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Quantum chemical studies on prototropic tautomerisation and protonation behaviour of 6-propyl-2-thiouracil

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Abstract

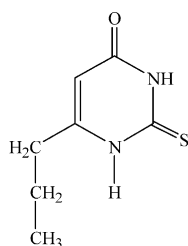
The preferred tautomeric form and protonation path of biologically active 6-propyl-2-thiouracil molecule was predicted using gas phase calculated relative stabilities, proton affinities and aqueous phase calculated acidity constants. It was predicted that 3H-forms were favored over 1H-forms in annular-tautomerism and oxo-thione forms favored over hydroxy-thiol forms in ring-chain tautomerism.

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Keywords: 6-Propyl-2-thiouracil; Quantum chemical studies; Prototropic tautomerism; Protonation

1. Introduction

Among the most widely used anti-thyroid agents for the treatment of hyperthyroidism (Grave disease) over the years are thioamides [1]. Thioamides inhibit formation of 3,5,3'-triiodothyronine (T3) and 3,5,3',5'-tetraiodothyronine (T4) hormones by depressing the incorporation of oxidised iodides to tyrosine, a precursor of T3 and T4 hormones [2]. Moreover, propyl-thiouracil (propycil, propylthyracil, thyreostat II or triotil) among the drugs is used for treatment of hyperthyroidism heavily. Therefore, we believe that it is very important to know the structure of this compound to clarify the structure reactivity relation to elucidate the iodine binding mechanism and we believe that it deserves a detailed theoretical study.



6-propyl-2-thiouracil

2. Method of calculation

Theoretical calculations were carried out at the restricted Hartree–Fock level using PM3 [3], AM1 [4], MNDO [5], semi-empirical SCF-MO methods in the MOPAC 7.0 program, implemented on an Intel Pentium IV computer, using a relative permittivity of 78.4 corresponding to water, with up to 60 surface segments per atom for the COSMO model [6] being used to construct a solvent accessible surface area based on van der Waals radii. All structures were optimized to a gradient norm of <0.1 in the gas phase and 0.1–1.0 in the aqueous phase, using the eigen vector method following. The absolute entropies of all structures were calculated from a complete vibrational analysis. Enthalpies were corrected to free energies using calculated entropies. Initial estimates of the geometry of all the structures were obtained by a molecular mechanics program (CS Chem Office Pro for Windows) [7], followed by full optimization of all geometrical variables (bond lengths, bond angles and dihedral angles), without any symmetry constraint, using the semi-empirical quantum-chemical methods in the MOPAC 7.0 program [8].

3. Results and discussion

3.1. Prototropic tautomerism and stability

Possible prototautomerisation along with protonation patterns for the studied molecules are depicted in

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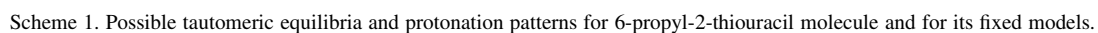


Table 1

Gas phase AM1, PM3 and MNDO calculated thermodynamic properties for the investigated compounds

Compound	ΔH_f (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)	$T\Delta S$ (kcal mol ⁻¹)	ΔG_f^a (kcal mol ⁻¹)	Dipole moment (D)
<i>AM1</i>					
1	-19.425	91.289	27.204	-46.629	5.431
2	15.894	97.177	28.958	-13.064	5.396
3	-14.428	93.063	27.732	-42.160	2.015
4	-9.211	91.242	27.19	-36.401	6.265
5	2.134	94.357	28.118	-25.984	6.428
6(7)	-16.718	92.188	27.472	-44.190	1.28
8	6.980	99.258	29.578	63.690	5.008
9	27.526	105.614	31.472	-3.946	6.220
10	0.173	104.421	31.117	-30.944	3.795
11	25.364	104.386	31.107	-5.743	5.992
12	8.721	102.228	30.463	-21.742	6.674
13	-2.530	108.815	32.426	-34.956	1.846
14	153.46	98.766	29.432	124.028	4.801
15	141.352	98.374	29.315	112.037	3.482
16	148.814	105.737	31.509	117.305	4.803
17	153.446	105.093	31.317	122.129	2.685
19	147.805	99.590	29.677	118.128	3.910
20	171.473	104.757	31.217	140.256	3.045
21	167.939	103.895	30.9607	-141.668	5.698
22	156.961	100.322	29.895	127.066	4.796
23	170.52	101.516	30.251	140.269	5.262
24	133.327	104.132	31.031	102.296	4.886
25	136.323	107.916	32.158	104.165	4.610
26	143.429	98.105	29.235	114.194	1.383
27	141.352	98.930	29.481	111.871	3.482
28	158.084	96.337	28.708	129.376	3.482
28	140.206	106.450	31.722	108.484	1.743
29	150.134	103.290	30.780	119.354	2.997
30	157.581	100.203	29.860	127.721	4.800
31	168.296	97.043	28.918	139.378	1.857
32	163.604	106.138	31.629	131.975	5.233
33	161.041	105.234	31.359	129.682	1.833
34	146.865	99.775	29.732	117.133	1.397
35	155.786	101.566	30.266	125.52	5.259
36	126.536	105.128	31.328	952.08	1.425
37	131.727	109.536	32.641	990.86	4.823
<i>PM3</i>					
1	-18.016	93.017	27.719	-45.735	5.575
2	19.434	93.568	27.883	-8.449	6.229
3	-24.99	93.769	27.943	-52.933	2.732
4	-9.470	92.776	27.647	-37.117	6.908
5	-8.935	98.260	29.281	-38.216	5.516
6(7)	-25.479	93.663	27.911	-53.390	2.107
8	-0.055	103.873	30.954	-31.009	3.892
9	26.888	109.428	32.609	-5.721	8.152
10	-12.184	103.500	30.843	-43.027	3.180
11	21.713	104.617	31.175	-9.462	6.808
12	-11.046	104.115	31.026	-42.072	5.598
13	-12.190	106.118	31.623	-43.813	2.517
14	151.618	95.226	28.377	123.241	4.211
15	178.770	100.460	29.937	148.833	3.351
16	138.530	109.916	32.754	105.775	3.959
17	152.187	105.304	31.380	120.807	3.300
18	168.068	99.978	29.793	138.775	3.965
19	145.716	97.401	29.025	116.691	4.581
20	177.418	102.244	30.468	14.695	4.732
21	164.791	104.011	30.995	13.379	6.384
22	154.184	97.776	29.137	125.047	4.210
23	164.444	98.467	29.343	135.307	6.089

