J. Phys. Chem. A **2006,** *110,* 4188−4195

Hydrogen Bonding of the Nucleobase Mimic 2-Pyridone to Fluorobenzenes: An ab Initio Investigation

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Received: December 6, 2005; In Final Form: January 10, 2006

The hydrogen-bonded complexes of the nucleobase mimic 2-pyridone (2PY) with seven different fluorinated benzenes (1-, 1,2-, 1,4-, 1,2,3-, 1,3,5-, 1,2,3,4-, and 1,2,4,5-fluorobenzene) are important model systems for investigating the relative importance of hydrogen bonding versus π-stacking interactions in DNA. We have shown by supersonic-jet spectroscopy that these dimers are hydrogen bonded and not π-stacked at low temperature (Leist, R.; Frey, J. A.; Leutwyler, S. *J. Phys. Chem. A* **2006**, *110*, 4180). Their geometries and binding energies D_e were calculated using the resolution of identity (RI) Møller−Plesset second-order perturbation theory method (RIMP2). The most stable dimers are bound by antiparallel N−H···F−C and C−H···O═C hydrogen bonds. The binding energies are extrapolated to the complete basis set (CBS) limit, D_e^{∞}, using the aug-cc-pVXZ basis set series. The CBS binding energies range from $-D_{e,\mathrm{CBS}} = 6.4-6.9$ kcal/mol and the respective dissociation energies from $-D_{0,\mathrm{CBS}} = 5.9-6.3$ kcal/mol. In combination with experiment, the latter represent upper limits to the dissociation energies of the π-stacked isomers (which are not observed experimentally). The individual C−H···O═C and N−H···F−C contributions to D_e can be approximately separated. They are nearly equal for 2PY·fluorobenzene; each additional F atom strengthens the C−H···O═C hydrogen bond by ~0.5 kcal/mol and weakens the C−F···H−N hydrogen bond by ~0.3 kcal/mol. The single H-bond strengths and lengths correlate with the gas-phase acid−base properties of the C−H and C−F groups of the fluorobenzenes.

I. Introduction

The coding, replication, and translation of genetic information has long been believed to be based on the specific hydrogen-bonding patterns of the Watson−Crick base pairs in double-stranded DNA. However, the importance of this hydrogen bond complementary paradigm has been called into question by Kool[1−8] and others.[9−11] In their investigations, nucleobase H-bonding groups such as N−H or C═O were replaced by "non-hydrogen-bonding" groups such as C−H or C−F. Thus, 2,4-difluorotoluene (F), which lacks strong H-bond donor or acceptor groups, has been used as a nonpolar structural mimic ("isostere") of thymine.[3,4] F has been found to pair very poorly and with no significant selectivity among natural bases when incorporated in DNA oligonucleotides;[1] nevertheless, DNA polymerase I efficiently and selectively replicates F opposite to adenine.[1,3,4,8] Other fluorinated aromatics have since been incorporated into modified DNAs.[6,7,9−11] Base pairing has been demonstrated between oligonucleotides involving benzene and pentafluorobenzene as hydrophobic nucleobase analogues and has been attributed to edge-to-edge attractive intermolecular forces.[10] Tetrafluorobenzene and tetrafluoroindole pair opposite themselves when incorporated into short DNA duplexes, with stabilities intermediate between the stable base pair thymine·adenine and of the mismatch pair thymine·cytosine.[7]

C−H and C−F groups are generally believed to be weak hydrogen bond donors and acceptors. Hence, the above results have been interpreted in terms of a combination of attractive intrastrand contributions (π-stacking stabilization, hydrophobic effects) with minimized interstrand steric repulsion due to the optimally shaped nucleobase mimics ("isosteres"). It is often claimed that the fluorinated nucleobase mimics lack hydrogen-bonding ability or even "that hydrogen bonding is absent".[4,12−14] The H-bonding propensity of 2,4-difluorotoluene has been carefully examined by proton chemical-shift measurements as a function of concentration in different solvents, with conflicting interpretations.[13,15] The 1,4-difluorotoluene·adenine complex has been calculated with different quantum chemical methods; weak electrostatic interactions between the H-bond acceptor and donor groups on A and F are predicted, resulting in weak hydrogen bonds.[14,16−19]

Ab initio studies have been performed on the individual N−H···F−C, C−H···F−C, and C−H···O═C hydrogen bonds occurring between nucleobases and fluorinated isosteres. The binding energy of the C−H···O═C hydrogen bond has been calculated for the formamide dimer, dimethylformamide dimer, and similar model dimers for peptide−peptide interactions.[20−23] The activation of C−H···O═C hydrogen bonds by α- and β-substituted fluorine atoms has also been studied by ab initio calculations.[20,24] Experimentally, several intermolecular O−H···F−C and C−H···F−C distances in complexes of difluoromethane and trifluoromethane have been determined by Caminati and co-workers using free jet microwave and millimeter wave spectroscopies.[25−29]

Here, we investigate the structures and binding energies of the complexes between the nucleobase mimic 2-pyridone and seven fluorobenzenes: fluorobenzene (FB), 1,2-difluorobenzene (1,2-FB), 1,4-difluorobenzene (1,4-FB), 1,2,3-trifluorobenzene (1,2,3-FB), 1,3,5-trifluorobenzene (1,3,5-FB), 1,2,3,4-tetrafluorobenzene (1,2,3,4-FB), and 1,2,4,5-tetrafluorobenzene (1,2,4,5-FB). We employ the resolution-of-identity Møller−Plesset second-order perturbation (RIMP2) method. Using the Dunning aug-cc-pV*X*Z (X = 2, 3, 4) basis set series, the binding energies

