Accurate Calculations of the Oxo–Hydroxy Tautomers of Uracil

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The geometric structures of the three lowest-energy tautomers of uracil have been calculated at the 6-31G** SCF level. Their relative energies have been calculated with the inclusion of correlation and zero-point energy effects. The dioxo-form is predicted to be the most stable, with the 2-hydroxy-4-oxo and 2-oxo-4-hydroxy forms being higher in energy by 46 and 52 kJ mol^{-1}, respectively.

The accurate prediction of the relative energies of the tautomers of the pyrimidine bases is of continuing interest, particularly in view of the possibility that the occurrence of the rare tautomeric forms leads to mechanisms of spontaneous mutations.[1] In the case of uracil, the 2-oxo-4-oxo form is agreed to be the most stable tautomer both theoretically[2] and experimentally.[3] However, there is current interest in the relative energies of the less stable, oxo–hydroxy, tautomers. The standard semiempirical molecular-orbital methods have been widely used to study the relative energies of the tautomers of uracil and other pyrimidine bases.[4] However, the results are generally unreliable and *ab initio* methods are needed to yield meaningful results. We have previously reported geometry optimization studies at the split-valence, 3-21G basis set level, of uracil and other pyrimidine bases to provide predictions of the relative stabilities of their tautomers.[2] Recently, Kwiatkowski *et al.*[5] have used structures calculated at this level, to assess the contributions from electron correlation to the relative stabilities of the tautomers of uracil and have concluded that it is unimportant. In this paper we use a higher level of calculation than has been used previously, to optimize the geometric structures of a number of tautomers of uracil, followed by calculations of the contribution of both electron correlation and zero-point vibrational energies to the energies of these tautomers. Such an accurate prediction of tautomer energetics which refer to isolated, gas phase molecules, is clearly a prerequisite for studying solvation effects.

Experimental

In this paper we study the dioxo form of uracil (**U1**) and the 2-hydroxy-4-oxo (**U2**) and 2-oxo-4-hydroxy (**U3**) forms of uracil. [We use the notation (**U1**), (**U2**), and (**U3**) introduced in our previous study of these species[2]]. These structures are shown in the Figure. The structures of these three molecules were optimized at the SCF level in a 6-31G** basis,[6] using the program GAMESS.[7] This split-valence basis includes polarization functions on all atoms, and is generally considered more reliable than basis sets without polarization functions. In our previous study of the tautomers of cytosine and guanine[8] we found that it was necessary to include correlation effects to predict accurately the relative energies of these tautomers. We here estimate the effect of electron correlation on the energies of the three tautomers studied [(**U1**), (**U2**), and (**U3**)] by the use of the second-order Moller–Plesset method[9] (MP2), calculated at the geometry optimized at the SCF 6-31G** level. Zero-point energies (ZPE) were calculated from the harmonic vibrational frequencies calculated at the SCF 6-31G** level. These calculations were carried out using the program CADPAC.[10] All calculations reported in this paper were carried out on the CRAY-XMP/48 at the Rutherford Appleton Laboratory.

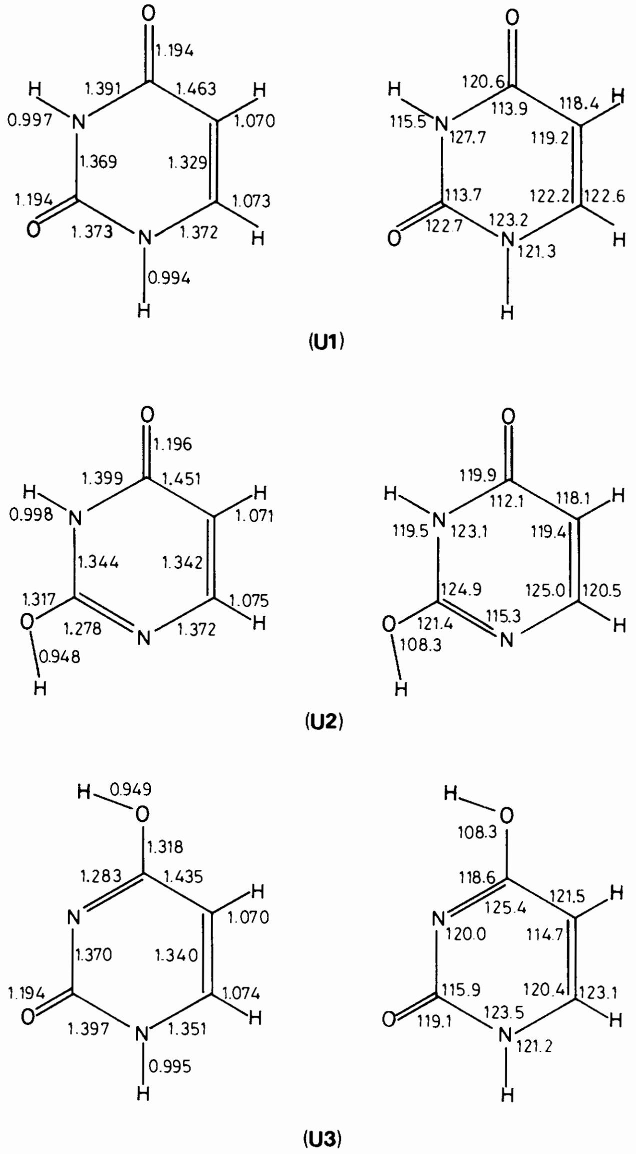

Figure. Optimised bond lengths and angles for the uracil tautomers, (**U1**), (**U2**), and (**U3**).

