The Structural Effects of Fluorine Substitution in Pyridine, Pyrimidine, and *s*-Triazine: An Ab Initio Study

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The structures of 2-fluoropyridine, 3-fluoropyridine, 4-fluoropyridine, pentafluoropyridine, 2-fluoropyrimidine, 5-fluoropyrimidine, and fluoro-*s*-triazine have been evaluated by the ab initio gradient method with a 4-21 basis set augmented as needed with polarization functions on nitrogen. The structural effects of fluorination on the parent heterocycle are very similar to the effects of fluorination on benzene studied earlier. The ring angle is enlarged by about 2° at the point of fluorination and the adjacent ring bonds are shortened, much more for an adjacent C-N than for C-C. Fluorination of pyridine at the C_2 position causes an increase of bond localization in the ring. Rotational constants calculated from the structural parameters corrected with standard offset values are in exceptionally close agreement with experimental constants where these are known.

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Introduction.

In recent studies, we have explored the capability of ab initio gradient calculations to evaluate the structures of some nitrogen-containing aromatic rings [1] and of a number of fluorinated benzenes [2]. The primary goal of those efforts was the determination of the structural perturbations introduced into the ring geometry by the substitution of one or more fluorine atoms on the benzene ring or of one or more nitrogen atoms in the ring itself. We now draw on the lessons learned in those studies to investigate the effect of fluorine substitution in various positions on pyridine, pyrimidine, and *s*-triazine rings.

If structure determinations are to lead to useful chemical knowledge, they must have very high accuracy and reliability, since substituent effects on a given skeletal structure are generally reflected in geometry changes on the order of at most a hundredth of an Ångström or a few degrees. Ab initio calculations to give such high accuracy directly would involve very large basis sets and extensive treatment of electron correlation; they are not currently possible for molecules of the size considered here. A solution of the problem that has now been demonstrated extensively consists of ab initio gradient calculation of the geometries with a moderate-sized basis set (roughly double-zeta) and the subsequent application of small, empirically derived offset values as additive corrections to bond distances.

The offset value for a given type of bond (*e.g.*, C-H, C-C, C=C) is found to be essentially invariant to changes in the molecular environment of the bond. This is a result of the fact that the molecular surroundings produce little alteration in the effect of electron correlation on the bond. Similarily, the small basis set error remaining at this level of calculation is essentially constant for a given bond type. Bond angles determined at this level are sufficiently accurate without any correction. This procedure has been used, for example, in the papers referred to above on fluorinated benzenes [2] and nitrogen heteroaromatics [1]. The accuracy obtainable in those cases appeared to be comparable to that resulting from high-quality microwave spectroscopic investigations.

It has been shown [1,2] that the effect of nitrogen or fluorine substitution on the structure of a benzene ring is quite systematic. For example, nitrogen substitution in the ring produces a sharp decrease from 120° in the ring atom at nitrogen, the decrease becoming progressively greater as the number of nitrogen atoms in the ring is increased. The CNC angle in pyridine is 116.7°, which decreases to 115.4° in pyrimidine and to 113.7° in *s*-triazine. Comparable consistent trends in both bond distances and in ring angles have been noted [2] for fluorine substitution on benzene. We are now interested in establishing structural trends when both types of substitution are present simultaneously.

Method.

All of the calculations reported here were performed with the program TEXAS [3] which solves the Roothaan-Hall equations for a basis set of contracted Gaussian functions and calculates the energy gradient analytically by the method of Pulay [4]. The basis set adopted was the standard 4-21 split valence shell set [5], augmented as needed by addition of d functions with an orbital exponent of 0.8 to the nitrogen atoms only. The presence of d functions in the basis set is known to be necessary to reproduce accurately the angles around atoms such as nitrogen or oxygen that have lone pairs of electrons [6].

