Predictions of Tautomeric Equilibria in 2-Hydroxypyridine and Pyridine-2-thiol: Correlation Effects and Possible Discrepancies with Experiment

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Calculations of the free energy differences between the tautomer pairs, 2-hydroxypyridine/2-pyridone, and pyridine-2-thiol/pyridine-2-thione, are reported using large (TZV2P) basis sets and electron correlation at the QCISD(T) level. For the hydroxy/oxo system the predicted energy difference (2.9 kJ mol^{-1}) is the same as the experimental value (2.9 ± 0.5 kJ mol^{-1}). For the thiol/thione system, the predicted energy difference (15.2 kJ mol^{-1}) is somewhat larger than the experimental value (9.9 ± 0.5 kJ mol^{-1}). The importance of correlation energy contributions beyond second order is highlighted.

Prototropic tautomerism of heterocyclic molecules has been studied extensively, particularly in the condensed phase. An accurate prediction of the relative energetics of the tautomers in the gas phase is a prerequisite for the development and assessment of models capable of the accurate prediction of condensed phase properties. Although it is not uncommon for more than one tautomer to be in sufficient abundance in solution for relative populations, and hence free energies, to be measured, in the gas phase it is usual for only one tautomer to be present in detectable concentrations. A notable exception is the 2-hydroxypyridine/2(1*H*)-pyridone system, where both tautomers can be observed in the gas phase at normal temperatures. For this reason this system has been extensively studied theoretically by treatments ranging from semiempirical MO methods[1,2] to *ab initio* calculations including extensive treatments of electron correlation.[3-7]

A variety of experimental gas phase measurements, including UV and IR spectroscopy,[8-10] X-ray[11] and UV[12] photoelectron spectroscopy all lead to the conclusion that the free energy difference between the hydroxy form (**1**) and the oxo form (**2**) is 2–3 kJ mol^{-1} in favour of the hydroxy form. An IR study[13] in inert gas matrices leads to an energy difference in agreement with this value, and for the closely related system, pyridine-2-thiol (**3**)/pyridine-2-thione (**4**),[14] predicts a free energy difference of 9.9 ± 0.5 kJ mol^{-1} in favour of the thiol.

A number of calculations have been reported[3-7] which predict the energetics of the hydroxypyridine/pyridone system. It is generally agreed that geometry optimisation at an *ab initio* level using at least a double zeta basis is required and that a basis that includes polarisation functions is needed for accurate energetics. Calculations have been reported by a number of authors using this approach at the SCF level and all predict the hydroxy form to be preferred by 3–6 kJ mol^{-1}. Zero point effects calculated at the SCF/6-31G** level[13] favour the hydroxy form by 0.7 kJ mol^{-1} and lead to a predicted energy difference close to the experimental range. However, when correlation effects are included, the situation is less clear. When the much used Møller–Plesset perturbation theory,[15] to second order (MP2), is applied to the calculation of the correlation energy,[3,16] substantial preferential stabilisation (*ca.* 6 kJ mol^{-1}) of the hydroxy form is predicted leading to an overall energy difference between the tautomers of 10 kJ mol^{-1}, a value significantly greater than the experimental value. This result is in agreement with a calculation of the second order correlation energy correction by Adamowicz.[5] Higher order contributions to the correlation energy estimated by Møller–Plesset perturbation theory (MP3, MP4) preferentially stabilise the pyridone form,[3] so that the resulting best estimate of the energy difference between the tautomers (4 kJ mol^{-1}) is in excellent agreement with the experimental data. However, there remains some doubt as to the convergence of the perturbation expansion. A configuration interaction calculation,[4] including single and double excitations (CISD) leads to a conclusion similar to that found in the Møller–Plesset calculations, namely that the hydroxypyridine is more stable than the pyridone by 4 kJ mol^{-1}. Contrary conclusions have been reached by Adamowicz[5] who used the coupled cluster method with single, double and triple excitations, to estimate correlation effects, and predicts that at 0 K, the total energy difference is 14.6 kJ mol^{-1} in favour of the hydroxy form. This is close to the MP2 value and suggests that corrections of order higher than two, have little effect on the energy difference. However, for computational reasons, Adamowicz used a scaling method to obtain the higher order correlation energy corrections. It is clearly important to establish whether a true discrepancy between theory and experiment exists in this case.