(continued on next page)

Table 1 (continued)

Compound	ΔH_f (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)	$T\Delta S$ (kcal mol ⁻¹)	ΔG_f^a (kcal mol ⁻¹)	Dipole moment (D)
24	131.144	99.864	29.759	101.385	3.769
25	131.100	99.131	29.541	101.559	4.571
26	139.621	97.887	29.170	110.451	1.665
27	163.564	96.104	28.638	134.925	3.544
28	136.140	104.497	31.140	105.000	1.374
29	156.697	103.672	30.894	125.853	3.126
30	150.406	94.281	28.095	122.311	4.207
31	158.699	92.230	27.484	131.215	2.048
32	148.653	102.562	30.563	118.090	3.894
33	142.903	104.752	31.216	111.687	1.393
34	142.282	95.304	28.400	113.882	1.677
35	154.408	98.440	29.335	125.073	5.224
36	129.729	106.050	31.602	98.127	1.230
37	136.891	100.698	30.008	106.883	4.280
<i>MNDO</i>					
1	-23.327	92.039	27.427	-50.754	4.931
2	1.532	93.970	28.003	-26.471	5.111
3	-29.994	92.478	27.558	-57.552	2.728
4	-23.763	91.788	27.352	-51.115	5.718
5	-6.666	90.452	26.954	-33.620	5.796
6(7)	-39.538	92.431	27.544	-67.082	1.719
8	3.517	101.052	30.113	-26.596	3.392
9	15.788	105.630	31.477	-15.689	6.913
10	-10.523	104.347	31.095	-41.618	2.991
11	12.452	101.090	30.124	-17.672	5.416
12	-1.077	102.760	30.622	-31.699	5.329
13	-21.419	103.467	30.833	-52.252	2.229
14	155.930	94.077	28.034	127.896	7.189
15	168.620	100.203	29.860	138.760	3.794
16	152.361	105.171	31.340	121.021	3.528
17	151.471	104.894	31.258	120.213	3.174
18	158.904	97.204	28.966	129.938	4.241
19	142.590	97.617	29.089	113.501	4.931
20	173.644	104.459	31.128	142.516	4.320
21	168.846	104.595	31.169	137.677	6.131
22	159.507	97.457	29.042	130.465	4.470
23	160.421	96.949	28.890	131.531	5.571
24	133.502	106.902	31.856	101.646	3.441
25	123.373	106.375	31.699	91.674	4.984
26	235.633	93.368	27.823	207.810	1.890
27	153.412	96.793	28.844	124.568	9.156
28	134.509	101.585	30.272	104.237	1.467
29	152.335	102.961	30.682	121.653	3.863
30	158.408	95.861	28.566	129.842	4.471
31	154.745	98.224	29.270	125.475	1.618
32	163.540	102.159	30.443	133.097	4.080
33	150.123	109.493	32.628	117.495	1.221
34	139.080	93.324	27.810	111.270	1.890
35	148.327	94.420	28.137	120.190	5.507
36	115.713	103.685	30.898	84.815	1.311
37	123.464	107.495	32.033	91.431	4.989

^a From $\Delta G_f = \Delta H_f - T\Delta S$.

Schemes 1 and 2. The computed thermodynamic energies and other physical parameters are given in Tables 1–7.

Both gas and aqueous phase calculated dipole moment values indicate bigger values for thione forms with all three methods (Tables 1 and 2) which might be an indication of stability of thione forms over thiol forms in general. A support to this last conclusion comes from the gas phase calculated

stabilities (Table 3). There exist two types of prototropic equilibria for 6-propyl-2-thiouracil molecule (Scheme 1) and these are annular and ring-chain tautomerisms.

