the 4 isomer could have taken place. Another possibility could be that even though the rate constant for the formation of the 2 isomer is greater than that of the 4 isomer, the 2 isomer could not even form as a transient species, simply because its equilibrium of formation is shifted toward the reagents under the reaction conditions.[24,25]

Among the commonly studied nucleophiles (complex hydrides, organometallic reagents, cyanide, hydroxide, alkoxides, dithionite, thiolates, amines, stabilized carbanions derived from nitromethane, ethyl acetoacetate, ethyl cyanoacetate, etc.), only the reactions of complex hydrides and organometallic reagents with a pyridinium ring can be considered to be irreversible; in both cases the nucleophilic attack occurs preferentially at the 2 position.[1]

In conclusion, the available experimental data suggest, as proposed by Lyle and Gauthier,[17] that the kinetic regioselectivity in nucleophilic addition to pyridinium and related cations is governed by the relative electron density at the carbon under attack, independent of the hard or soft character of the nucleophile.[26] This view is also supported by the work of Ritchie on cation-anion combination reactions.[27] Ritchie showed that the rates of combination of a large collection of nucleophiles (including hard and soft ones) with preformed carbocations follow the simple "constant selectivity" N_+ relationship (eq 1), in which k

$$\log k = \log k_0 + N_+ \quad (1)$$

is the rate constant for the reaction of a cation with a given nucleophilic system (i.e., a given nucleophile in a given solvent), k_0 is the rate constant for a reference nucleophile and is dependent only on the identity of the cation, and N_+ is a parameter dependent only on the nucleophilic system. If the nucleophilic attack at the 2 and 4 positions were rate determining (this has been shown to be the case for the methoxide addition to thiopyrylium and pyrylium cations),[11,25] each site should independently follow the Ritchie equation. This would imply that the regionselectivity is constant, i.e., independent of the nature of the nucleophile. Of course since the N_+ relationship encompasses a wide reactivity range, a scatter that would be insignificant for eq 1 could involve a significantly different regioselectivity. However, the Ritchie equation strongly indicates that frontier orbital interactions are not significant in determining the reactivity of cation-anion combination reactions[28] and thus the kinetic regioselectivity of nucleophilic attack to pyridinium and related cations.

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A Theoretical Study Using ab Initio Methods of Tautomerism in Cytosine in the Gas Phase and in Water

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The four lowest energy tautomers of cytosine have been modeled in the gas phase and in aqueous solution using ab initio methods. A basis set that includes polarization functions on all atoms is needed to predict the correct ordering of the tautomers in the gas phase. The effect of solvent has been modeled using both the self-consistent reaction field and polarized continuum methods. The results are consistent and agree with experiment for all but the 3(*H*)-amino-oxo form, where only the self-consistent reaction field method is in accord with experimental observations.

There is continuing interest in an accurate evaluation of the tautomeric behavior of the purine and pyrimidine bases due in large measure to the biological implications of mispairing by the rare tautomeric forms of these bases.[1] While gas-phase studies are of fundamental interest, the effect of the environment, such as solvation, must also be considered if molecular modeling studies on these molecules are to have relevance in a biological context. It is well-known that solvent and solid-state effects can be critical in determining the tautomeric equilibrium in such heterocyclic systems. The tautomerism in cytosine has been extensively studied both experimentally[2] and theoretically.[3-6] Of the six possible tautomers of this molecule, four have been identified experimentally and are generally considered to be of lower energy than the remaining two. It is these four species, **1**, **2**, **4**, and **5** (to be consistent with the labeling of Kwiatkowski et al.[4]), which are studied theoretically in this paper.

