Accurate Prediction of the Relative Energies of the Tautomers of Cytosine in the Gas Phase and in Aqueous Solution

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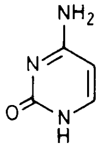
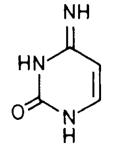
Geometry optimisation of the six tautomers of cytosine in a 3-21G basis, and subsequent inclusion of solvent effects, yields relative stabilities in agreement with experimental data for aqueous solution: the ordering of the stabilities is predicted to be different in the gas phase from that in aqueous solution.

The relative stability of the tautomers of the pyrimidine bases (uracil, thymine, and cytosine) is of fundamental importance to the structure and functioning of nucleic acids.[1] The occurrence of rare tautomers has been put forward as a possible mechanism of spontaneous mutation.[1,2] Although the most stable tautomer of each species has been determined experimentally,[3] the relative energies of the rare tautomers are difficult to measure, so that accurate theoretical treatments can make an important contribution in this area.

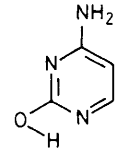
Ab initio theoretical studies including geometry optimisation using a 3-21G basis have shown that the relative energies of the 2-pyridone/2-hydroxypyridine tautomers can be predicted to 10 kJ mol^{-1},[4] an accuracy far superior to that obtained from semi-empirical treatments. Previous theoretical studies of cytosine have led to very different predictions of the relative stabilities of its six possible tautomers.[5] To clarify this situation we have carried out geometry optimisation calculations in the 3-21G basis[6] of the six tautomers of cytosine in order to predict their relative stabilities in the gas phase, and furthermore, we have taken account of base–water interactions to yield relative stabilities in aqueous solution which may be compared with available experimental data.



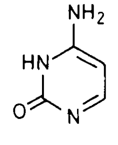
I



II



III



IV

Table 1. Relative energies (kJ mol^{-1}) and dipole moments (Debye) of cytosine tautomers.

Tautomer	Gas phase energy	Dipole moment	Base–water interaction energy	Aqueous solution energy
I	0	7.2	−59.2	0
II	1.7	5.3	−32.1	28.8
III	15.9	3.7	−15.8	59.3
IV	29.8	8.6	−84.5	4.5

The calculations were carried out using the program GAMESS[7] on the CDC 7600 computer of the University of Manchester Regional Computing Centre. The relative energies of the four most stable tautomers of cytosine I—IV are given in Table 1. The remaining two tautomers are predicted to be more than 45 kJ mol^{-1} less stable than IV and are hence not discussed further herein. In agreement with experiment I is predicted to be the most stable tautomer, the relative stabilities in the gas phase being predicted to be I > II > III > IV. However, Dreyfus *et al.*[8] using temperature-jump spectroscopy to study the tautomerism of cytosine and 3-methylcytosine in aqueous solution have obtained relative stabilities in the order I > IV > II, III being unobserved, in disagreement with our gas phase predictions. However, it is well-known that such tautomeric equilibria are sensitive to phase change, the equilibrium constant for 2-pyridone/2-hydroxypyridine changing by 10^3 between the gas phase and solution.[9]

The electrostatic base–water interactions (ignoring base–water hydrogen bonding)[10] may be estimated by the reaction field continuum model,[11] using the molecular dipole moments calculated from our *ab initio* wavefunction, together with the molecular polarizabilities calculated by the method of Miller and Savchik,[12] yielding the values shown in Table 1. The modification of the calculated gas phase stabilities by these values leads to a change in the relative stabilities due mainly to the large dipole moment of IV. The order of stabilities in the aqueous phase is now predicted to be I > IV > II, in agreement with experiment,[8] with III being too high in energy to be observed. It should be noted that we have used a rather crude model to include solvation effects which estimates only enthalpic terms. Thus, the relative energies calculated for the aqueous phase are not as accurate as those predicted for the gas phase. However, in spite of this reservation it is encouraging that agreement with solution data is achieved. We thus conclude that state of the art *ab initio* calculations predict a different order of stabilities of the tautomers of cytosine in the gas phase and in aqueous solution.

Received, 28th September 1983; Com. 1291

References

1 P. O. Lowdin, *Adv. Quantum Chem.*, 1965, **2**, 213.
2 B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.*, 1971, **13**, 77.
3 J. S. Kwiatkowski and B. Pullman, *Adv. Heterocycl. Chem.*, 1975, **18**, 199.
4 M. J. Scanlan, I. H. Hillier, and A. A. MacDowell, *J. Am. Chem. Soc.*, 1983, **105**, 3568.
5 T. J. Zielinski and R. Rein, *Int. J. Quantum Chem.*, 1978, **14**, 851; M. H. Palmer, J. R. Wheeler, J. S. Kwiatkowski, and B. Lesyng, *J. Mol. Struct. (Theochem.)*, 1983, **92**, 283; A. Buda and A. Sygula, *ibid.*, 1983, **92**, 255.
6 J. S. Binkley, J. A. Pople, and W. J. Hehre, *J. Am. Chem. Soc.*, 1980, **102**, 939.
7 M. Dupuis, D. Spangler, and J. J. Wendoloski, GAMESS, NRCC Software Catalog, Vol. 1, Program No. 2G01, 1980.
8 M. Dreyfus, O. Bensaude, G. Dodin, and J. E. Dubois, *J. Am. Chem. Soc.*, 1976, **98**, 6338.
9 P. Beak, *Acc. Chem. Res.*, 1977, **10**, 186.
10 W. G. Richards, 'Quantum Pharmacology,' Butterworths, London, 1983.
11 R. Rein, V. Renugopalakrishnan, S. Nir, and T. J. Swissler, *Int. J. Quantum Chem.*, 1975, **S2**, 99.
12 K. J. Miller and J. A. Savchik, *J. Am. Chem. Soc.*, 1979, **101**, 7206.