The annular tautomerism exists in $2 \rightleftharpoons 4$ and $3 \rightleftharpoons 5$ equilibria and the obtained stabilities (RS) suggest the stability of molecule 4 (i.e. 1H form) over the molecule 2 (i.e. 3H form) with stability values of 25.105, 28.904

Table 2

Aqueous phase AM1, PM3 and MNDO calculated thermodynamic properties for the investigated molecules

Compound	ΔH_f (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)	$T\Delta S$ (kcal mol ⁻¹)	ΔG_f^a (kcal mol ⁻¹)	Dipole moment (D)
<i>AM1</i>					
1	-45.646	91.057	27.134	-72.781	2.015
2	-36.638	95.220	28.375	-65.013	14.138
3	-45.643	91.046	27.131	-72.774	9.565
4	-39.183	91.047	27.132	-66.315	13.585
5	-32.948	92.930	27.693	-60.641	11.961
6(7)	-30.408	93.372	27.824	-58.232	2.596
8	-22.452	98.659	29.400	-51.852	8.700
9	-15.208	102.896	30.663	-45.871	14.206
10	-31.649	100.968	30.088	-61.737	6.587
11	-20.077	100.523	29.955	-50.032	13.098
12	-28.328	103.053	30.709	-59.037	12.456
13	-26.126	104.318	31.086	-57.212	3.092
14	70.672	92.605	27.596	43.075	8.588
15	72.587	95.400	28.429	44.157	9.331
16	91.434	101.723	30.313	61.120	8.523
17	96.565	98.575	29.375	67.189	7.527
18	72.672	95.028	28.318	44.353	9.447
19	76.422	97.183	28.960	47.461	5.701
20	95.931	100.226	29.867	66.063	8.391
21	97.075	105.722	31.505	65.569	7.831
22	70.667	93.794	27.950	42.716	8.584
23	76.631	102.385	30.510	46.120	7.638
24	78.848	98.943	29.485	49.362	7.524
25	81.211	101.839	30.348	50.862	6.952
26	74.335	96.302	28.698	45.637	1.692
27	72.564	95.500	28.459	44.105	9.345
28	90.637	102.942	30.676	59.960	2.740
29	92.714	101.838	30.347	62.366	7.535
30	70.596	91.358	27.224	43.371	8.595
31	75.659	96.268	28.687	46.971	3.491
32	74.944	99.534	29.661	45.282	8.848
33	77.906	103.775	30.924	46.981	2.251
34	74.311	96.559	28.774	45.536	1.716
35	76.106	93.460	27.851	48.254	7.646
36	77.395	104.849	31.245	46.150	1.926
37	79.923	101.797	30.335	49.587	6.673
<i>PM3</i>					
1	-51.363	91.391	27.234	-78.597	10.581
2	-40.959	96.724	28.823	-69.782	15.484
3	-43.948	93.784	27.947	-71.895	5.154
4	-46.257	92.776	27.647	-73.904	14.813
5	-43.114	94.266	28.091	-71.205	11.326
6(7)	-39.777	94.569	28.181	-67.958	3.691
8	-37.584	98.185	29.259	-66.843	9.568
9	-27.634	103.756	30.919	-58.553	17.715
10	-44.731	103.269	30.774	-75.505	4.986
11	-25.889	102.458	30.532	-56.421	11.251
12	-42.781	102.000	30.396	-73.177	11.136
13	-49.412	103.594	30.871	-80.283	3.641
14	66.546	94.220	28.077	38.468	7.114
15	72.269	93.134	27.753	44.515	11.963
16	77.578	102.091	30.423	47.154	6.696
17	85.576	95.874	28.570	57.005	9.765
18	73.579	95.807	28.550	45.028	11.434
19	71.515	95.597	28.487	43.027	6.805
20	87.267	106.350	31.692	55.574	12.625
21	88.878	105.872	31.549	57.328	8.886
22	66.594	93.936	27.992	38.601	7.119
23	74.365	102.930	30.673	43.691	7.726

(continued on next page)

Table 2 (continued)

Compound	ΔH_f (kcal mol ⁻¹)	ΔS (cal mol ⁻¹ K ⁻¹)	$T\Delta S$ (kcal mol ⁻¹)	ΔG_f^a (kcal mol ⁻¹)	Dipole moment (D)
24	69.613	101.842	30.348	39.264	6.150
25	74.802	100.727	30.016	44.785	6.680
26	69.654	95.054	28.326	41.327	1.556
27	72.590	92.348	27.519	45.070	10.618
28	89.647	103.452	30.828	58.818	9.390
29	83.697	102.263	30.474	53.222	1.843
30	66.689	93.600	27.892	38.796	7.109
31	71.448	95.017	28.315	43.132	3.902
32	67.694	102.414	30.519	37.174	6.096
33	—	—	—	—	—
34	69.662	95.070	28.330	41.331	1.557
35	73.167	94.347	28.115	45.051	7.725
36	76.726	103.864	30.951	45.774	1.326
37	80.650	100.459	29.936	50.713	6.044
<i>MNDO</i>					
1	-45.277	91.412	27.240	-72.517	8.214
2	-43.493	95.473	28.450	-71.944	12.622
3	-45.928	93.138	27.755	-73.683	4.877
4	-49.046	91.592	27.294	-76.340	11.800
5	-42.507	93.999	28.011	-70.518	10.412
6(7)	-52.562	93.613	27.896	-80.458	3.082
8	-22.589	98.659	29.400	-51.989	6.757
9	-25.304	96.768	28.836	-54.140	14.83
10	-42.068	97.720	29.120	-71.188	5.414
11	-30.583	99.240	29.573	-60.156	14.535
12	-38.401	100.200	29.859	-68.260	10.065
13	-32.584	104.777	31.223	-63.807	4.230
14	70.394	93.744	27.935	42.458	7.189
15	68.963	92.451	27.550	41.412	8.349
16	94.977	103.004	30.695	64.281	5.632
17	94.431	102.119	30.431	63.999	6.875
18	71.918	96.426	28.734	43.183	9.042
19	64.903	94.747	28.234	36.668	7.185
20	89.929	101.078	30.121	59.807	9.165
21	84.061	102.369	30.505	53.555	5.415
22	70.403	93.994	28.010	42.392	7.188
23	65.052	103.610	30.875	34.176	8.196
24	74.937	101.675	30.299	44.637	5.769
25	68.534	101.968	30.386	38.147	7.371
26	61.359	93.983	28.006	33.352	2.148
27	68.965	92.687	27.620	41.344	8.349
28	94.599	104.153	31.037	63.561	7.347
29	83.850	104.288	31.077	52.772	1.800
30	70.361	93.920	27.988	42.372	7.189
31	62.789	94.247	28.085	34.703	2.871
32	78.113	103.464	30.832	472.807	6.006
33	65.644	100.518	29.954	35.689	1.206
34	61.362	94.002	28.012	33.349	2.151
35	64.162	93.876	27.975	36.186	8.193
36	64.528	105.517	31.444	33.083	1.135
37	62.230	102.361	30.503	31.726	6.951