10.1021/jp057101+ CCC: $33.50

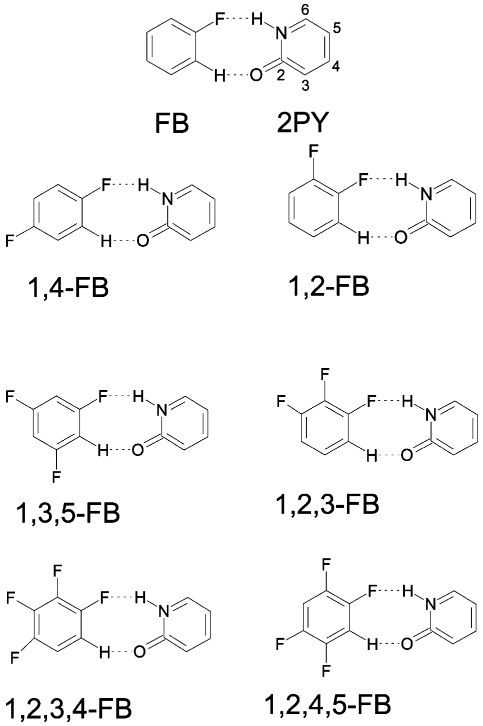

Figure 1. Molecular structures, abbreviations, and atom numbering of the hydrogen-bonded 2PY·fluorobenzene complexes.

are extrapolated to the complete basis set (CBS) limit. The most stable dimers exhibit neighboring antiparallel C—H···O═C and N—H···F—C hydrogen bonds, and the CBS limit H-bond stabilization energies are in the range 6−7 kcal/mol. The stabilization energies of the individual N—H···F—C and C—H···O═C hydrogen bonds were calculated by twisting the monomers by 90° around either H-bond. For 2-pyridone·fluorobenzene, the N—H···F—C and C—H···O═C hydrogen bond strengths are very similar. With increasing degree of fluorination, the individual C—H···O═C and N—H···F—C hydrogen bond energies increase by ∼50% and decrease by ∼30%, respectively. These trends in individual H-bond strengths can be correlated with the gas-phase acid/base properties of the fluorobenzene monomers.

We have experimentally investigated the same seven dimers using mass-selective laser spectroscopic techniques in supersonic molecular beams and have shown that the observed vibronic spectra are exclusively due to hydrogen-bonded 2PY·fluorobenzene dimers.[30] No spectra that are attributable to π-stacked or T-shaped dimers have been observed, leading us to conclude that the H-bonded dimers have larger dissociation energies than the respective π-stacked dimers. This implies that, for isosteric fluorinated nucleobase (i.e., optimally shaped replacements for the canonical nucleobase), the attractive interstrand hydrogen bond interactions are important contributions to the stable and selective base pairing, in contrast to previous interpretations.

II. Computational Results

A. Binding Energies. Figure 1 shows the structures of the hydrogen-bonded 2PY·fluorobenzene complexes. These were calculated with resolution-of-identity Møller−Plesset second-order perturbation theory (RIMP2) using Turbomole 5.7.[31] The very efficient handling of four-center integrals in the RIMP2 method[31] allows us to decrease the computational cost by approximately 1 order of magnitude in comparison to the exact MP2 method, but with almost no loss in computational accuracy, as has been shown for hydrogen-bonded DNA pairs.[32] The structures were fully optimized with the aug-cc-pVTZ basis set; the aug-cc-pVDZ and aug-cc-pVQZ energies were calculated at the aug-cc-pVTZ geometries. Stringent optimization criteria were employed (max. energy change $<10^{-6}$ E_h/particle; max. gradient $2\cdot10^{-4}$ E_h a_0^{-1}). The resulting binding energies were corrected for basis set superposition error with the counterpoise (CP) correction scheme.[33]

Extrapolations to the complete basis set (CBS) limit were based on the aug-cc-pVXZ (X = 2, 3, 4) basis set series,[34,35] using the extrapolation formula $D_e(X) = D^\infty + A\, e^{-(X-1)} + B\, e^{-(X-1)^2}$ of Dunning and co-workers.[36] Both the counterpoise-corrected and -uncorrected binding energy limits $D_{e,CBS}^{CPC}$ and $D_{e,CBS}$ are given in Table 1. The differences between the corrected and uncorrected $D_{e,CBS}$ values are in the range 0.01−0.07 kcal/mol or ≤1.0% of $D_{e,CBS}$. We take the average of the extrapolated $D_{e,CBS}^{CPC}$ and $D_{e,CBS}$ values as the CBS limit binding energy D_e^∞ in Table 1.

For those fluorobenzenes with adjacent F atoms (1,2-FB, 1,2,3-FB, 1,2,3,4-FB and 1,2,4,5-FB), structures involving parallel N−H···F−C and C−H···F−C hydrogen bonds are also possible. However, these are ∼50% less strongly bound, and we have not found any experimental evidence for isomers;[30] hence, they are not considered further below.

Figure 2 shows the basis-set dependence of the counterpoise-corrected and uncorrected binding energies for 2PY·1,3,5-FB and 2PY·1,2,4,5-FB, which are the least and most strongly bound complexes, respectively. The uncorrected binding energies approach the CBS limit smoothly from below as a function of the basis set size. The counterpoise corrections on the MP2 binding energies are about 50% for the double-ζ basis set, decreasing to ∼0.5−0.6 kcal/mol or about 7.5% of the binding energy for the aVQZ basis set. The CP-corrected binding