Table 1

Calculated Geometries of the Fluoropyridines [a]

Parameter	Pyridine [b] 4-21	Pyridine [b] 4-21*	2-Fluoropyridine 4-21	2-Fluoropyridine 4-21*	3-Fluoropyridine 4-21	3-Fluoropyridine 4-21*	4-Fluoropyridine 4-21
$N_1—C_2$	1.333	1.327_8	1.301	1.296	1.329	1.324	1.333
$C_2—C_3$	1.382	1.3833	1.381	1.383	1.375	1.376	1.382
$C_3—C_4$	1.384	1.3817	1.377	1.375	1.373	1.371	1.375
$C_4—C_5$	1.384	1.3817	1.391	1.389	1.383	1.381	1.375
$C_5—C_6$	1.382	1.3833	1.376	1.376	1.383	1.384	1.382
$C_6—N_1$	1.333	1.327_8	1.340	1.337	1.334	1.328	1.333
$C_2—X_2$	1.071	1.0736	1.357	1.362	1.069	1.071	1.070
$C_3—X_3$	1.070	1.0704	1.068	1.067	1.364	1.365	1.068
$C_4—X_4$	1.072	1.0719	1.071	1.071	1.069	1.069	1.362
$C_5—H_5$	1.070	1.0704	1.069	1.069	1.070	1.070	1.068
$C_6—H_6$	1.071	1.0736	1.069	1.072	1.069	1.072	1.070
$\angle C_6N_1C_2$	118.4	116.7_4	118.3	116.0	119.3	117.4	118.5
$\angle N_1C_2C_3$	122.8	123.9_6	124.7	126.4	121.1	122.3	122.9
$\angle C_2C_3C_4$	118.5	118.4_3	116.9	116.8	120.7	120.8	117.3
$\angle C_3C_4C_5$	119.0	118.4_9	119.6	118.9	117.8	117.1	121.3
$\angle C_4C_5C_6$	118.5	118.4_3	118.3	118.3	118.9	118.7	117.3
$\angle C_5C_6N_1$	122.8	123.9_6	122.2	123.7	122.2	123.7	122.9
$\angle NC_2X_2$	116.4	116.1_5	117.2	116.4	118.4	118.2	116.7
$\angle C_2C_3X_3$	120.4	120.2_7	120.3	120.1	119.4	119.1	122.1
$\angle C_3C_4X_4$	120.5	120.7_6	120.0	120.4	120.2	120.5	119.4
$\angle C_4C_5H_5$	121.1	120.3_0	121.1	121.3	120.7	120.9	120.6
$\angle C_5C_6H_6$	120.8	119.8_9	121.6	120.6	121.1	120.1	120.4
μ		2.17		3.91		2.28	0.31
E + 344.			−.76022	−.79842	−.75194	−.78699	−.75496
ΔE			0 [c]	0 [c]	5.2	7.2	3.3

[a] Distances in Å, angles in °, dipole moments in Debye units, total energy (E) in atomic units, relative energy (ΔE) in kcal mol^{-1}. See Figure 1 for labelling of atoms. The 4-21* basis set has d functions on the N atom only. [b] Ref [1]. [c] Chosen for comparison of relative energies.

Table 2

Ring Distortion Produced by Fluorination [a]

	Fluorobenzene	2-Fluoropyridine	3-Fluoropyridine	4-Fluoropyridine
Δ	$+2.3_5°$	+2.4°	+2.4°	+2.3°
Δ_o	$-1.4_2°$	−1.6°	−1.4°, −1.7°	−1.2°
Δ_m	$+0.3_2°$	+0.4°	+0.3°	+0.1°
Δ_p	$-0.1_5°$	−0.1°	−0.3°	—

[a] Δ is the change in angle, compared with benzene or pyridine, at the point of substitution; the other entries are changes in angles at C in the *ortho*, *meta*, or *para* positions.

Use of a larger basis set for the calculations would not have obviated the need for application of offset value corrections to obtain the best estimate of the absolute values of bond distances, although the numerical value of the corrections would have been slightly different. There would be no greater accuracy in the corrected values obtained, and, perhaps of greater importance, no significant difference in the relative values obtained for a given bond parameter in the families of related molecules. Such comparisons are the object of most chemical interest in molecular structures rather than the absolute distances. For the

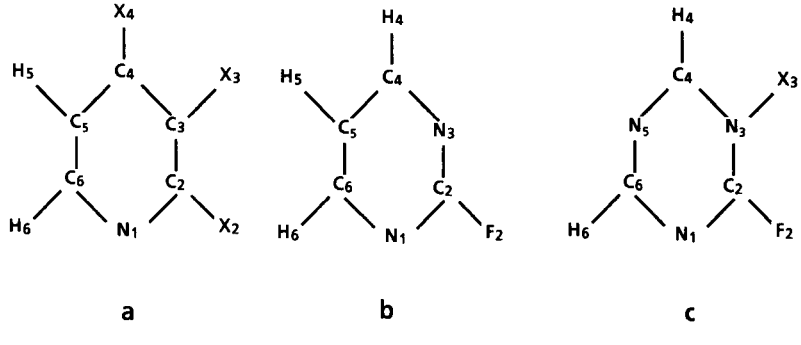

Figure 1. Labelling of the atoms in (**a**) the pyridines, (**b**) 2-fluoropyrimidine, and (**c**) fluoro-*s*-triazine.