^a From $\Delta G_f = \Delta H_f - T\Delta S$.

and 25.295 kcal mol⁻¹ with AM1, PM3 and MNDO methods, respectively. Similarly, RS values suggest the stability of molecule **3** (i.e. 3H form) over the molecule **5** (i.e. 1H form) with stability values of -16.562, -16.055 and -23.328 kcal mol⁻¹ with AM1, PM3 and MNDO methods. The calculation results of the fixed models of

molecules **2–5** for **9** ⇌ **11** and **10** ⇌ **12** equilibria found to support the above conclusion (Table 3).

The ring-chain tautomerism exist for **1** ⇌ **2**, **1** ⇌ **4**, **1** ⇌ **5**, **2** ⇌ **3**, **2** ⇌ **6(7)**, **3** ⇌ **6(7)**, **4** ⇌ **5**, **4** ⇌ **6(7)**, **5** ⇌ **6(7)** equilibria. The stability of molecule **1** over molecules **2–5** is confirmed by AM1 calculated RS values

Table 3
The gas phase computed relative stabilities, RS, of studied molecules

Process		RS ^a (kcal mol ⁻¹)		
Annular tautomers	Ring-chain tautomers	AM1	PM3	MNDO
<i>Main tautomers</i>				
–	1 ⇌ 2	– 35.319	– 37.450	– 24.859
–	1 ⇌ 3	– 4.997	6.974	6.667
–	1 ⇌ 4	– 10.214	– 8.546	0.436
–	1 ⇌ 5	– 21.559	– 9.081	– 16.641
–	2 ⇌ 3	30.322	44.424	31.526
2 ⇌ 4	–	25.105	28.904	25.295
–	2 ⇌ 6(7)	32.612	44.913	41.070
3 ⇌ 5	–	– 16.562	– 16.055	– 23.328
–	3 ⇌ 6(7)	2.290	0.489	9.544
–	4 ⇌ 5	– 11.345	– 0.535	– 17.097
–	4 ⇌ 6(7)	7.507	16.009	15.775
–	5 ⇌ 6(7)	18.852	16.544	32.872
<i>Fixed models</i>				
–	8 ⇌ 9	– 44.244	– 26.943	– 12.271
–	8 ⇌ 10	– 16.891	12.129	14.040
–	8 ⇌ 11	– 42.082	– 21.768	– 8.935
–	8 ⇌ 12	– 25.439	10.991	4.594
–	9 ⇌ 10	27.353	39.072	26.311
9 ⇌ 11	–	2.162	5.175	3.336
–	9 ⇌ 13	30.056	39.078	37.207
10 ⇌ 12	–	– 8.548	– 1.138	– 9.446
–	10 ⇌ 13	27.894	0.006	10.896
–	11 ⇌ 12	16.643	32.759	13.529
–	11 ⇌ 13	27.894	33.903	33.871
–	12 ⇌ 13	– 10.214	1.144	20.342

The minus sign indicates the stability of oxo and thione forms.

^a RS = ΔH_f (oxo, thione) – ΔH_f (hydroxy, mercapto).