TABLE 1: Calculated Binding Energies D_e and Basis Set Superposition Errors (BSSE) of the Hydrogen-Bonded 2-Pyridone·Fluorobenzene Dimers[a]

method	resolution of identity MP2[b]									PW91[c]	
basis set	aug-cc-pVDZ		aug-cc-pVTZ		aug-cc-pVQZ		RIMP2 CBS limits			6-311++G(d,p)	
	D_e	BSSE	D_e	BSSE	D_e	BSSE	$D_{e,CBS}$	$D_{e,CBS}^{CPC}$	D_e^∞	D_e	ΔZPE
2PY·FB	−8.45	2.44	−7.41	1.28	−6.83	0.52	−6.47	−6.46	−6.47	−6.08	0.54
2PY·1,2-FB	−8.57	2.45	−7.54	1.32	−6.95	0.54	−6.59	−6.54	−6.56	−6.26	0.56
2PY·1,4-FB	−8.68	2.46	−7.64	1.31	−7.06	0.54	−6.70	−6.65	−6.68	−6.35	0.55
2PY·1,2,3-FB	−8.60	2.46	−7.57	1.33	−6.97	0.54	−6.60	−6.55	−6.57	−6.28	0.52
2PY·1,3,5-FB	−8.33	2.47	−7.35	1.34	−6.76	0.56	−6.39	−6.33	−6.36	−5.95	0.50
2PY·1,2,3,4-FB	−8.93	2.51	−7.89	1.37	−7.27	0.56	−6.89	−6.83	−6.86	−6.64	0.54
2PY·1,2,4,5-FB	−8.91	2.54	−7.92	1.42	−7.29	0.58	−6.90	−6.85	−6.87	−6.62	0.53

[a] Using resolution of identity MP2 theory with the aug-cc-pVXZ (X = 2, 3, 4) basis sets and the PW91 density functional with the 6-311++G(d,p) basis set. All values in kcal/mol. [b] Geometries optimized with aug-cc-pVTZ basis. For the total energies, see Supporting Information. [c] PW91/6-311++G(d,p) optimized geometries.

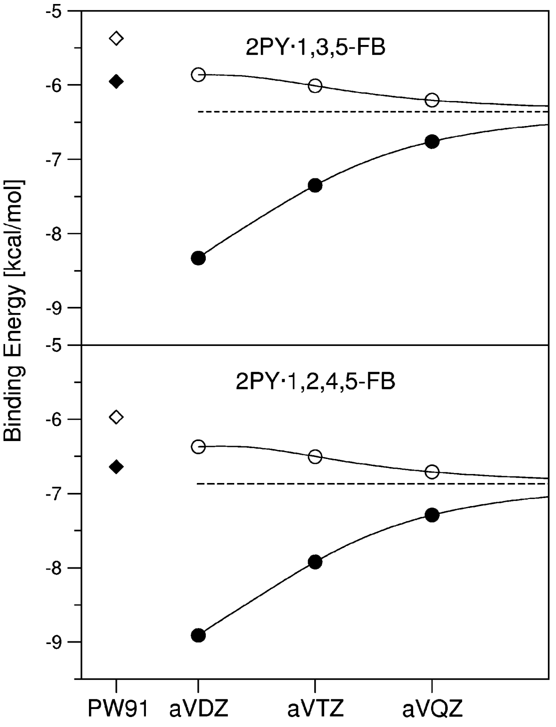

Figure 2. Complete basis set (CBS) extrapolations of the binding energies D_e (●) and counterpoise-corrected binding energies D_e^{CPC} (○) of (a) 2-pyridone·1,3,5-trifluorobenzene and (b) 2-pyridone·1,2,4,5-tetrafluorobenzene. The CBS limit energy is indicated by a dashed line. The respective PW91/6-311++G(d,p) binding energies are marked by ◊.

energies approach the CBS limit smoothly from above and are always closer to the limiting $D_{e,CBS}$ than the uncorrected binding energies.

Figure 3 shows the separate Hartree−Fock (SCF) and correlation energy (RIMP2) contributions to the total binding energy of these two complexes. Several points should be noted: (i) Despite their structural similarity, the two complexes show quite different relative contributions to the binding energy: the 2PY·1,3,5-FB complex is 65% bound by correlation, while for 2PY·1,2,4,5-FB, the Hartree−Fock and correlation contributions are about equal. (ii) For the SCF contribution, the BSSE is smaller than for the correlation contribution for all basis set sizes; this is generally found for hydrogen-bonded complexes. (iii) For the SCF contribution, the aug-cc-pVQZ basis set is nearly saturated, i.e., the BSSE approaches zero. (iv) With respect to the correlation part, basis set saturation is not yet reached, and the BSSE is still ~0.5 kcal/mol for the aug-cc-pVQZ basis set. In other words, the remaining BSSEs in Figure 2 arise almost entirely from the MP2 correlation energy contribution.

Figure 4 compares the binding energies for all seven complexes calculated with (a) the Hartree−Fock method, (b,c) the B3LYP and PW91 density functionals, and (d) the CBS extrapolated RIMP2 method. Note that the SCF and RIMP2 calculations employ the aVQZ basis, while the DFT methods employ the smaller 6-311++G(d,p) basis set. One sees that there is a trend to increasing stability with an increasing number of F atoms, but the 2PY·1,3,5-FB (and to a lesser degree the 2PY·1,2,4,5-FB complex) deviates from the trend. The exceptions are the same with all four methods of calculation and are most striking at the SCF level. The CBS $D_{e,CBS}$ binding energies lie in a relatively narrow range between −6.36 kcal/mol for 2PY·1,3,5-FB and −6.87 kcal/mol for 2PY·1,2,4,5-FB.