Results

The optimized structures of the three tautomers are shown in the Figure and the calculated energies are given in the Table.

Table. Total SCF energies (E^{SCF}), electron correlation energies calculated by means of MP2 (E^{MP2}) and zero point energies (E^{ZP}) (all in au), and relative energies (kJ mol^{-1}) for tautomers of uracil. All calculations were carried out at the 6-31G**//6-31G** level.

System	E^{SCF}	E^{MP2}	E^{ZP}	
(U1)	−412.481 83	−1.213 46	0.094 60	
(U2)	−412.463 42	−1.214 33	0.094 51	
(U3)	−412.460 12	−1.215 33	0.094 50	
	ΔE^{SCF}	ΔE^{MP2}	ΔE^{ZP}	ΔE^{Total}
(U1) − (U2)	−48.3 (−72.1)[a]	2.3	0.3	−45.7
(U1) − (U3)	−56.9 (−81.8)[a]	4.9	0.3	−51.7

[a] Values obtained at the 3-21G//3-21G level.[2]

The relative energies of the structures optimized at the 6-31G** level, calculated using this basis, differ considerably from the values obtained from the use of the 3-21G basis,[2] which includes no polarization functions. The results in the Table show that the oxo–hydroxy forms *i.e.* (**U2**) and (**U3**) are preferentially stabilized by 24–25 kJ mol^{-1} over the dioxo form (**U1**), upon inclusion of polarization functions. This effect is also evident in the work of Kwiatkowski *et al.*[5] who calculate the (**U1**) − (**U3**) energy difference using a 6-31G* basis and a geometry optimized at the 3-21G level (6-31G*//3-21G). However, the (**U1**) − (**U3**) energy difference that they report (−62.5 kJ mol^{-1}) is somewhat larger than our value (−56.9 kJ mol^{-1}). Turning now to the effect of electron correlation, we see (Table) that the stability of the rare tautomers [(**U2**), (**U3**)] compared with that of the dioxo form [(**U1**)] is increased at the MP2 level of including correlation effects. Thus, the increased relative stability of the tautomer (**U3**) is 4.9 kJ mol^{-1}, whilst Kwiatkowski *et al.*[5] find a corresponding value of only 0.6 kJ mol^{-1}. For systems of the size studied here, the zero-point vibrational energies are usually estimated using semiempirical methods. However, we here calculate this quantity for the three tautomers at the *ab initio* level using the 6-31G** basis, to provide values that we can quote with more confidence than we attach to the semiempirical values. We find that zero-point energies do not contribute significantly to the relative energies of the three tautomers of uracil studied here (Table), in contrast with our previous *ab initio* study of cytosine,[8] and previous semiempirical estimates for somewhat similar systems.[11]

The resultant effect of these three contributions to the tautomer stabilities is the prediction that the two hydroxy forms [(**U2**), (**U3**)] are less stable than the dioxo form by 45.7 and 51.7 kJ mol^{-1}, respectively. These values are significantly smaller than previous *ab initio* estimates both at the 3-21G//3-21G SCF level[2] and at the 6-31G*//3-21G level, including correlation effects.[5] As far as comparison with experimental data is concerned, an estimate of the relative enthalpies of the (**U1**)–(**U3**) pair in the vapour phase has been given by Beak and White[12] to be −79 ± 25 kJ mol^{-1}, which is close to the value calculated in this paper, and to those given by previously published *ab initio* calculations.

Conclusions

The calculations on the three tautomers of uracil presented in this paper are designed to yield relative energies at a higher level of accuracy than previously reported *ab initio* values. As expected, the dioxo form is predicted to be the most stable, whilst of the two oxo–hydroxy forms studied, the 2-hydroxy-4-oxo form is found to be more stable than the 2-oxo-4-hydroxy form by 6 kJ mol^{-1}. The calculated energy separation of (**U1**) and (**U3**) (51.7 kJ mol^{-1}) suggests a frequency of spontaneous mutation of *ca.* 10^{-9}.

Although the SCF contribution to the relative stabilities is dominant in the case of uracil, correlation effects cannot be ignored in an accurate determination of these relative energies, whilst zero-point effects are much less significant. One of the most important reasons for carrying out calculations of the type reported here is that an accurate estimate of free molecule energetics is a necessary prerequisite for the study of environment effects, particularly solvent. Simulation studies of hydration free energy differences for pairs of tautomers having structures similar to uracil yield values of up to about 20 kJ mol^{-1} for such differences.[11] Clearly, free molecule energetics need to be predicted at the level reported in this paper for the further consideration of solvent effects to be useful.

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