Table 4
Aqueous phase AM1, PM3 and MNDO calculated pK_a values for the investigated molecules

Neutral base (B)	Conjugate acid (BH ⁺)	AM1		PM3		MNDO		Protonation
		$\delta\Delta G_{(\text{BH})}^{+ \text{ a}}$ (kcal mol ^{−1})	pK _a ^b	$\delta\Delta G_{(\text{BH})}^{+ \text{ a}}$ (kcal mol ^{−1})	pK _a ^b	$\delta\Delta G_{(\text{BH})}^{+ \text{ a}}$ (kcal mol ^{−1})	pK _a ^b	
<i>Main tautomers</i>								
1	14	−3.346	−2.454	5.925	4.345	−9.885	−7.249	thione
1	15	−4.428	−3.247	−0.122	−0.089	−8.839	−6.482	oxo
2	18	3.144	2.306	8.180	5.999	−10.037	−7.360	1N
2	19	0.036	0.026	10.181	7.466	−3.522	−2.583	thione
3	22	−2.98	−2.185	12.494	9.162	−10.985	−8.056	1N
3	23	−6.384	−4.682	7.404	5.429	−2.769	−2.031	oxo
4	26	0.558	0.409	7.759	5.690	−4.602	−3.375	thione
4	27	2.09	1.533	4.016	2.945	−12.594	−9.235	3N
5	30	8.498	6.232	12.989	9.525	−7.800	−5.720	3N
5	31	4.898	3.592	8.653	6.345	−0.131	−0.096	oxo
6(7)	34	8.742	6.411	13.701	10.047	−8.717	−6.392	1N
6(7)	35	6.024	4.418	9.981	7.319	−11.554	−8.473	3N
<i>Fixed models</i>								
8	16	−0.462	−0.339	8.993	6.595	−11.18	−8.199	Thione
8	17	−6.531	−4.789	−0.858	−0.629	−10.898	−7.992	Oxo
9	20	0.576	0.422	8.863	6.499	−8.857	−6.495	1N

(continued on next page)

Table 4 (continued)

Neutral base (B)	Conjugate acid (BH ⁺)	AM1		PM3		MNDO		Protonation
		$\delta\Delta G_{(\text{BH})}^+$ ^a (kcal mol ⁻¹)	pK _a ^b	$\delta\Delta G_{(\text{BH})}^+$ ^a (kcal mol ⁻¹)	pK _a ^b	$\delta\Delta G_{(\text{BH})}^+$ ^a (kcal mol ⁻¹)	pK _a ^b	
9	21	1.07	0.785	7.109	5.213	-2.605	-1.910	Thione
10	24	1.411	1.035	8.221	6.029	-10.735	-7.872	1N
10	25	-0.089	-0.065	2.700	1.980	-4.245	-3.113	oxo
11	28	2.518	1.846	7.751	5.684	-18.627	-13.660	thione
11	29	0.112	0.082	13.347	9.788	-7.838	-5.748	3N
12	32	8.191	6.007	12.639	9.268	-10.45	-7.663	3N
12	33	6.492	4.761	—	—	1.141	0.837	oxo
13	36	9.148	6.708	-3.067	-2.249	8.200	6.013	1N
13	37	5.711	4.188	-8.006	-5.871	9.557	7.008	3N

H₂O: $\Delta H_f = -68.49$ kcal mol⁻¹; $\Delta S = 45.09$ cal mol⁻¹ K⁻¹; $\Delta G_f = -81.93$ kcal mol⁻¹; for H₃O⁺: $\Delta H_f = 44.33$ kcal mol⁻¹; $\Delta S = 46.12$ cal mol⁻¹ K⁻¹; $\Delta G_f = 30.58$ kcal mol⁻¹ for AM1 calculation. H₂O: $\Delta H_f = -61.92$ kcal mol⁻¹; $\Delta S = 45.00$ cal mol⁻¹ K⁻¹; $\Delta G_f = -75.33$ kcal mol⁻¹; for H₃O⁺: $\Delta H_f = 61.37$ kcal mol⁻¹; $\Delta S = 45.99$ cal mol⁻¹ K⁻¹; $\Delta G_f = 47.66$ kcal mol⁻¹ for PM3 calculation. H₂O: $\Delta H_f = -69.30$ kcal mol⁻¹; $\Delta S = 48.66$ cal mol⁻¹ K⁻¹; $\Delta G_f = -83.81$ kcal mol⁻¹; for H₃O⁺: $\Delta H_f = 36.37$ kcal mol⁻¹; $\Delta S = 50.30$ cal mol⁻¹ K⁻¹; $\Delta G_f = 21.28$ kcal mol⁻¹ for MNDO calculation.

^a $\delta\Delta G(\text{BH}^+) = [\Delta G(\text{B}) + \Delta G(\text{H}_3\text{O}^+)] - [\Delta G(\text{BH}^+) + \Delta G(\text{H}_2\text{O})]$.

^b $\text{p}K_a = (\delta\Delta G_{(\text{BH}^+)})/(2.303RT)$.

Table 5

Gas phase AM1, MNDO and PM3 calculated proton affinities (PA; kcal mol⁻¹) for the investigated molecules

Neutral base (B)	Conjugate acid (BH ⁺)	Proton affinities (PA; kcal mol ⁻¹)		
		AM1	PM3	MNDO
<i>Main tautomers</i>				
1	14	194.315	187.943	195.724
1	15	206.423	175.253	207.832
2	18	225.010	209.828	228.550
2	19	235.289	226.142	238.829
3	22	195.811	177.699	185.249
3	23	182.252	176.785	171.690
4	26	214.560	107.804	214.301
4	27	216.637	190.025	216.378
5	30	211.753	202.126	200.684
5	31	201.038	205.789	189.969
6(7)	34	203.617	188.582	194.856
6(7)	35	194.696	179.335	185.935
<i>Fixed models</i>				
8	16	225.366	218.356	218.331
8	17	220.734	219.246	213.699
9	20	223.253	209.344	222.615
9	21	226.787	214.142	226.149
10	24	234.046	223.175	221.689
10	25	231.050	233.304	218.693
11	28	252.358	245.143	248.707
11	29	242.430	227.317	238.779
12	32	212.317	202.583	192.550
12	33	214.880	216.000	195.113
13	36	238.134	230.068	228.474
13	37	232.943	222.317	223.283

