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Semiempirical and *Ab Initio* Calculations of Tautomerism in 2,3-Dihydroxypyrazine

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Semiempirical (AM1 and PM3) and *ab initio* (MP2/6-31 + G*//HF/6-31 + G*) calculations on the relative stabilities of different tautomers of 2,3-dihydroxypyrazine show that this species exists not only in solution but also in the gas phase predominantly as a dioxo tautomer.

Owing to its significance in many chemical and biological reactions, the tautomerism of heterocyclic compounds continues to be a matter of intense experimental and theoretical research.[3] Solvent effects often play an important role in organic chemistry and many chemical equilibria may be substantially modified by a change of the molecular environment.[23] Most theoretical and experimental studies have concentrated on the tautomerism in 2-hydroxypyridine, uracil, thymine and cytosine.[8–13] A theoretical study[28] at the AM1 and 3-21G levels on the tautomerism of hydroxypyrazine and mercaptopyrazine has shown that hydroxypyrazine and its oxo form are present in almost equal proportions while the thiol is of greater concentration than the thione. To our knowledge there previously have been neither theoretical nor experimental investigations involving 2,3-dihydroxypyrazine. A similar compound, 2,3-dioxopiperazine, has been studied both experimentally and theoretically and it was found that the dioxo form is the most stable species in the solid state.[29] In this regard, it appeared interesting to study tautomerism in 2,3-dihydroxypyrazine. This compound can exist in three tautomeric forms, two of which exist in more than one conformer (Fig. 1). Our aim in this study is to use semiempirical (AM1[1] and PM3[2]) and *ab initio* calculations to predict the stabilities of the 2-hydroxy-3-oxo and 2,3-dioxo tautomers of 2,3-dihydroxypyrazine.

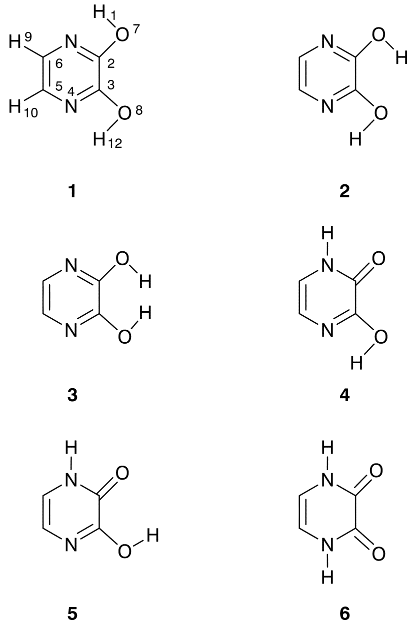

Fig. 1 Optimized conformations of 2,3-dihydroxypyrazine

Table 4 Absolute errors in relative energies (kcal mol^{-1}), dipole moments (Debye), and ionization potentials (eV) obtained from AM1 and PM3 methods in the gas phase (w.r.t. 6-31 + G*)

	RE (kcal mol^{-1})		DM (Debye)		IP (eV)	
Structure	AM1	PM3	AM1	PM3	AM1	PM3
1	0.0	0.0	0.088	0.172	0.278	0.402
2	0.18	0.74	0.529	0.830	0.331	0.412
3	4.52	9.81	0.961	0.390	0.408	0.476
4	1.01	2.28	0.594	0.923	0.129	0.129
5	3.21	3.80	0.384	0.980	0.128	0.096
6	1.28	4.00	1.206	1.981	0.164	0.152
Average errors	1.77	3.44	0.627	0.879	0.240	0.278

The geometries of the investigated tautomers were optimized at the AM1 and PM3 levels in the gas phase and in aqueous solutions without any symmetry constraints. Solvent effects in aqueous solution are calculated using the Self-Consistent Reaction Field (SCRF) method[24] available in the VAMP5.5 program.[33] The optimizations of the molecular geometries were carried out within C_{2v} (**1**, **3**, **6**) and C_s (**2**, **4**, **5**) symmetries using the Hartree–Fock method[37] with the 6-31 + G* basis set.[38] The effect of electron correlation on the calculated relative energies was investigated by performing Moeller–Plesset calculations[40] truncated at second order (MP2) with the 6-31 + G* basis set.