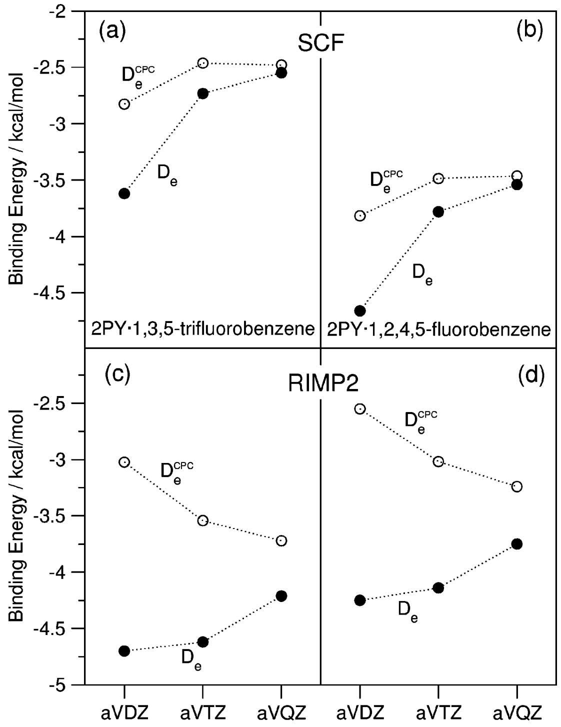

Figure 3. Contributions to the total hydrogen bond binding energies of (a,c) 2-pyridone·1,3,5-trifluorobenzene and (b,d) 2-pyridone·1,2,4,5-tetrafluorobenzene. Top: Hartree−Fock (SCF) contribution. Bottom: RIMP2 contribution.

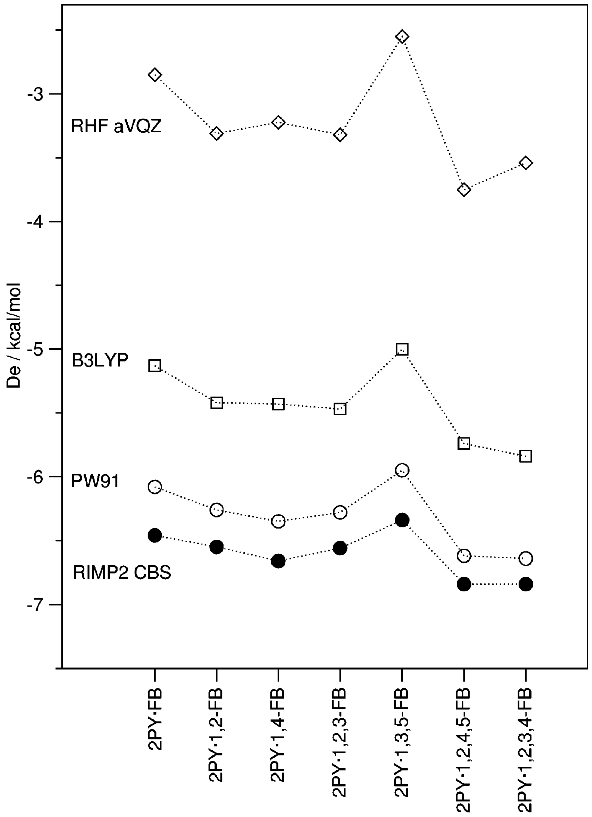

Figure 4. Hydrogen bond binding energies of the 2-pyridone·fluorobenzene complexes at different levels of calculation. From top to bottom: Hartree−Fock level with the aVQZ basis set, B3LYP and PW91 density functional levels with the 6-311++G(d,p) basis set, RIMP2 complete basis set extrapolation.

We have previously shown that the PW91 density functional combined with the 6-311++G(d,p) basis set gives very good

TABLE 2: Single Hydrogen Bond Binding Energies $D_e(1)$ and $D_e(2)$ (in kcal/mol) of the 2-Pyridone·Fluorobenzene Complexes, Calculated for 90° Twisted Geometries[a]

	$D_e(1)$ (C—H···O═C)	$D_e(2)$ (N—H···F—C)	$D_e(1) + D_e(2)$	D_e planar	rel. deviation[b]
		90° Torsion Around Acceptor Group			
2PY·FB	−2.97	−3.34	−6.31	−6.08	+3.8%
2PY·1,2-FB	−3.57	−3.33	−6.90	−6.26	+10.2%
2PY·1,4-FB	−3.50	−3.33	−6.83	−6.35	+7.6%
2PY·1,2,3-FB	−3.95	−3.24	−7.18	−6.28	−14.3%
2PY·1,3,5-FB	−3.70	−2.98	−6.68	−5.95	+12.3%
2PY·1,2,3,4-FB	−3.43	−3.31	−6.74	−6.64	−1.6%
2PY·1,2,4,5-FB	−4.54	−3.08	−7.62	−6.62	+15.2%
		90° Torsion Around Donor Group			
2PY·FB	−2.80	−2.68	−5.48	−6.08	−9.8%
2PY·1,2-FB	−3.22	−2.37	−5.59	−6.26	−10.6%
2PY·1,4-FB	−3.20	−2.55	−5.75	−6.35	−9.4%
2PY·1,2,3-FB	−3.53	−2.19	−5.72	−6.28	−9.1%
2PY·1,3,5-FB	−3.44	−2.19	−5.63	−5.95	−5.4%
2PY·1,2,3,4-FB	−3.43	−2.28	−5.70	−6.64	−14.0%
2PY·1,2,4,5-FB	−4.09 (69.0%)	−1.84 (31.0%)	−5.94	−6.62	−10.3%
		90° Torsion Around Hydrogen Bond			
2PY·FB	−2.34	−2.80	−5.14	−6.08	−15.3%
2PY·1,2-FB	−2.82	−2.39	−5.21	−6.26	−16.7%
2PY·1,4-FB	−2.80	−2.60	−5.39	−6.35	−15.1%
2PY·1,2,3-FB	−3.18	−2.11	−5.29	−6.28	−15.9%
2PY·1,3,5-FB	−3.24	−2.12	−5.36	−5.95	−9.9%
2PY·1,2,3,4-FB	−3.67	−2.28	−5.94	−6.64	−10.3%
2PY·1,2,4,5-FB	−3.97	−1.75	−5.70	−6.62	−13.7%

[a] All calculations at the PW91/6-311++G(d,p) level. [b] Deviation of the sum of $D_e(1)$ and $D_e(2)$ from the interaction energy at the optimum geometries, cf. previous column.

agreement with experiment for the structural parameters of the H-bonded (2-pyridone)$_2$ and (uracil)$_2$ self-dimers, as well as binding energies, being within <0.8 kcal/mol of those from MP2 CBS extrapolations.[37,38] On the basis of this experience, the 2PY·fluorobenzene complexes were also optimized with at the PW91/6-311++G(d,p) level, using *Gaussian 03*.[39] The most stringent optimization criterium (energy gradient ($<2 \times 10^{-6}$ $E_h\, a_0^{-1}$) and the ultrafine numerical integration grid were used. Normal-mode calculations were carried out at the minimum-energy geometries using analytical second derivatives. Table 1 includes the PW91 binding energies D_e. We find that also here the PW91 D_es are very close to the MP2 CBS binding energies $D_{e,CBS}$, being ~0.3 kcal/mol (5%) smaller on average. The PW91 method is seen to perform very well also for the weaker N—H···F—C and C—H···O═C hydrogen bonds occurring in these complexes.

