The Uracil–Fluoride Interaction: *Ab Initio* Calculations including Solvation

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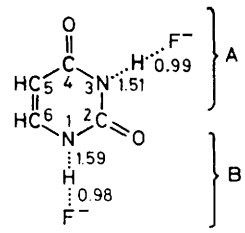
Ab initio calculations show that a uracil–fluoride complex is thermodynamically stable even when hydrated, and the implications of this finding for nucleic acid biochemistry are briefly discussed.

In a recent communication,[1] Clark and Taylor have reported i.r. spectroscopic evidence for a strong $N \cdots H \cdots F^-$ hydrogen bond in the uracil–fluoride system. A detailed understanding of the chemical properties of uracil, the simplest of the nucleic acid bases, is of biochemical importance, and towards this goal *ab initio* calculations of the uracil–water interaction,[2] the tautomerism of uracil,[3] and its vibrational spectra[4] have recently appeared. We have previously investigated the interaction between certain amides and the fluoride anion by means of *ab initio* calculations and spectroscopic studies, revealing an unexpectedly strong $N \cdots H \cdots F^-$ hydrogen bond with potentially important implications for protein biochemistry.[5] In the light of the new i.r. evidence for the uracil–fluoride interaction[1] we have now performed *ab initio* calculations incorporating solvation effects on the uracil–fluoride complex and its components to elucidate the strength and orientation of this interaction, in an attempt to assess its potential importance for nucleic acid biochemistry.



	Hydrogen bond energy /kJ mol^{-1}		Interaction energy /kJ mol^{-1}	
	ΔE	$\Delta E_{hydr.}$	$\Delta E'$	$\Delta E'_{hydr.}$
A	−120	−42	−308	−10
B	−66	+7	−378	−23

Figure 1. The hydrogen bonds of uracil–fluoride (bond lengths are in Å).

Ab initio LCAO–MO–SCF geometry optimisations on uracil (UH) and both the N-1 and N-3 forms of the uracil anion (U^-), and the uracil–fluoride complex (UHF^-) were performed in the 4-31G basis set[6] with the program GAUSSIAN 76,[7] starting from the experimental structure for uracil.[8] The H–F, N–H, C–N, and C–O bonds were optimised to within 1 pm assuming the molecules to be planar and the hydrogen bond to be linear, since our previous study of amide–fluoride systems[5] demonstrated that these bonds are the ones that are significantly perturbed by hydrogen bond formation. Intermolecular interaction energies with respect to both UH + F^- and U^- + HF were computed for both the N-1 and N-3 forms of UHF^- using the ATMOL 3 programs[9] with the [4s2p/2s1p] basis set[10] described previously.[5] Finally, the non-specific solvation method,[11] implemented in GAUSSIAN 76, was employed with the 4-31G basis set[6] to estimate the hydration energy of each molecular species, taking the dielectric constant of water, ϵ 80 and the cavity radius r_0 equal to the molecular van der Waals' radius.[11] (Owing to the basis set size restrictions of GAUSSIAN 76 it was not possible to perform the non-specific solvation calculations in the [4s2p/2s1p] basis set. However, our previous study[11] demonstrated that the computed solvation energies are stable against further extensions of the 4-31G basis set.) The calculated energies are presented in Table 1, and the data for the hydrogen bonds are shown in Figure 1.

It has been agreed[12] that the hydrogen bond energy of a system A···H···B is to be defined with respect to the lower energy pair AH + B or A + HB. This being so, then the hydrogen bond energies of the isolated uracil–fluoride complex are defined with respect to U^- + HF and are given as such in Figure 1. These free-state hydrogen bond energies, ΔE, show the N(3)···H···F^- bond to be the stronger with a hydrogen bond energy comparable with those of $RCONH_2\cdots F^-$ (−149 kJ mol^{-1}) [5] and $RCO_2H\cdots F^-$ (−105 kJ mol^{-1})[13] but not as strong as that of HF_2^- (−214 kJ mol^{-1}).[14] However, although the energy *differences* define the hydrogen bond energy, the more stable complex is UHF^-(N-1) (Figure 2). The same is true in the solvated system.

Recently we have used a solvent sphere model to get better estimates of hydrogen bond energies in a solvated environment.[11] Applying this model to the uracil–fluoride complex in a hydrated environment produces marked changes in the hydrogen bond and interaction energies as shown in Figures 1 and 2. (For the sake of consistency we have retained the same definition of hydrogen bond energy and interaction energy as used for the isolated systems.)

The hydration energies decrease the hydrogen bond and interaction energies and surprisingly UHF^-(N-1) is now predicted to be thermodynamically unstable with respect to HF and U^-(N-1). However in biological systems the uracil ring is covalently bonded to the ribose ring through N-1 so that we need consider only the hydrogen bonding at N-3. Moreover, the interaction energies $\Delta E'$ have more relevance to the species as they would occur in nature. The solvent environment is the critical factor, and the choice of suitable values for the cavity radius in the calculations makes $\Delta E_{hydr.}$ values uncertain.

The greater hydration energies of U^-(N-3) and UHF^-(N-3) over U^-(N-1) and UHF^-(N-1) are mainly due to the greater dipole moment of UHF^-(N-3) and U^-(N-3). The greater hydration energies of U^-(N-3) and U^-(N-1) over UHF^-(N-3) and UHF^-(N-1) are mainly due to the smaller r_0 values for the U^- species.