Relative energies for the structures displayed in Fig. 1 are listed in Table 2. A plot of relative energies at different theoretical levels in the gas phase and in aqueous solution is shown in Fig. 2. Compared to HF/6-31 + G*, the average errors in calculating different properties using AM1 and PM3 procedures are given in Table 4.

All calculated forms of **1**, **2**, **4**, **5**, **6** (Fig. 1) are minima on the potential energy surface of 2,3-dihydroxypyrazine, while structure **3** is a saddle point of second order and is, therefore, removed from further discussion. The energy

Table 2 Relative energies (kcal mol^{-1}) for the investigated molecule at semiempirical and *ab initio* levels

	Gas phase		Aqueous solution			
Structure	AM1	PM3	AM1	PM3	6-31 + G*	MP2/6-31 + G*//HF/6-31 + G*
1	0.0	0.0	0.0	0.0	0.0	0.0
2	1.19	0.63	–1.12	–1.15	1.37	1.02
3	10.63	5.34	4.84	0.10	15.15	14.16
4	–0.65	0.62	–4.92	–3.45	–1.66	0.86
5	–0.30	0.29	–4.98	–3.69	–3.51	–1.49
6	–7.24	–4.52	–13.31	–10.12	–8.52	–3.82

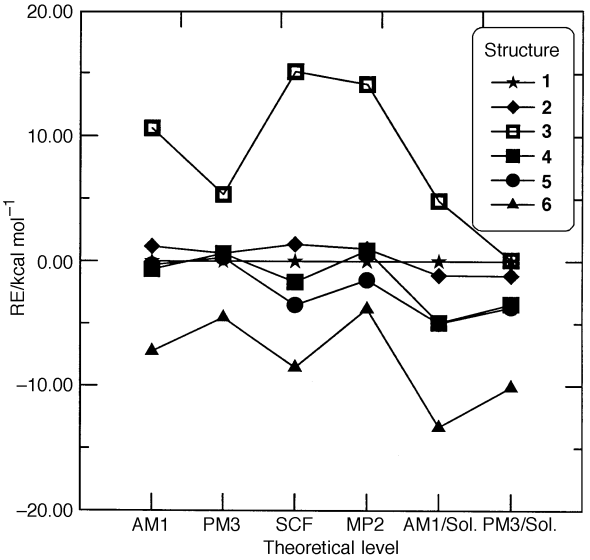

Fig. 2 Plot of relative energies versus theoretical levels. All energies are relative to that of **1**. SCF represents HF/6-31 + G* and MP2 represents MP2/6-31 + G*//HF/6-31 + G*

barrier required for transformation of the dihydroxy forms **1** to **2** amounts to 3 kcal mol^{-1} while that for conversion of the dihydroxy **1** to the hydroxyoxo **4** tautomer is ≈43 kcal mol^{-1}, at the AM1 level in the gas and liquid phases. Inspection of Fig. 2 shows that the dioxo tautomer **6** is the most stable species at all the theoretical levels while the relative stabilities of the hydroxyoxo forms **4**, **5** depend on the calculational level, as these are close enough energetically.

In polar solvents, the tautomeric equilibrium of 2,3-dihydroxypyrazine is shifted in favor of the more polar oxo forms.[22,41] The dioxo form **6** was found to be the most stable structure, with the stability in solution increased by ≈6 kcal mol^{-1} compared to that found in the gas phase. In solvents of high relative permittivity, the stability of the hydroxyoxo forms **4**, **5** also increases, which indicates that 2,3-dihydroxypyrazine is present in solution predominantly as hydroxyoxo and dioxo tautomers. These results may explain the predominance of the similar compound, 2,3-dioxopiperazine, in the solid state.[29] The α-diketone is thus stable in the gas and condensed phases and can undergo condensation and other reactions at the carbonyl groups.

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Techniques used: Semiempirical (AM1 and PM3), *ab initio* and self-consistent reaction field theory calculations.

References: 43

Table 1: Heats of formation (AM1 and PM3, in kcal mol^{-1}) and total energies (*ab initio*, in a.u.) for the investigated species

Table 3: Dipole moments (Debye) and ionization potentials (eV) for the investigated species in the gas phase

Table 5: Optimized geometries for different structures in the gas phase

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