The DFT method also allows us to calculate the vibrational frequencies and the vibrational zero-point energy, which is not currently possible with the MP2 or RIMP2 methods using such large basis sets. In Table 1, we include the change of the PW91 vibrational zero-point energies ΔZPE upon complex formation. From these, the dissociation energies D_0 can be obtained by addition to the D_e values.

B. Single Hydrogen Bond Energies. There is no simple recipe for apportioning the strengths of single hydrogen bonds in a doubly H-bonded system, since it is impossible to remove one hydrogen bond without influencing the second to some extent. We calculate approximate single H-bond binding energies by twisting the moieties around either of the H-bonds by 90°. Since the hydrogen bonds are nonlinear, the 90° twist can be effected (i) around the acceptor bond (F—C or O═C), (ii) around the donor bond (C—H or N—H), or (iii) around the hydrogen bond axis (H···O). Table 2 shows in columns 2 and 3 the single H-bond energies obtained for these three cases. The fourth column gives the sum of the two single H-bond energies, which is compared to the total D_e at the optimized planar geometry in column 5. All calculations were performed at the PW91/6-311++G(d,p) level.

(i) Twisting around the acceptor bonds results in single H-bond interaction energies that add up to *more* than the total D_e at the optimum planar geometry for four out of the seven complexes. The implication is that the two H-bonds are anticooperative. (ii) Twisting around the donor bonds results in single H-bond interaction energies that in all cases add up to 10−15% less than the total energy at the optimum geometry. This implies that the two H-bonds are cooperative, which is to be expected for a dimer in which the hydrogen-bonding groups are joined to π-electron systems. (iii) Finally, twisting around the hydrogen bond axes results in single H-bonds that add up to 9−14% less than the total energy at the optimum geometry, indicating a slightly smaller H-bond cooperativity than when twisting around the donors bonds. All three evaluation protocols for single H-bond energies show that each molecule acts simultaneously as both proton donor and acceptor. The relatively small nonadditivities found here show that the effects of the delocalized π-electrons of the 2-pyridone and fluorobenzene moieties on the hydrogen bond strength ("resonance-enhanced hydrogen bonding"[40]) are small.

As Table 2 shows, two trends occur with increasing fluorination: (1) The strength of the C—H···O═C hydrogen bond increases by ~50%, from −2.8 kcal/mol for fluorobenzene to −4.0 kcal/mol for the tetrafluorobenzenes. (2) The strength of the N—H···F—C hydrogen bond *decreases* by ~30%, from −2.7 kcal/mol in fluorobenzene to −1.8 kcal/mol in the tetrafluorobenzenes. The numbers given are for 90° twist around the donor bond; very similar values are calculated when twisting by 90° around the H-bond.

C. Hydrogen Bond Geometries. Table 3 gives the H-bond distances calculated at the RIMP2/aug-cc-pVTZ level. The H···F hydrogen bond distances lie between 1.99 Å for FB and 2.053 Å for 1,2,4,5-FB. The bond distances increase systematically with increasing number of F atoms. This trend agrees with the

TABLE 3: Selected Hydrogen Bond Structural Parameters of the 2-Pyridine·Fluorobenzene Complexes, Calculated at the RIMP2/aug-cc-pVTZ Level[a]

	2PY·FB	2PY·1,2-FB	2PY·1,4-FB	2PY·1,2,3-FB	2PY·1,3,5-FB	1,2,4,5-FB	2PY·1,2,3,4-FB
H_N···F	1.987	2.014	2.001	2.034	2.022	2.043	2.053
N···F	2.998	3.027	3.013	3.047	3.036	3.055	3.066
∠	173.8	175.8	177.1	178.5	179.3	176.3	179.9
H_C···O	2.201	2.181	2.171	2.162	2.127	2.092	2.129
C···O	3.275	3.252	3.244	3.231	3.185	3.154	3.200
∠	170.2	169.8	168.7	168.3	166.0	164.8	168.6

[a] Angles in deg, distances in Å. Cartesian coordinates are given in Supporting Information.

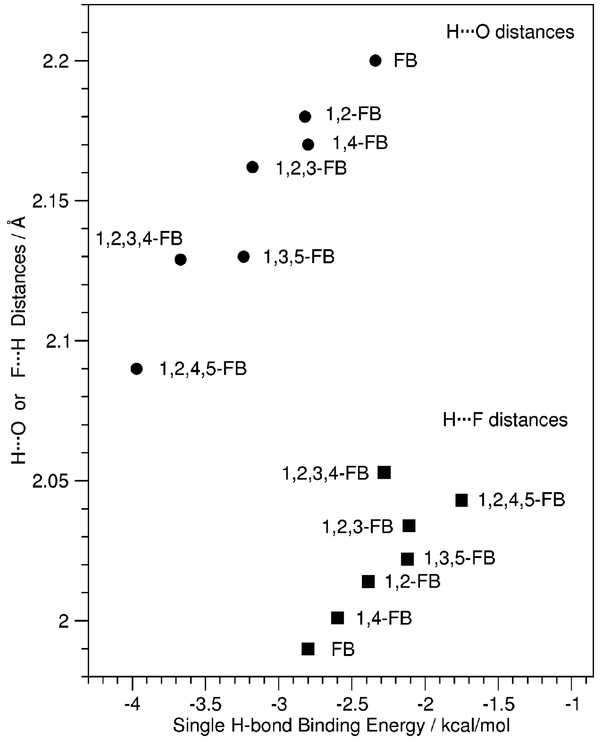

Figure 5. Calculated single N—H···F—C binding energies of the 90° twisted 2-pyridone·fluorobenzene dimers vs the RIMP2/aug-cc-pVTZ calculated C—H···O and N—H···F hydrogen bond distances.