Table 3

Moments of Inertia of the Fluoropyridines

	Calculated	Experimental	SD [a]
2-Fluoropyridine			
I_a	85.951	86.081 [b]	86.100
I_b	187.065	187.180 [b]	191.847
I_c	273.016	273.283 [b]	277.947
3-Fluoropyridine			
I_a	86.489	86.690 [c]	86.245
I_b	191.388	191.614 [c]	195.786
I_c	277.876	278.345 [c]	282.032

[a] Ref [8]. These moments of inertia were obtained from a structure constructed to fit the observed moments, subject to a number of assumptions. [b] Ref [10]. [c] Ref [9].

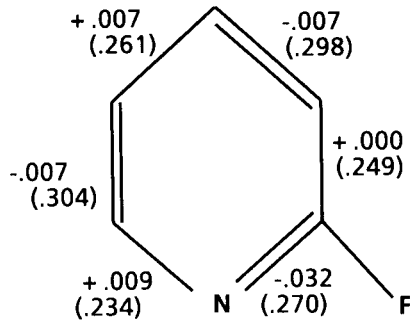

Figure 2. Differences in ring bond lengths between 2-fluoropyridine and pyridine and (in parentheses) π-overlap populations of the ring bonds.

same reason, consideration of electron correlation would have been equally unnecessary in attempting to obtain either more accurate relative or absolute values. On the other hand, use of a minimal basis set ab initio calculation or of semi-empirical methods does not produce sufficient constancy in the bond length errors to permit confident corrections to be applied leading to the level of accuracy sought here.

The force relaxation method was used for the geometry optimizations, assuring that all structural parameters are relaxed to their equilibrium values simultaneously. Convergence was equivalent to at least ± 1 in the last digit quoted or to ± 3 in a figure shown as a subscript. The absolute accuracy to be expected in such a calculation is fully discussed in our earlier paper [2].

Fluoropyridines.

The equilibrium structures calculated for the three possible monofluoropyridines are shown in Table 1. The structure previously calculated [1] in exactly the same manner for the parent molecule, pyridine, is also given for comparison. Before commenting on the absolute values of the structural parameters, we shall consider the changes in structure caused by fluorine substitution. Because of the close similarity in the molecules compared, we expect to achieve a very high reliability and accuracy in the relative values obtained. Such accuracy has been demonstrated, for example, in comparisons of the differing lengths of CH bonds in a methyl group in an asymmetric environment [7], where the differences are apparently reliable to thousandths of an Ångström or better.

Table 4

Structures of the Fluorinated Pyrimidines and *s*-Triazine [a]

Parameter	Pyrimidine [b]	2-Fluoropyrimidine	5-Fluoropyrimidine	*s*-Triazine [b]	Fluoro-*s*-triazine
$N_1—C_2$	1.330	1.313	1.331	1.332	1.315
$N_3—C_4$	1.334	1.335	1.332	1.332	1.332
$C_4—C_5$ (or N_5)	1.381	1.382	1.374	1.332	1.332
$C_2—X_2$	1.068	1.342	1.066	1.067	1.332
$C_4—H_4$	1.070	1.069	1.068	1.067	1.066
C_5 (or N_5)-X_5	1.069	1.069	1.360	1.067	1.066
$\angle C_6N_1C_2$	117.4	116.6	118.0	116.1	115.5
$\angle N_1C_2N_3$	125.0	127.1	124.7	123.9	125.5
$\angle N_3C_4C_5$ (or N_5)	121.6	121.6	120.1	123.9	123.7
$\angle C_4C_5$ (or N_5) C_6	116.9	116.5	119.2	116.1	116.0
$\angle N_1C_2X_2$	117.5	116.5	117.7	118.1	119.0
$\angle N_3C_4H_4$	116.8	116.4	118.5	118.1	117.8
$\angle C_4C_5X_5$	121.5	121.7	120.4		
μ	2.28	4.97	0.47	0	2.28
E	−262.10305	−360.69546	−360.68365	−278.03996	−376.63157
ΔE		0	7.4		

[a] Distances in Å, angles in °, dipole moments in Debye units, total energy (E) in atomic units, relative energy (ΔE) in kcal mol^{-1}. See Figure 1 for labelling of atoms. All calculations used 4-21 basis set. C_{2v} symmetry assumed. [b] Ref [1].

