR results that the hydroxy-oxo form **1b** was predominant with some contribution from the dioxo structure **1e**. The Japanese workers [37] also concluded from the NMR measurements that 4,6-dihydroxypyrimidine **1** exists mainly as the hydroxy-oxo form **1b** with smaller quantities of the dioxo form **1e**. Later the same Russian group [38-39] demonstrated that the betaine form **1f** is predominant in water. A.R. Katritzky and co-workers [40] showed by UV, IR, NMR, and pK_a comparisons of **1** that 4,6-dihydroxypyrimidine **1** exists in water predominantly as the betaine structure **1f** together with a substantial amount of the hydroxy-oxo form **1b**.

The semi empirical AM1, PM5, and high level 6-311++G(d,p) calculations show that the most stable form **1f** exists predominantly in water with a substantial amount of **1b** by 6-311++G(d,p) and **1e** by AM1, which are excellent agreement with the experimental estimation obtained by A.R. Katritzky and co-workers [40]. The next most stable tautomers for **1e** by AM1 and PM5, and for **1b** by 6-311++G(d,p) are more than 1.77, 4.55, and 1.18 kcal/mol higher, respectively. According to PM3 results, the form **1e** is somewhat more stable than **1f** being the next most stable tautomer. The 6-31G(d) calculations predicted the structure **1b** to be slightly more stable than **1f**, which is less stable only 0.27 kcal/mol than **1b**. The all semi empirical and DFT calculations indicated that there is no contribution to the tautomeric equilibria from the other tautomeric forms **1a, 1c,** and **1d**.

3.2 4-Methoxy-pyrimidine-6-one (2)

4-Methoxy-pyrimidine-6-one **2**, which is also fixed-form model compound of **1a, 1c**, and **1d**, could exist in four tautomeric forms **2a-2d**, which was shown on the evidence of UV and NMR [40] measurements that **2b** form predominates in aqueous media.

Because of the methyl group in 4-methoxy-pyrimidine-6-one **2** *syn* and *anti* conformers for **2** also was taken into account to obtain more accurate results. According to the semi empirical and DFT calculations employed on 4-methoxy-pyrimidine-6-one **2**, the tautomer **2b** is the most stable form among the four tautomers. Although all semi

empirical methods predicted **2a** as the next most stable tautomer, both 6-31G(d) and 6-311++G(d,p) estimated that **2d** is the next most stable structure among the possible existing tautomeric forms **2a-2d**. The semi empirical and DFT calculations showed that **2c** and **2d** tautomeric forms are of negligible importance in the tautomeric equilibria in aqueous solution.

3.3 The monoanion of 4, 6-dihydroxypyrimidine (3)

The monoanion of 4,6-dihydroxypyrimidine **3** could have in three tautomeric forms **3a-3c**.

The anion of 4,6-dihydroxypyrimidine **3** on the UV comparisons [40] exist as **3b** with contribution from **3c**.

Except PM3 calculation, the rest of the methods used in the present study estimated that the monoanion of 4,6-dihydroxypyrimidine **3b** is the most stable structure, which is the more stable 5.69 by AM1, 6.08 by PM5, 5.48, by 6-31G(d), and 6.45 kcal/mol by 6-311++G(d,p), respectively than the next most stable tautomeric forms **3c** by AM1, PM5, and 6-31G(d) and **3a** by 6-311++G(d,p). All these results are well agreement with the experimental data mentioned above. According to PM3 results, the most stable tautomeric form **3c** is more stable than the next most stable tautomeric form **3b** being less stable only 0.25 kcal/mol than **3a.**

3.4 2,5-Dihydroxypyrimidine (4)

2,5-Dihydroxypyrimidine **4** was suggested tentatively to exist as a mixture of the oxo-hydroxy **4a** and betaine structure **4b** [41]. The UV and IR studies of Z. Budensinsky and co-workers also demonstrated that 2,5-dihydroxypyrimidine **4** predominates in **4a** form [42].

The all methods employed in this work, AM1, PM3, PM5, 6-31G(d), and 6-311++G(d,p) predicted the oxo-hydroxy structure **4a** as the most stable tautomeric form among the possible existing six tautomeric forms, which is excellent consistent with the experimental data . The B3LYP calculations indicated that tautomeric form **4d** has a negligible amount of contribution to the tautomeric equilibria. According to the results, it can be said that the remaining of the tautomeric forms **4b, 4c, 4e,** and **4f** have no importance in contribution to the equilibria.

3.5 4,5-Dihydroxypyrimidine (5)

From infrared spectral study, 4,5-dihydroxypyrimidine **5** was tentatively shown by IR to exist in the hydroxy-oxo form **5e** [34], which was also supported by IR spectra work from H. Brederech and co-workers [43].

Except PM3 and PM5 calculations, which predict the **5i** as the most stable tautomeric form, the remaining methods used in the present study showed that the 4,5-dihydroxypyrimidine **5** exist in the hydroxy-oxo form **5e** with a small amount of contribution from **5f** by AM1 and 6-311++G(d,p) and **5i** by AM1, which is well agreement with the existing data above. According to PM3 calculations, the 4,5-dihydroxypyrimidine **5** in water exist as a mixture of two tautomers, with the **5i** form predominating over the **5f**, **5c**, and **5e** . The difference in energy between **5i** and **5f** is only 0.05 kcal/mol in other words; **5i** is 0.05 kcal/mol more stable than **5f**. The contribution from **5c** and **5e** is negligible. The PM5 estimated that the form **5i** is 1.12 and 1.18 kcal/mol more stable than the next two most stable tautomeric forms **5f** and **5e,** respectively.

4. Conclusion

The results presented in this paper indicates that AM1 and high level B3LYP/6-311++G(d,p) even B3LYP/6-31G(d) methods can be used for the prediction of relative stabilities of heterocycles tautomers in aqueous solution when the appropriate solvation models are used. Although PM5 estimated the right tautomeric forms for **1-4** but it failed for **5** so it does not seem to be stable as much as DFT methods. The PM3 is poor to predict the relative stabilities of the tautomeric forms for heterocycles because the parameters used in PM3 are probably not suitable for this type of heterocycles.

The relative free energy order for the investigated tautomers in aqueous solution is the same compared to the relative energy order in DFT calculations.

Acknowledgements

I thank Anadolu University Research Fund for supporting this study (AÜAF project number: 01 1066, 2001).

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