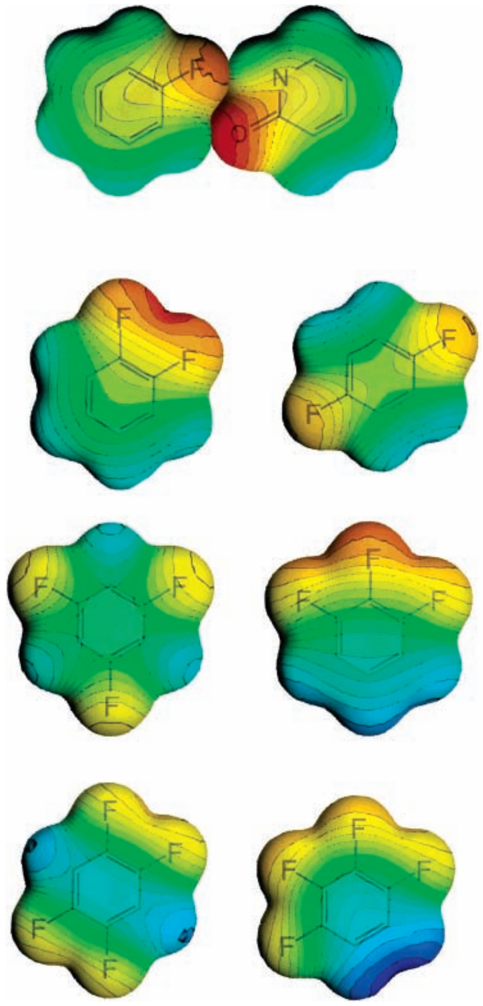

Figure 6. Calculated electrostatic potentials of 2-pyridone (top right), shown as complexed to fluorobenzene, and of the seven fluorobenzenes investigated here. Calculations at the Hartree−Fock/6-311++G(d,p) level, the scale is from −0.15 (red) to +0.15 (blue).

calculated hydrogen bond strengths, which also decrease with increasing degree of fluorination, as shown in Figure 5. The N—H···F—C hydrogen bond distances in 2PY·fluorobenzene and 2PY·1,4-fluorobenzene are the shortest X—H···F hydrogen bonds calculated or measured up to now; see also the Discussion section. A database search of 1996[41] revealed only one N—H···F—C contact below 2 Å; however, this was an intramolecular N—H···F—C bond with an angle of about 140°. The N—H···F bond angles lie between 173° and 179°.

On the other hand, the H···O distances of the C—H···O═C hydrogen bonds decrease systematically with increasing degree of fluorination from 2.20 Å for 2PY·fluorobenzene to 2.09 Å for 2PY·1,2,3,4-fluorobenzene. Again, this fully agrees with the calculated trend of the single H-bond strengths, as shown in Figure 5.

D. Monomer Properties. Given that the 2-pyridone moiety is constant throughout, we have attempted to rationalize the systematic changes of the energies and distances of the individual H bonds as a function of the degree of fluorination, based on the properties of the fluorobenzene monomers. The most obvious properties are the charges on the H and F atoms. The fluorobenzenes considered in this study are linked via adjacent C—H donor and F—C acceptor sites. The electrostatic potential (ESP) of each monomer was mapped onto the respective van der Waals surface and is shown in Figure 6. The ESPs allow us to rationalize the overall trends in individual H-bond strengths, e.g., increasing the degree of fluorination renders the remaining hydrogen atom(s) more electropositive. One also sees that the F atoms become *less negative* as the degree of fluorination is increased. Since each F atom has an electron-withdrawing inductive effect, this means that the F atoms "compete" for a finite amount of available electron charge. Some finer points can also be interpreted, such as the relative strengths of the N—H···F—C interactions in 1,2- versus 1,4-fluorobenzene and the relative strengths of the C—H···O═C interactions in 1,2,3-FB as compared to 1,3,5-FB and in 1,2,3,4-FB versus 1,2,4,5-FB.

On the other hand, the calculated partial atomic charges correlate only moderately well with the individual H-bond

TABLE 4: Monomer Properties of the Fluorobenzene F-acceptor and H-Donor Atoms[a]

	CHELPG atomic charges		NBO atomic charges		proton affinity[b]	gas-phase acidity[b]
	F (acceptor)	H (donor)	F (acceptor)	H (donor)	F (acceptor)	H (donor)
fluorobenzene	−0.253	+0.142	−0.335	+0.231	147.7	383.3
1,2-fluorobenzene	−0.197	+0.149	−0.316	+0.234	140.4	375.6
1,4-fluorobenzene	−0.244	+0.157	−0.333	+0.234	142.3	377.0
1,2,3-fluorobenzene	−0.184	+0.167	−0.311	+0.235	135.3	371.0
1,3,5-fluorobenzene	−0.224	+0.222	−0.321	+0.251	137.1	363.9
1,2,3,4-fluorobenzene	−0.176	+0.181	−0.310	+0.240	136.2	364.7
1,2,4,5-fluorobenzene	−0.169	+0.224	−0.309	+0.253	130.4	355.3

[a] Atomic partial charges calculated with the CHELPG[42] and NBO[43] methods, calculated gas-phase basicities and gas-phase acidities (kcal/mol). All values calculated using PW91/6-311++G(d,p). [b] Calculated gas-phase reaction enthalpies at 298.15 K, see text.