A recent IR study of cytosine isolated in a low-temperature matrix has resulted in spectral assignments in terms of the amino-oxo form (**1**) and amino-hydroxy form (**4**).[7] We have shown that IR frequencies computed for

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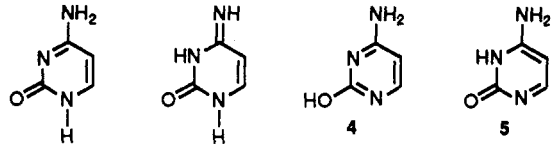
these two species are consistent with such an assignment.[8] However, in the crystalline state and in polar solvents such as water, cytosine exists in the amino–oxo form (1). None of the other forms have been directly observed experimentally in aqueous solution. However, indirect evidence suggests that form 1 predominates by factors of about 800 and 10^4–10^5 over forms 5 and 2, respectively.[9] Previous theoretical studies have been confined to geometry optimization at the split valence level (3-21G),[3] followed by energy calculations using larger basis sets (6-31G*, DZP),[4,5] with electron correlation up to triple excitations being included by the use of coupled cluster calculations.[5]



1 2 4 5

In view of the routine nature of SCF calculations on molecules of the size studied here, a split-valence basis with polarization functions on all atoms would seem to be the minimum acceptable basis set to use. However, the level of the basis set required for the geometry optimization needs to be ascertained, together with the importance of zero-point and correlation effects. In addition, a method of accurately modeling the solvation effects is needed, in order that reliable estimates of tautomeric equilibria in solution can be made. It is these aspects of modeling the isolated tautomers, and their solvation, that are addressed in this paper.

Computational Methods

Free-Molecule Calculations. We have previously presented structures of all six tautomers of cytosine optimized at the 3-21G level.[3] We have optimized the structures of the four tautomers of lowest energy at this level using a 6-31G** basis, as previously described for three of these species.[10] For molecules containing conjugated amino groups such as aniline, geometry optimization using a basis containing polarization functions, such as the one used here, is needed to correctly predict the structure of the amino group.

Correlation effects were estimated using second-order Moller Plesset theory (MP2) calculated at the optimized 6-31G** geometry. Zero-point energies (ZPE) were obtained from the harmonic vibrational frequencies calculated at the Hartree Fock 6-31G** level. These latter calculations were carried out using the program CADPAC,[11] while all other calculations were carried out using the program GAMESS.[12] Calculations were carried out on the CRAY XMP/48 of the Rutherford Appleton Laboratory and on Hewlett-Packard 700 Series workstations.

Calculation of Solvation Energies. As far as solvation effects are concerned, these may be estimated either by simulation studies (molecular dynamics) in which the solvent molecules are explicitly considered or alternatively by models which consider the solvent as a dielectric continuum. For tautomeric equilibria, the *differences* in solvation energies ($\Delta\Delta G_{solv}$) between different tautomers may be obtained via the free energy perturbation (FEP) method, implemented within molecular dynamics. Using this technique, Kollman et al.[13] have obtained a value for $\Delta\Delta G_{solv}$ of −17 kJ mol^{-1} for the mutation 2 → 1. However, such simulation studies are computationally intensive, and although they consider the solvent–solute interactions at a molecular level, solute polarization is ignored.

A range of continuum models have been implemented both within semiempirical and ab initio molecular orbital (MO) methods by modification of the one-electron Fock operator. The most widely used methods incorporate the Onsager reaction field model into MO calculations following Tapia and Goscinki.[14] This method has been incorporated into the semiempirical MO package, MOPAC,[15] and has subsequently been used to study the effect of solvent upon a variety of tautomeric equilibria. We have incorporated this method into the ab initio code GAMESS and used it to study the effect of different solvents upon the tautomeric equilibria involving hydroxypyridines.[16]

Briefly, in this method the effect of the reaction field leads to an additional one-electron term in the Fock matrix ($\mathbf{F}_{\mu\nu}$)

$$\mathbf{F}_{\mu\nu} = \mathbf{F}^{\circ}_{\mu\nu} - g\bar{\mu}\,\langle\chi_\mu|\hat{\mu}|\chi_\nu\rangle \qquad (1)$$