$\text{PA} = 367.2 + \Delta H_f(\text{B}) - \Delta H_f(\text{BH}^+)$. $\delta\Delta G = \Delta G(\text{product}) - \Delta G(\text{reactant})$. $K_T = e^{-(\delta\Delta G/RT)}$. $\text{p}K_T = -\log K_T$. $\text{p}K_T = \text{p}K_a(\text{enol model}) - \text{p}K_a(\text{keto} \times \text{model})$ Charton's equations [9]. The minus sign indicate a shift to right side of equilibrium.

Table 6
The aqueous phase calculated tautomeric equilibrium constants K_T of studied molecules

Process		AM1				PM3		MNDO		
Annular tautomer	Ring-chain tautomer	$\delta\Delta G^a$ (kcal mol ⁻¹)	K_T^b	pK_T^c	$\delta\Delta G^a$ (kcal mol ⁻¹)	K_T^b	pK_T^c	$\delta\Delta G^a$ (kcal mol ⁻¹)	K_T^b	pK_T^c
<i>Main tautomers</i>										
–	1 ⇌ 2	7.768	2.001×10^{-6}	5.698	8.815	3.414×10^{-7}	6.466	0.573	3.798×10^{-1}	0.420
–	1 ⇌ 3	0.007	9.882×10^{-1}	0.005	6.702	1.211×10^{-5}	4.916	– 1.166	0.716×10^1	– 0.855
–	1 ⇌ 4	6.466	1.805×10^{-5}	4.743	4.693	3.607×10^{-4}	3.442	– 3.823	0.637×10^3	– 2.804
–	1 ⇌ 5	12.14	1.241×10^{-9}	8.905	7.392	3.777×10^{-6}	5.422	– 1.739	1.886×10^1	– 1.275
–	2 ⇌ 3	– 7.761	4.937×10^5	– 5.693	– 2.113	3.549×10^1	– 1.550	– 1.739	1.886×10^1	– 1.275
2 ⇌ 4	–	– 1.302	12.717	– 1.104	– 4.122	3.136×10^3	– 3.496	– 4.396	5.355×10^3	– 3.728
–	2 ⇌ 6(7)	6.781	1.060×10^{-5}	4.974	1.824	4.590×10^{-2}	1.338	– 8.514	1.760×10^6	– 6.245
3 ⇌ 5	–	12.133	5.109×10^{-11}	10.291	0.690	2.598×10^{-1}	0.585	3.165	2.060×10^{-3}	2.684
–	3 ⇌ 6(7)	14.542	2.147×10^{-11}	10.668	3.937	1.293×10^{-3}	2.888	– 6.775	0.933×10^5	– 4.970
–	4 ⇌ 5	5.674	6.878×10^{-5}	4.162	2.699	1.047×10^{-2}	1.980	5.822	5.357×10^{-5}	4.271
–	4 ⇌ 6(7)	8.083	1.175×10^{-6}	5.929	5.946	4.344×10^{-5}	4.362	– 4.118	0.104×10^4	– 3.020
–	5 ⇌ 6(7)	2.009	3.358×10^{-2}	1.478	3.247	4.149×10^{-3}	2.382	– 9.94	1.959×10^7	– 7.292
			Protonation type	pK_T^d	Protonation type	pK_T^d	Protonation type	pK_T^d		
<i>Fixed models</i>										
	8 ⇌ 9	20 ⇌ 17	1N	5.211	1N	7.128	1N	1.497		
–		21 ⇌ 16	Thione	1.124	Thione	– 1.382	Thione	6.289		
	8 ⇌ 10	24 ⇌ 16	1N	1.374	Oxo	– 0.566	1N	0.327		
–		25 ⇌ 16	Oxo	0.373	Oxo	– 4.615	1N	5.086		
	8 ⇌ 11	28 ⇌ 17	Thione	6.635	Thione	6.313	Thione	– 5.668		
–		29 ⇌ 16	3N	0.421	3N	3.193	3N	13.947		
	8 ⇌ 12	32 ⇌ 16	3N	6.346	3N	2.673	3N	0.536		
		33 ⇌ 16	Oxo	5.100	Oxo	– 6.595	Oxo	9.036		
	9 ⇌ 10	20 ⇌ 25	1N	0.487	1N	4.519	Oxo	– 3.382		
–		20 ⇌ 24	1N	– 0.613	1N	0.470	1N	1.377		
9 ⇌ 11	–	28 ⇌ 21	Thione	1.061	Thione	0.471	Thione	– 11.750		
		29 ⇌ 20	3N	– 0.34	1N	3.289	3N	0.747		
	9 ⇌ 13	36 ⇌ 20	1N	6.286	1N	– 8.748	1N	12.508		
		37 ⇌ 20	3N	3.766	1N	– 12.370	3N	13.503		
	10 ⇌ 12	32 ⇌ 24	3N	4.972	1N	3.239	3N	0.209		
		33 ⇌ 25	Oxo	4.826	Oxo	– 1.980	Oxo	3.950		
	10 ⇌ 13	36 ⇌ 24	1N	7.737	1N	– 8.278	1N	13.885		
		37 ⇌ 24	3N	4.300	1N	– 11.900	3N	14.880		
–	11 ⇌ 12	29 ⇌ 32	Oxo	– 5.925	3N	0.520	3N	1.825		
		29 ⇌ 33	Oxo	– 4.679	3N	9.788	3N	– 6.675		
–	11 ⇌ 13	36 ⇌ 29	1N	6.626	3N	– 12.037	1N	11.761		
		37 ⇌ 29	3N	4.106	3N	– 15.659	3N	12.756		
–	12 ⇌ 13	36 ⇌ 32	1N	0.701	3N	– 11.517	1N	13.676		
		37 ⇌ 32	3N	– 1.819	3N	– 15.139	3N	14.671		