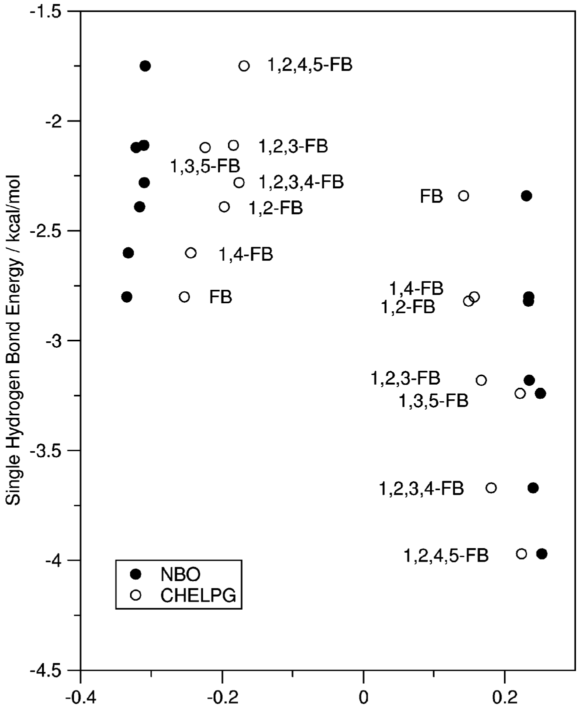

Figure 7. Calculated single N—H···F—C and C—H···O═C hydrogen bond energies plotted vs the calculated natural bond orbital (●) and CHELPG partial charges (○) of the hydrogen-bonded fluorobenzene H and F atoms.

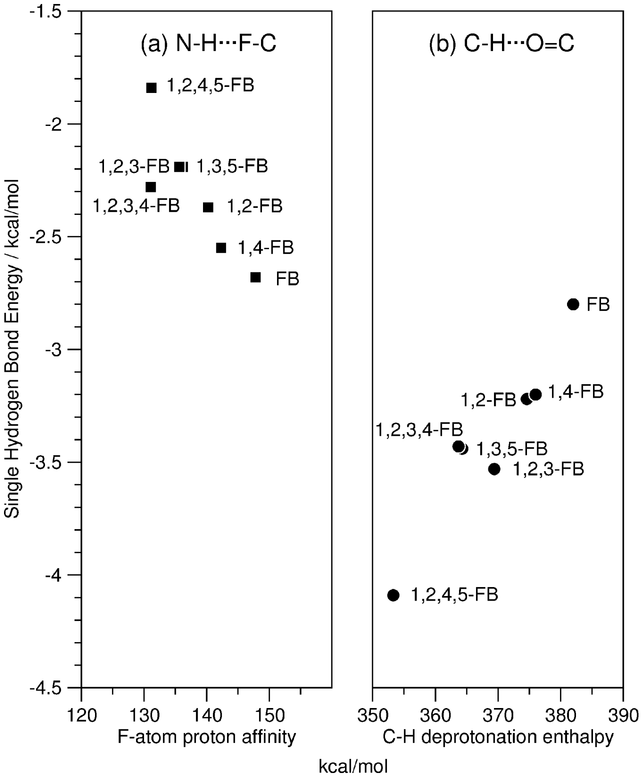

Figure 8. (a) Single N—H···F—C hydrogen bond energies vs the gas-phase proton affinity of the H-bonded fluorobenzene F atom. (b) Single C—H···O═C hydrogen bond energies vs the gas-phase C—H deprotonation enthalpies of the H-bonded fluorobenzene H atom.

strengths. This holds for Mulliken atomic charges (not shown), CHELPG charges, in which the charges are fitted from the electrostatic potential,[42] and NBO charges, which are fitted using the natural bond orbital (NBO) method.[43] The CHELPG and NBO charges of the H and F atoms are given in Table 4. The correlations with the single H-bond strengths are not very convincing, as shown in Figure 7.

Alternatively, the donor properties of the C−H groups can be characterized by the standard enthalpies of the gas-phase deprotonation reaction AH → A^- + H^+ at 298 K, i.e., the gas-phase acidity.[21,44,45] Similarly, the acceptor strength of the C−F groups is quantified by the gas-phase proton affinity, i.e., the negative enthalpies of the reactions B + H^+ → BH^+. The calculated protonation site is at the F atom, i.e., giving C−F−H^+. We have checked that the protonated fluorobenzenes are stable with respect to dissociation into hydrofluoric acid and the corresponding (fluoro)phenyl cations. Note that 1,2,4,5-tetrafluorobenzene is a moderate gas-phase acid, comparable to hydrofluoric acid and phenol.

The standard reaction enthalpies at 298.15 K are calculated at the PW91/6-311++G(d,p) level and are given in Table 4. Figure 8 shows the results: In the left panel, the calculated N—H···F—C hydrogen bond energies are plotted versus the calculated proton affinities of the C—F groups; on the right, the calculated C—H···O═C hydrogen bond energies are plotted versus the calculated gas-phase acidities of the C—H groups. With the exception of 1,2,3,4-fluorobenzene, the observed correlations between the hydrogen bond properties and the gas-phase acid/base properties are good.