Here χ_μ and χ_ν are the basis functions, $\bar{\mu}$ and $\hat{\mu}$ are the dipole moment and dipole moment operator, respectively, and g depends upon the dielectric constant of the solvent (ϵ) and on the radius of the spherical cavity (a_o)

$$g = 2(\epsilon - 1)/(2\epsilon + 1)a_o^3 \qquad (2)$$

The free energy of solvation (ΔG_{solv}) can then be evaluated as

$$\Delta G_{solv} = \langle\psi|H|\psi\rangle - \langle\psi_o|H_o|\psi_o\rangle + g\bar{\mu}^2/2 \qquad (3)$$

where (ψ, H) and (ψ_o, H_o) refer to the solvated and gas-phase molecule, respectively. While this self-consistent reaction field (SCRF) method models the interaction of the dipole of the solute with the polarizable solvent characterized by the value of ϵ, no account is taken of local solvent–solute interactions. A molecule that posesses a number of functional groups (e.g. amide) which will interact strongly with a polar solvent may, due to cancellation effects, have no resultant dipole, and hence no solvent interaction within the SCRF model. For example, we have studied tautomers of maleic hydrazide where the SCRF method drastically underestimates the solvation energy.[17]

These deficiencies may be overcome by the use of more realistic shapes for the solute cavity and by the use of a more accurate representation of the solute charge distribution. An efficient approximate procedure to implement these improvements has been developed by Tomasi and co-workers.[18] The method involves the generation of a cavity from spheres centered at each atom in the molecule and the calculation of apparent point charges on the cavity surface representing the polarization of the solvent. The magnitude of these charges is proportional to the derivative of the solute electrostatic potential at each point calculated

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Table I. Total SCF Energies (E^{SCF} in au) and Zero-Point Energies (ZPE, kJ mol^{-1}) Calculated at the SCF Level for Tautomers of Cytosine[a]

tautomer	E^{SCF} 6-31G**//3-21G	E^{SCF} 6-31G**//6-31G**	ZPE 6-31G**//6-31G**
1	-392.6300 (3.9)	-392.6311 (7.1)	279.1 (-0.9)
2	-392.6288 (7.1)	-392.6301 (9.6)	282.6 (2.6)
4	-392.6315 (0)	-392.6338 (0)	280.0 (0)
5	-392.6184 (34.4)	-392.6199 (36.5)	

[a] The relative energies (kJ mol^{-1}) are given in parentheses.

from the molecular wave function. The point charges may then be included in the one-electron Hamiltonian, thus inducing polarization of the solute. An iterative calculation is carried out until the wave function and the surface charges are self-consistent. This method, which we denote the polarizable continuum method (PCM) has been implemented by us in the program GAMESS.

The degree of solvation predicted by both the SCRF and PCM models will be critically dependent upon cavity size. For the spherical cavity of the SCRF model, the radius can be chosen either from simple geometric considerations, or from the molar volume, V_m ($a_o = (3V_m/4\pi N)^{1/3}$, N = Avogadro's number). For the PCM model, the individual sphere radii must naturally depend upon atom type, but should also vary with formal atomic charge, and are expected to be basis set dependent. Appropriate parameters have been developed by Aguilar and del Valle[19] to allow the atomic radii to be calculated in terms of Mulliken charge and basis set.

We have estimated the electrostatic contribution to the solvation free energy of the four cytosine tautomers using both the SCRF and PCM models. We have employed a 6-31G** basis and used the geometry obtained at the 3-21G level (6-31G**//3-21G). In the SCRF calculations we employ a cavity radius of 3.53 Å, following Katritzky and Karelson,[6] while for the PCM calculations we use atomic radii obtained from Mulliken charges for the gas-phase calculation, in conjunction with the parameters from ref 19.