^a $\delta\Delta G = \Delta G(\text{product}) - \Delta G(\text{reactant})$.

^b $K_T = e^{-(\delta\Delta G/RT)}$.

^c $pK_T = -\log K_T$.

^d $pK_T = pK_a(\text{enol model}) - pK_a(\text{keto model})$ Charton's equation [9]. The minus sign indicate a shift to right side of equilibrium.

Table 7

Gas and aqueous phase AM1, PM3 and MNDO calculated q (charges on atoms) for the investigated molecules

Process			q (charges on heteroatoms) gas phase			q (charges on heteroatoms) aqueous phase		
Neutral base (B)	Conjugate acid (BH ⁺)	Protonation	AM1	PM3	MNDO	AM1	PM3	MNDO
<i>Main tautomers</i>								
1	14	Thione	0.357	0.296	0.321	0.358	0.207	0.257
1	15	Oxo	–	–0.141	–0.180	–0.218	–0.203	–0.211
2	18	1N	0.228	0.279	0.264	0.168	0.535	0.235
2	19	Thione	0.356	0.275	0.308	0.247	0.133	0.204
3	22	1N	–0.197	0.353	–0.228	–0.186	0.466	–0.215
3	23	Oxo	–0.180	–0.147	–0.184	–0.247	–0.230	–0.233
4	26	Thione	0.345	0.277	0.307	0.265	0.154	–0.219
4	27	3N	–	0.186	–0.318	–0.202	0.474	–0.268
5	30	3N	–0.293	0.129	–0.324	–0.259	0.302	–0.292
5	31	Oxo	–0.170	–0.145	–0.163	–0.249	–0.234	–0.232
6(7)	34	1N	–0.189	0.365	–0.227	–0.158	0.509	–0.196
6(7)	35	3N	–0.233	0.297	–0.269	–0.188	0.472	–0.227
<i>Fixed models</i>								
8	16	Thione	0.348	0.263	0.296	0.393	0.205	0.219
8	17	Oxo	–0.182	–0.152	–0.185	–0.217	–0.197	–0.213
9	20	1N	–0.213	0.258	–0.273	–0.148	0.516	–0.240
9	21	Thione	0.447	0.326	0.357	0.305	0.145	0.209
10	24	1N	–0.201	0.348	–0.227	–0.169	0.516	–0.189
10	25	Oxo	–0.188	–0.157	–0.192	–0.246	–0.223	–0.234
11	28	Thione	0.334	0.264	0.292	0.291	0.162	0.217
11	29	3N	–0.268	0.208	–0.316	–0.201	0.462	–0.270
12	32	3N	–0.292	0.121	0.328	–0.256	0.290	–0.289
12	33	Oxo	–0.178	–0.153	–0.169	–0.252	–0.233	–0.230
13	36	1N	–0.194	0.361	–0.231	–0.156	0.526	–0.190
13	37	3N	–0.227	0.313	–0.269	–0.183	0.483	–0.269

(i.e. $RS < 0$). Whereas, PM3 calculated RS values do not indicate the stability of molecule **1** (i.e. thione–oxo form) over molecule **3** (i.e. thiol–oxo form) ($RS > 0$) and MNDO RS values do not indicate stability of molecule **1** over molecules **3** and **4** (i.e. thione–enol form) ($RS > 0$). Stability of molecule **6(7)** (i.e. thiol–enol form) over molecules **3**, **4** and **5** (i.e. oxo–thiol form) were confirmed by three methods (i.e. $RS > 0$). Similarly, the stability of

molecule **4** over molecule **5** confirmed by all three methods ($RS < 0$). The calculated RS values for the fixed models are confirmative the above conclusion (Table 3).