The effect of nitrogen atom d functions on the calculated geometries is in line with previous observations [1,5,6]. Without them, the angle at nitrogen is calculated about 2° too large. The added functions also produce a shortening of adjacent bonds with little effect elsewhere in the molecule. Particularly significant is the fact that differences in related bond lengths in the different molecules is nearly the same with either basis set; the calculated changes in the N_1-C_2 bond length, for example, are identical with either basis.

The substitution of a fluorine atom on a benzene ring has been shown [2] to cause the ring angle at the point of substitution to increase by 2.35°. As shown in Table 1, the ring angle at the point of fluorination increases (compared with that in pyridine) by 2.4°, 2.4° and 2.3° in the three monofluoropyridines, using the values from the 4-21* basis set where available. Such remarkable constancy suggests that interaction of a fluorine atom with the aromatic ring is nearly identical for pyridine and for benzene. Other geometric parameters may next be examined to test this conjecture.

The ring distortion produced by fluorination of benzene is taken up by a 1.42° decrease of the ring angle at the adjacent (*ortho*) carbon atom, a 0.32° increase at the *meta* carbon, and a 0.15° decrease at the *para* position [2]. These alterations in ring angles are shown in Table 2 along with comparable values for the pyridines. For the latter compounds, the comparison is, of course, with the comparable angles in pyridine. While the quantitative comparison appears to be right at the limit of accuracy of the method, the qualitative picture is clear. For all of the fluorinated pyridines, as well as for fluorobenzene, the angular ring distortion takes the form of an increase in the ring angle at the point of fluorination, a decrease in the angle at the *ortho* position (regardless of whether the atom there is carbon or nitrogen), a slight angle enlargement at the *meta* position, and a very small decrease at the *para* position. Further evidence is obtained that fluorination anywhere in the pyridine ring has a very similar effect to fluorination of benzene.

Fluorination at C_4 position causes a shortening by 0.009 Å in the adjacent C-C bonds and little effect on the other ring distances. The same thing is seen in 3-fluoropyridine, where the adjacent bonds are shortened by 0.009 and 0.007 Å. This seems to be a simple consequence of electron withdrawal by the fluorine atom from the local bond system.

The effect on ring bond lengths by fluorination at the C_2 position is much different, however, A major shortening, by 0.032 Å, is produced in the adjacent N-C_2 bond, indicating the greater ease of withdrawing electrons from N than from C. The disruption of the electron distribution involves also the π system of the ring, as can be seen by the alternating changes in bond lengths proceeding around the ring in the direction N-C_2 to C_6-N to C_5-C_6 *etc.* (see Figure 2). The final link in the ring, C_2-C_3 is unchanged from pyridine. This can be understood as a cancellation between the +0.007 Å to be expected from the change in the π system and the similar amount of σ shortening of the adjacent C-C bond seen in the 3-fluoro- and 4-fluoropyridines.

The increased localization of electron density in the 2-fluoropyridine ring indicated by the bond length alternation can also be investigated by π-overlap populations derived from a Mulliken analysis. These overlap populations are shown in Figure 2 and again suggest slight electron localization toward the limit which would be represented by the alternating single and double bonds shown in the figure.

The C-F bond distances show a slight trend in the same order as the molecular stabilities, with 2-F shorter than 4-F by 0.005 Å and 4-F shorter than 3-F by 0.002 Å. In this case it is probably more accurate to make comparisons using the 4-21 basis set where varying effects depending on proximity to the d functions on N are not present. In all cases, the C-F bond is shorter than in fluorobenzene [2] by amounts varying from 0.005 to 0.012 Å.

The C-H bond distances show no significant variation. In all three monofluoropyridines there seems to be a small amount of attractive interaction between the fluorine and hydrogen, as indicated by the smaller CCH angle towards fluorine.