In addition to the electrostatic contribution (ΔG_{el}) to the solvation free energy, the contributions of the dispersive interactions and the cavitation energy should be formally considered. We have estimated the dispersion contributions within the philosophy of the PCM approximation as developed by Floris and Tomasi,[20] the cavitation energy being evaluated following the procedure of Huron and Claverie.[21] The resulting estimates of the sum of these contributions for each of the four tautomers studied differed by less than 3 kJ mol^{-1}. This is not unexpected in view of the similar structures and sizes of these species. In view of this result, and the approximate nature of these estimates, we have only considered the electrostatic contribution to the free energy of solvation. The relative free energies of the tautomers in solution (G_{rel}) were then estimated from ΔG_{el}, and the relative energies of the isolated gas-phase molecules at the 6-31G**//6-31G** level (Table I).

Computational Results

In Table I, we show the total and relative energies of the four cytosine tautomers calculated with a 6-31G** basis,

Table II. Electrostatic Contribution (ΔG_{el}) to Solvation Free Energies at 6-31G**//3-21G Level, Calculated by the SCRF Method, and Total Relative Free Energies (G_{rel}, kJ mol^{-1})

tautomer	dipole moment (D)	ΔG_{el}	G_{rel}
1	7.2	-44.7	0
2	5.3	-22.7	24.5
4	3.4	-10.2	27.5
5	8.6	-66.1	8.0

Table III. Electrostatic Contribution (ΔG_{el}) to Solvation Free Energies at the 6-31G**//3-21G Level, Calculated by the PCM Model, and Total Relative Free Energies (G_{rel}, kJ mol^{-1})

tautomer	ΔG_{el}	G_{rel}
1	-86.2	0
2	-70.5	18.2
4	-60.7	18.4
5	-89.2	26.4

employing molecular geometries optimized both at the 3-21G and 6-31G** levels. The molecular geometries of 1 and 4 at the 6-31G** level have previously been reported by us.[8] We find the relative ordering of the tautomers, 4 < 1 < 2 < 5, is the same for both calculations, with relative energies differing by less than 4 kJ mol^{-1} for the two sets of structures. This predicted order is different from that found using either a 3-21G basis (1 < 2 < 4 < 5)[8] or a 6-31G* basis (1 < 4 < 2 < 5)[1] and shows the need for polarization functions on *all* atoms. A similar conclusion has been reached from studies using a DZP basis.[5]

We note that use of a 6-31G**, rather than a 3-21G geometry, increases the energy separation somewhat between these four tautomers. In view of the relatively high energy of 5, we have not estimated a zero-point contribution for this species. However, the zero point energy, calculated at the 6-31G**//6-31G** level, is very similar for 1 and 4, but is slightly larger for 2 and thus does not affect the ordering of the tautomers.

An estimate of the effects of electron correlation at the MP2 level for 1, 2, and 4 predicts correlation energies for all three tautomers that differ by less than 2 kJ mol^{-1}, in the order 4 < 1 < 2, so that the energy separation of the three tautomers is increased slightly. Thus, at all the levels of theory used here, a 6-31G** basis predicts the energy ordering of the tautomers to be 4 < 1 < 2 < 5, in agreement with matrix isolation studies,[7] which show both 4 and 1 to be present with 4 being dominant. Our best estimate of the energy separation of tautomers 1 and 4 (~7 kJ mol^{-1}) is close to values in the range 3–6 kJ mol^{-1} obtained from infrared intensity measurements.[4] At the semiempirical AM1 level,[6] the predicted ordering is 1 < 4 < 2, with an energy separation of 1 and 4 of 2.7 kJ mol^{-1}. Thus, the AM1 method appears to lack the accuracy possessed by high level ab initio treatments, in predicting the correct magnitude of the small energy separation of tautomers 1 and 4.

We turn now to our estimates of the solvation free energies obtained from the SCRF and PCM calculations. The SCRF model yields electrostatic contributions to the solvation free energy that are predominantly determined by the dipole moment of the solute. Indeed, inspection of the values in Table II show that they are essentially proportional to μ^2 as expected. The large variation in the value of the dipole moment between the four tautomers results in a substantial change in their relative ordering upon solvation. The hydroxy–amino form (4) which was the *most* stable in the gas phase, is now the *least* stable in aqueous solution, and the oxo–amino form (5), which was the least stable in the gas phase, is now close in energy

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to that of the other oxo–amino form (1) that is predicted to be the most stable in aqueous solution.