3.2. Tautomeric equilibrium constants and protonation

Possible protonation patterns for the studied molecules are shown in Schemes 1 and 2. Aqueous phase calculated

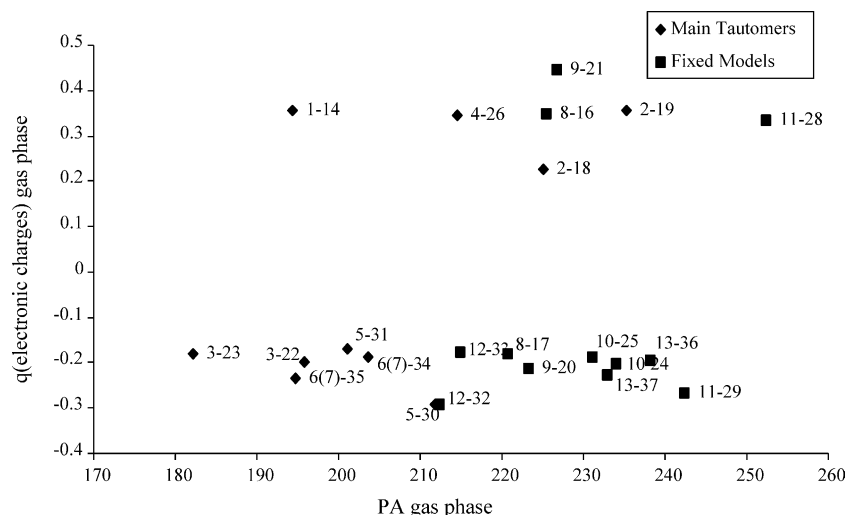


Fig. 1. The correlation diagram of proton affinities (PA) vs. to AM1 gas phase calculated electronic charges.

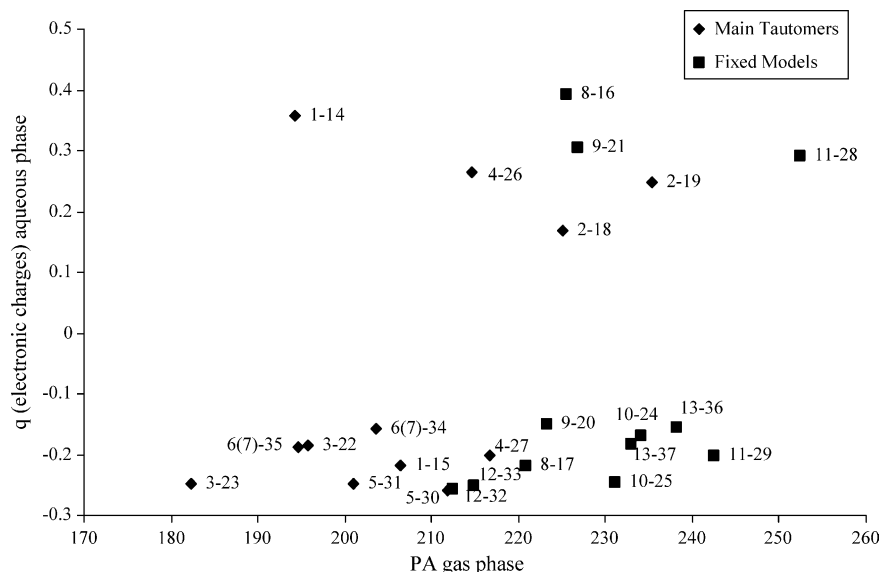


Fig. 2. The correlation diagram of proton affinities (PA) vs. to AM1 aqueous phase calculated electronic charges.

acidity constants pK_a and gas phase calculated proton affinities (PA) were given in Tables 4 and 5, respectively. Since, the pK_a value of thiouracil was reported as 7.5. It seems that the closest value to the experimental value comes from PM3 calculation for $2 \rightleftharpoons 19$ (i.e. 7.467) protonation which indicates thione protonation. Another PM3 obtain result that fits to the experimental result is 7.32 for $6(7) \rightleftharpoons 35$. A support to the preference of $2 \rightleftharpoons 19$ comes from PA values of gas phase calculations. The PM3 calculated PA value for $2 \rightleftharpoons 19$ protonation value is 226.142 and for protonation is 179.335. Therefore, we can easily conclude that $2 \rightleftharpoons 19$ protonation pattern is a suitable one. The AM1 and MNDO gas phase PA values also support above conclusion (Table 5).

It seems that the protonation mechanism of molecule 1 (i.e. 2-thione-4-oxo form) is similar to protonation mechanism of its model molecule 8 (i.e. 1,3-dimethyl-2-thione-4-oxo form) and it is a thione protonation (Figs. 1 and 2). Similarly, protonation pattern of molecule 2 is similar to the protonation pattern of its model molecule 9 (i.e. 2-thione-3-methyl-4-methoxy form) and it is a thione protonation (i.e. $9 \rightleftharpoons 21$ equilibrium). The protonation mechanism of molecule 4 (i.e. 1H-2-thione-4-hydroxy form) is similar to the molecule 11 (i.e. 1methyl-2-thione-4-hydroxy form) and it is a thione protonation (i.e. $11 \rightleftharpoons 28$ equilibrium).

Similar conclusion can be driven for the other molecules by comparing the PA with the model molecules and (their changes to predict whether its oxo or aza protonation.

Therefore, we can say that the possibility of oxo protonation for molecule 3 (i.e. 3H-2-mercapto-4-oxo form) is bigger than that of aza protonation. Similarly, oxo protonation for molecule 5 (i.e. 1H-2-mercapto-4-oxo form) is favored over aza protonation. For molecule 6(7) (i.e. 2-mercapto-4-hydroxy form) the 1N protonation preferred over the 2N protonation.

With the exception of $2 \rightleftharpoons 4$ equilibrium, all aqueous phase calculated tautomeric equilibrium constant values indicate the preference of 3H-forms over the 1H-forms (Tables 6 and 7) as the RS values has indicated.

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