In view of his finding that higher order terms are small, Adamowicz and co-workers have studied tautomerism in diazinones and diazinethiones,[17] with correlation being estimated at second order [SCF + MBPT(2)]. They find that the trend is for this treatment to overestimate significantly the stability of the thiol form. For example, for the pyridine-2-thione/pyridine-2-thiol system, the experimental[14] energy difference is 9.9 ± 0.5 kJ mol^{-1} in favour of the thiol, whilst the theoretical estimate[14] is 27.6 kJ mol^{-1}. There is thus some doubt as to the predictive value of calculations including correlation effects to second order. In this paper we present new calculations on both the 2-hydroxypyridine/2-pyridone and pyridine-2-thione/pyridine-2-thiol systems in an attempt to resolve these discrepancies.

Computational Details

Geometry optimisation of the four molecules was carried out at the SCF level using a 6-31G** basis.[18] SCF calculations at these geometries were carried out using two different basis sets. The first was a DZP[19] basis having polarisation functions with exponents of 0.85, 0.8, 0.75, 0.532 and 0.75 for oxygen, nitrogen, carbon, sulfur and hydrogen respectively. A larger TZV2P basis[20] was also employed, in an attempt to obtain energies close to the Hartree–Fock limit. The zero point energy was estimated using harmonic frequencies calculated using a

Table 1 Energies (a.u.) of tautomers **1–4**.[a] Relative energies (kJ mol^{-1}) in parentheses

	2-Pyridone (**1**)	2-Hydroxypyridine (**2**)	Pyridine-2-thione (**4**)	Pyridine-2-thiol (**3**)
DZP(SCF)	−321.629 99 (0)	−321.632 61 (−6.9)	−644.243 09 (0)	−644.245 39 (−6.0)
TZV2P(SCF)	−321.678 77 (0)	−321.680 96 (−5.8)	−644.314 39 (0)	−644.315 14 (−2.0)
DZP[QCISD(T)]	−322.670 61 (0)	−322.672 02 (−3.7)	−645.252 16 (0)	−645.255 09 (−7.7)
ZPE	(0)	(−0.7)[b]		(−10.8)
Best estimate[c]	(0)	(−3.3)		(−14.5)
G[d]	(0)	(−2.9)		(−15.2)

[a] All at 6-31G**(SCF) geometry. [b] Ref. 13. [c] TZV2P(SCF) value, corrected by correlation energy at DZP[QCISD(T)] level and ZPE. [d] T = 298 K.

6-31G** basis and using the traditional scaling factor of 0.9. These have previously been reported[13] for molecules **1** and **2**. We have carried out calculation of the frequencies for the sulfur-containing molecules (**3** and **4**). All SCF calculations were carried out using the parallel version of the program GAMESS[21] on the INTEL iPSC/860 at the SERC, Daresbury Laboratory.

The correlation energy of the four molecules was estimated beyond second order [MP2 or MBPT(2)]. To include higher orders of electron excitation in a size-consistent manner, we have employed the quadratic configuration interaction method with singles and doubles, including a perturbation correction for triple excitations [QCISD(T)],[22] as implemented in GAUSSIAN 90.[23]

For computational feasibility the correlated wavefunction calculations were carried out using the DZP basis, omitting the filled core orbitals and the corresponding virtual orbitals, from the expansion. The correlation energy difference between the two tautomers at the DZP[QCISD(T)] level was combined with the SCF energy differences at the TZV2P//6-31G** level, and the zero point energies at the 6-31G**//6-31G** level, to yield the best estimate of the relative energies of the tautomers given in Table 1. Finally, the thermodynamic free energy differences at 298 K were estimated using molecular properties calculated at the 6-31G**//6-31G** level.