III. Discussion

In 1963, Allerhand and Schleyer investigated C−H groups as proton donors by infrared spectroscopy. From a large survey of different compounds, they concluded qualitatively that the strength of hydrogen bonds with C−H as the donor depends (a) on the hybridization of the carbon atom, as C(sp^1)−H > C(sp^2)−H > C(sp^3)−H, and (b) on the number of electron-withdrawing atoms adjacent to carbon group.[46] The enhancement of the C−H donor strength by neighboring electronegative groups is often called "activation".[20,24] Vargas et al. have computationally investigated C−H···O interactions in hydrogen-bonded formamide and *N′*,*N′*-dimethylformamide (DMF) dimers, several of which involve C(sp^2)−H based C−H···O═C hydrogen bonds.[21,22] For the DMF dimer **1**[21] that is held together by formyl C—H···O hydrogen bonds, they calculated $D_e = 2.68$ kcal/mol (MP2/aug-cc-pVTZ, CP-corrected) and a H_C···O distance of 2.36 Å. The isomorphous formamide dimer **5**[22] has a calculated $-D_e = 2.56$ kcal/mol (MP2/aug-cc-pVQZ, CP-corrected) and a H_C···O distance of 2.32 Å (MP2/aug-cc-pVTZ). The formyl C—H···O═C hydrogen bond strengths calculated by Vargas et al. are comparable to the *weakest* C—H···O═C single hydrogen bond calculated in this work (for 2PY·fluorobenzene), which is 2.3−2.8 kcal/mol. However, the fluorobenzene C—H···O═C hydrogen bond strengths increase up to 4.0−4.1 kcal/mol for 2PY·1,2,4,5-FB.

Radom et al. have recently calculated the H-bonding properties of fluorinated ethene, ethane, and methane with NH_3 as acceptor.[24] β-Fluoroethene is directly comparable to the fluorobenzenes in this work: In both cases, the C atoms are sp^2 hybridized and have a fluorine atom in the β-position activating the C—H group. The calculated C—H···NH_3 hydrogen bond energy is 1.00 kcal, which is only about ≈40% of that of the weakest C—H···O═C hydrogen bond calculated here. The activation effect reported in ref 24 is 0.52 kcal/mol per fluorine atom in the β-position.

In relation to 1-fluorobenzene, we find an average activation the C—H···O═C hydrogen bond by additional F atoms. Table 2 shows that the activation is between 0.45 and 0.7 kcal/mol per additional F atom. The influence of the F substituent *positions* relative to the C—H donor group is weak for the difluoro- and trifluorobenzenes; on the other hand, the 1,2,4,5-tetrafluorobenzene shows a considerably stronger C—H···O═C bond than 1,2,3,4-tetrafluorobenzene.

Using free jet millimeter-wave and microwave spectroscopies, Caminati and co-workers have pioneered quantitative measurements of the lengths of weak C—H···F—C and O—H···F—C hydrogen bonds.[25,27−29] They have also tentatively estimated the strengths of C—H···F—C and of C—H···O hydrogen bonds, using experimental rotational and centrifugal distortion constants. With the assumption of hydrogen bond additivity, they estimate an approximate binding energy of −1.8 kcal/mol for the single O—H···F—C linkage of HO—H···difluoromethane.[26] This value agrees nicely with the −1.75 kcal/mol that we calculated for the N—H···F—C hydrogen bond in the 2PY·1,2,4,5-fluorobenzene complex, which is the weakest of the series.

IV. Conclusions

In supersonic jets, the seven complexes 2PY·fluorobenzene (2PY·FB, 2PY·1,2-FB, 2PY·1,4-FB, 2PY·1,3,5-FB, 2PY·1,2,3-FB, 2PY·1,2,4,5-FB, and 2PY·1,2,3,4-FB) are experimentally observed in hydrogen-bonded geometries exclusively.[30] This shows that the H-bonds in these systems are stronger than the π-stacking energies. Calculation of accurate hydrogen bond energies using the resolution-of-identity MP2 method and large basis sets show that the C—H···O═C and N—H···F—C hydrogen bond strengths in these complexes are quite strong: Extrapolations of the D_e values to the complete basis set (CBS) limit give $-D_{e,CBS} = 6.36-6.87$ kcal/mol, increasing by ~8% between mono- and tetrafluorobenzene.

Calculations with the PW91 density functional method and the 6-311++G(d,p) basis set yield D_e values that are in good agreement with the RIMP2 CBS limit binding energies, being consistently 0.25−0.4 kcal/mol smaller. The great advantage of the DFT method is that it allows us to calculate the vibrational frequencies and zero-point energies, the vibrational partition function, and the thermodynamic functions. This is not currently possible with the RIMP2 or MP2 methods for such large systems and basis sets. In contrast, the B3LYP binding energies are consistently too low by about 1.5 kcal/mol or 20% and are not recommended for binding energies. The vibrational frequencies, zero-point energies (ZPE), and the changes of ZPE upon dimerization (ΔZPE) were calculated with the PW91 DFT method. When added to the RIMP2 complete basis set extrapolated D_e^∞ values, one obtains $-D_0$ values that range between 5.86 kcal/mol for 2PY·1,3,5-FB to 6.34 kcal/mol for 2PY·1,2,4,5-FB. Since the experiment does not show any indication of π-stacked isomers,[30] these values also represent upper estimates for the π-stacking energies of these complexes.

The strengths of the individual H-bonds were evaluated by twisting the 2-pyridone and fluorobenzene moieties by 90° relative to each other. The individual C—H···O═C and N—H···F—C hydrogen bond strengths add up to the total calculated interaction to within 10−15%. The near-additivity of these H-bonds shows that cooperative effects such as “resonance-assisted” hydrogen bonding are small.

In 2PY·fluorobenzene, the C—H···O═C and N—H···F—C have approximately the same strength of 2.8 kcal/mol. With an increasing number of F atoms, the C—H···O═C hydrogen bond strength increases up to ~4.5 kcal/mol; this is countered by the simultaneous decrease of the N—H···F—C hydrogen bond strength to ~1.8 kcal/mol in the tetrafluorobenzenes.

Acknowledgment. This work was supported by the Schweiz. Nationalfonds (project nos. 2000-68081.02 and 200020-105490). We thank Prof. Willem Klopper (Universität Karlsruhe) for helpful comments.

Supporting Information Available: Additional theoretical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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