As far as tautomers 1, 2, and 4 are concerned, the PCM treatment results in *relative* electrostatic contributions to the solvation free energy that are similar to those from the SCRF method, giving an energy ordering in aqueous solution, 1 < 2 < 4. However, the solvation energies of 1 and 5 are now predicted to be very close, due to the same functional groups being present, rather than considerably different, as in the SCRF treatment, due to their considerably different dipole moments. Thus, in the SCRF treatment the relative energies are 1 < 5 < 2 < 4, while the PCM calculation gives 1 < 2 < 4 < 5.

Turning now to a comparison with experiment, temperature jump spectroscopy[2] shows that in aqueous solution, cytosine exists mainly as the 1(*H*)-amino–oxo form (1), in agreement with the prediction of both computational methods. However, experimentally, the other oxo–amino form (5) is found to be higher in energy than 1 by 15 kJ mol^{-1}, with the imine form (2) a further 9 kJ mol^{-1} higher in energy.[2] This experimental ordering, 1 < 5 < 2, clearly agrees well with the results of the SCRF model, while the PCM treatment is seen to give an incorrect ordering of the tautomers. We note that both methods predict values of the relative solvation free energies of tautomers 1 and 2 in excellent agreement with that obtained from the FEP method (17 kJ mol^{-1}).[13]

Conclusions

The ab initio calculations described here show that it is necessary to include polarization functions on all atoms to predict the correct relative energies of the tautomers of cytosine, with electron correlation and zero-point energies being relatively unimportant. It is found that geometry optimization at the 3-21G level is adequate. The inclusion of solvation effects by both SCRF and PCM models yields relative energies of tautomers 1 and 2 in excellent agreement with the experimental estimate. However, it is only the SCRF model that predicts the two oxo–amino tautomers to be close in energy in water, in agreement with experiment. This is somewhat surprising in view of the more accurate representation of the solute charge distribution which is expected to result from the PCM description.

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Theoretical Structures of Methylenecyclopropane-2-carboxamide and Related Three-Membered Rings with Exocyclic Unsaturation. The Origin of a Ground-State Distortion

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Crystal structures of methylenecyclopropane-2-carboxamide reported by Van Derveer et al. and Schultz et al. show a distortion of the exocyclic methylene group such that it bends in the direction of the substituted ring carbon. Ab initio molecular orbital calculations were performed on a series of methylenecyclopropane derivatives, including methylenecyclopropane-2-carboxamide, as well as 2-formylcyclopropanone and 2-formylcyclopropanimines, in order to determine the origin of this ground-state distortion. Electron-withdrawing substituents cause a 3° to 4° distortion of the exocyclic methylene group toward the substituted ring carbon. Two electronic interactions, working alone or in tandem, are possible explanations for the distortion of the exocyclic methylene group. The first interaction proposed is between the π^* orbital of the substituent and a Walsh orbital of the three-membered ring, which causes a distortion of the three-membered ring. The distorted ring causes a distortion of the exocyclic methlene group. The second interaction proposed is between the π^* orbital of the substituent and the π orbital of methylenecyclopropane. The exocyclic methylene group distorts toward the substituent in order to increase the stabilizing interaction.

Introduction

Since the discovery that methylenecyclopropane (MCP) undergoes a degenerate thermal rearrangement,[1] MCP and its derivatives have been the focus of numerous experimental[2] and theoretical[3,4] studies. Recently, Van Derveer et al. reported the X-ray crystal structure of MCP-2-carboxamide, which showed distortion of the exocyclic methylene group toward the substituted ring carbon and the vinyl hydrogens tilted out of the plane of the carbon skeleton. These distortions are in the same direction as the motions which occur during the preferred rearrangement pathway.[5] Because of our interests in the effects of substituents on the stereochemical outcome of reactions and on ground-state distortions,[6] we undertook an ab initio

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