Results

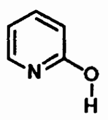
The computational results are summarised in Table 1. We consider first the 2-hydroxypyridine/2-pyridone system at the SCF level. There is a slight reduction (1 kJ mol^{-1}) in the predicted energy difference on expansion of the basis from DZP to TZV2P. The zero point energy difference at the 6-31G**//6-31G** level favours the hydroxy form, but the calculated value (0.7 kJ mol^{-1}), is less than that at the 3-21G level[7] (2.7 kJ mol^{-1}). The correlation energy, calculated at the QCISD(T) level favours the pyridone form (by 3.2 kJ mol^{-1}), so that the best estimate for the energy difference at 0 K is 3.3 kJ mol^{-1} in favour of the hydroxypyridine which leads to a ΔG_{298} value of 2.9 kJ mol^{-1}. This is in excellent agreement with the experimental values in the range 2.9 ± 0.5 kJ mol^{-1}.

Turning to the thione/thiol system, previous calculations[14] have shown that the SCF energy difference is strongly basis set dependent, being 32.4 kJ mol^{-1}, in favour of the thione with a 3-21G* basis and 5.5 kJ mol^{-1} in favour of the thiol using a DZP basis. Our DZP value (6.0 kJ mol^{-1}) is close to the previous value. However, on expanding the basis (TZV2P), the difference is reduced to 2.0 kJ mol^{-1}. Correlation effects favour the thiol, in contrast to the finding for **1** and **2**. The zero point energy difference (10.8 kJ mol^{-1}) is again in favour of the thiol, and is close to the 3-21G* value (10.9 kJ mol^{-1}). The best estimate of the thione/thiol energy difference at 0 K is thus 14.5 kJ mol^{-1} in favour of the thiol, and a corresponding ΔG_{298} value of 15.2 kJ mol^{-1}. This is rather larger than the experimental estimate of 9.9 ± 0.5 kJ mol^{-1}, but is in considerably better agreement than the value of 27.6 kJ mol^{-1} obtained at the SCF + MBPT(2) level.

Discussion

For both systems studied herein, the hydroxy or thiol form is predicted to be the most stable at the SCF level. Correlation effects calculated at the QCISD(T) level affect the relative energies of the tautomers in the two systems in different ways. Thus, for the hydroxypyridine/pyridone system, the electron correlation is predicted to favour the oxo form and yields an energy difference that is essentially in exact agreement with experiment and with previous values obtained using MP4 and CISD treatments. These calculations are thus at variance with the conclusion of Adamowicz[5] that higher order corrections (in MBPT) from three to infinite, have little effect on the final estimate of relative tautomer energies. Clearly, the scaling procedure used by Adamowicz requires further investigation.

The case of the thiol/thione system is more computationally demanding. Here there is a significant change in the energy difference on expanding the basis from double to triple zeta. Hence, we cannot be so confident about our correlation energy contributions calculated at the DZP level. Furthermore, we note that in our calculation, the largest contribution to the energy difference arises from zero point effects. Here the correlation effects are predicted to stabilize preferentially the thiol form (**3**) compared to (**4**), in contrast to the oxo/hydroxy case (**2**, **1**). Calculations by Lapinski *et al.*[17] yield a greater differential stabilisation of the thiol (**3**), compared to that of the hydroxy (**1**) at MBPT(2). Thus, our calculations suggest that for *both* pairs of tautomers, higher order corrections beyond MBPT(2) favour the oxo and thione tautomers, and the size of the second order correction determines which tautomer of each pair is preferentially stabilized by correlation effects.



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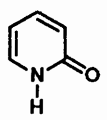

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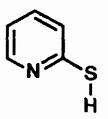

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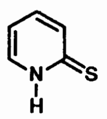

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Our final energy difference between **3** and **4**, 15.2 kJ mol^{-1} is still somewhat larger than the experimental estimate (9.9 kJ mol^{-1}), although it is a considerable improvement over the value of 27.6 kJ mol^{-1} obtained when correlation effects up to MBPT(2) were included. Indeed, our calculations suggest that the systematic deviations between the experimental and calculated free energy differences for a series of hydroxy/oxo and thiol/thione tautomers[17] may be ascribed to the lack of higher order contributions to the correlation energy.

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