No gas-phase experimental structural studies of 4-fluoropyridine have been reported. The 2-fluoro- and 3-fluoro- derivatives have been studied by Sharma and Doraiswamy [8-10] using microwave spectroscopy. Full structural information could not be obtained from their experiments since only two independent moments of inertia were obtained for each molecule. They presented structures that could be fitted to the measured moments of inertia, but they were based on certain assumptions, primarily a C-F bond length of 1.354 Å transferred from fluorobenzene. The C_3-C_4 bond length in 2-fluoropyridine was also assumed to be unchanged from pyridine so that the alternation in the ring distances was not observed. In spite of these assumptions which were made necessary because of the limited data, Sharma and Doraiswamy correctly found the angular deformation of the ring produced by fluorination.

The best absolute values of the structural parameters that can be obtained from our data result from the use of the offset value corrections as described previously [1,2,5,6] and in the Introduction. The corrections to be applied to convert the distances in Table 1 to the best estimated r_o structure are $+0.012_5$ Å for both C-C and C-N bonds, +0.012 Å for C-H bonds, and −0.026 Å for C-F bonds,

the latter being known with less precision. Correction to an r_e structure would require offset values of about +0.011 Å for C-C and C-N, +0.007 Å for C-H and −0.027 Å for C-F. The best estimate of the bond angles comes directly from the 4-21* calculation with no correction. It should be emphasized that these offset values are not in any sense fitted to the compounds of the present study but are known from previous work.

The only possible check on the accuracy of the absolute values of the structural parameters derived here is to see how well the r_o parameters reproduce the direct experimental observable: the moments of inertia. This comparison is shown in Table 3. The experimental results should be correct to the last digit shown. It can be seen that the agreement from our computed structure is remarkably good, considerably better in fact than that from the structure, constructed specifically to fit the rotational constants.

A semi-empirical study of the geometry of the fluoropyridine by Dewar *et al.* [11] has appeared, based on work done after the present ab initio study was completed. Some of the trends shown here could also be observed from that study, but not the finer details.

Fluoropyrimidines and Fluorotriazine.

The structures of 2-fluoropyrimidine, 5-fluoropyrimidine and fluoro-*s*-triazine, all calculated with the 4-21 basis set, are shown in Table 4. The bond parameters not specifically listed are related to those shown by the molecular C_{2v} symmetry in all cases.

All of the trends noted for the fluorinated pyridines are continued in the fluorinated pyrimidines and triazine. The adjacent ring bond lengths are shortened by amounts similar to those seen in pyridine. It is interesting to see that the −0.032 Å shortening for an adjacent C-N bond in pyridine is replaced by a change of −0.017 Å in each of the two adjacent C-N bonds in 2-fluoropyrimidine and in fluorotriazine. The ring bond angle at the point of fluorination is again increased by about 2° with an alternation decreasing in magnitude at positions further around the ring.

The C-F bond length varies in a manner directly related to its proximity to ring N atoms. In the substituted pyridines, the C-F bond is 0.006 Å shorter in the *ortho* position than in the *meta* or *para*. An *ortho* relationship to two N atoms in 2-fluoropyrimidine causes a shortening of 0.021 Å while a similar cation enhanced by a third nitrogen in a *para* position (in fluorotriazine) causes a decrease of 0.031 Å. Such large changes in bond lengths indicate very extensive transfer of electron density from the N atoms to C-F bonding orbitals.

No experimental data are available for comparison. The best estimate of the true r_e and r_o structures can be made by adding the offset values discussed in the previous section to the parameters in Table 4.

Summary.

The effects of nitrogen substitution in a benzene ring and fluorine substitution on benzene are essentially additive. Fluorine substitution on pyridine, pyrimidine, or *s*-triazine produces: (1) An enlargement by about 2° in the ring angle at the point of substitution. (2) Alternating angle decreases and increases diminishing in magnitude at ring positions further from the point of substitution. (3) A decrease in length by about 0.008 Å in an adjacent C-C bond and much larger decreases in an adjacent C-N bond (0.032 Å for one adjacent C-N bond or 0.017 Å in each of two such adjacent bonds). (4) A tendency for C-H bonds adjacent to a C-F bond to bend about 1° in the direction of the F atom. (5) A direct relation between C-F bond length and position with respect to a N atom (0.006 Å shorter in an *ortho* position than in *meta* or *para*, 0.02 Å shorter if *ortho* to two atoms, and 0.03 Å shorter if *ortho* to two N atoms and *para* to another).

The ring bonds in 2-fluoropyridine were unique in giving evidence, both from structure and from π-overlap populations, of an increase in π localization compared with pyridine.

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