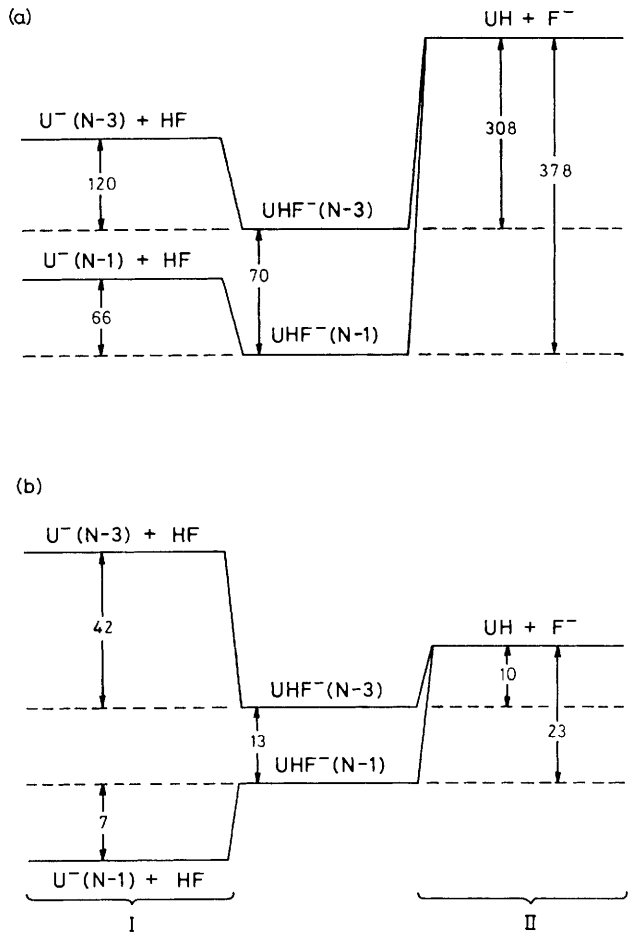
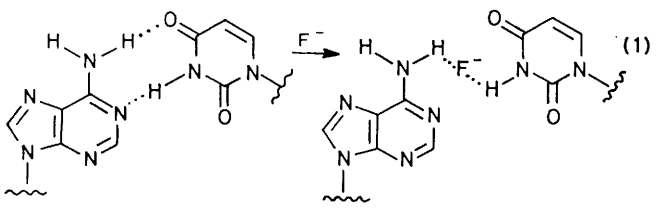


Figure 2. The energetics of (a), the isolated and (b), the hydrated uracil–fluoride system: I, hydrogen bond energies/kJ mol^{-1}; II, interaction energies/kJ mol^{-1}.

Table 1. Total energies (Hartrees) and hydration energies (kJ mol^{-1}) of the molecular species.

Species	E_0 4-31G	E_0 [4s2p/2s1p]	r_0/Å[a]	$\Delta E_{hydr.}$ 4-31G
UH	−411.79324	−412.24276	3.8	−20
U^-(N-3)	−411.18815	−411.68987	3.8	−250
U^-(N-1)	−411.23472	−411.73702	3.8	−188
UHF^-(N-3)	−511.12453	−511.77398	4.4	−212
UHF^-(N-1)	−511.15223	−511.80067	4.6	−155
HF	−99.88729	−100.03847	1.7	−40
F^-	−99.24782	−99.41406	1.4	−490

[a] Based on the van der Waals' radii of A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441.



(1)

In the RNA duplex it is N(3)–H which is involved in hydrogen bonding to the nitrogen ring atom of uracil's base-pair, adenine. At the same time the C-4 carbonyl group acts as a hydrogen bond acceptor for the NH_2 group of the adenine ring. Could one F^- disrupt both of these hydrogen bonds? Multiple strong hydrogen bonds to a single F^- are known in $KF.(CH_2CO_2H)_2$[15] and in the polyfluorides.[14] The KF–succinic acid complex crystallizes from aqueous solution with each fluoride ion hydrogen bonded to two carboxylic acid groups. Thus it may be possible for a single F^- completely to disrupt the uracil–adenine link [as in equation (1)], but this will depend very much upon the details of local solvation processes.

If our calculations and hypothesis are correct then we have a mechanism whereby F^- could play a disruptive role towards RNA and DNA; thymine in the latter should hydrogen bond equally as well as uracil with F^-. The experimental evidence[1] supports a strong interaction.

It is generally assumed that the simple fluoride ion is such a weak nucleophile in water that it is chemically unreactive towards organic molecules and hence is safe to add to drinking water as a preventative of dental caries. Its chemical activity towards enzymes[16] has been assumed to lie in its ligand ability towards the metal centres in such substances, leading to deactivation, or in a few cases stimulation.[17] It is even claimed that at low concentrations fluoride is essential for the growth of animals including man.[18]

Reports of fluoride causing birth defects, allergic responses, and even cancer[19] may be based on debatable evidence especially as there seemed no way in which a weak nucleophile such as aqueous F^- could operate to produce them. Recently it has been demonstrated that F^- can interfere with non-metal enzymes and even NADH, the key co-enzyme.[20] It was postulated that its ability to hydrogen bond to a proton donor site in the molecule was responsible. We now believe that the NH group of a uracil or thymine base could be the site of such an interaction. Strong hydrogen bonding may provide the fluoride ion with a mechanism and the necessary energy to cause fundamental biochemical changes, given the right environment. Whether in fact it does operate in this way in the living cell remains to be seen.

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