

FLUOROPYRAZOLES: AN *AB INITIO* STUDY

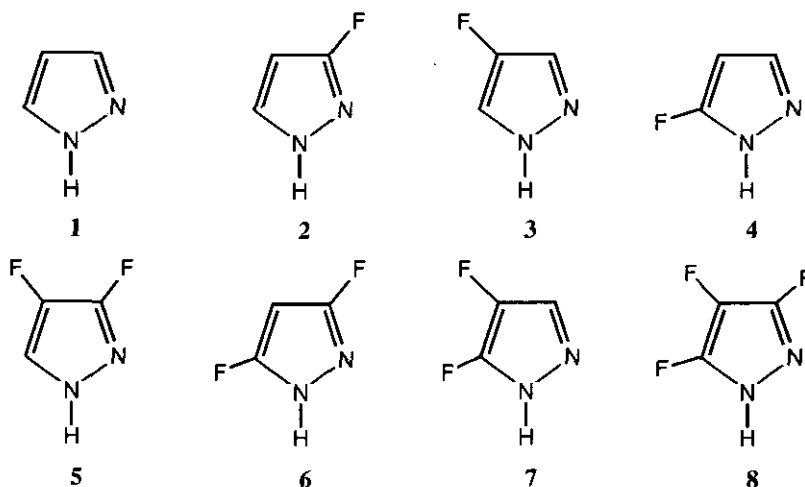
Rosa María Claramunt,^{1,*} Ibon Alkorta,² and José Elguero²

¹ Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, Senda del Rey, s/n, E-28040 Madrid, Spain

² Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

Abstract- Quantum mechanic calculations have been done at the RHF and MP2 levels with the STO-3G, 6-31G**, 6-311G** basis sets on pyrazole itself and seven *N*-unsubstituted *C*-fluoropyrazoles. These calculations have been used to discuss the molecular structure of these compounds in relation to their aromaticity. The corresponding ¹H, ¹³C, ¹⁵N and ¹⁹F chemical shifts were calculated using the GIAO perturbation method.

In 1988, García and Vilarrasa reported MNDO calculations of fluoroazoles.¹ These compounds, and particularly fluoropyrazoles, have since then been the subject of several publications,²⁻⁷ which disclose the interest of these molecules. Moreover, MNDO calculations are today substandard for these small molecules. Therefore, we decided to calculate, using *ab initio* methods of increased quality, the energies, dipole moments and chemical shifts of seven fluoropyrazoles (2-8). Pyrazole itself (1) was also included for comparative purposes.



RESULTS AND DISCUSSION

Theoretical calculations: energies and dipole moments

We have reported in Table 1 the results of the RHF/STO-3G, RHF/6-31G**, RHF/6-311G** and MP2//6-311G** (hereinafter MP2) calculations. They are consistent and show the expected decrease in energy with the increasing level of the basis set used.

Table 1. Energy in Hartrees^a of pyrazoles (**1-8**) and matrix of the model

Comp.	STO-3G	6-31G**	6-311G**	MP2/6-311G**	ΔE (kcal mol ⁻¹)	3	4	5	FF
1	-221.977260	-224.8032823	-224.848826	-225.610329	0.00	0	0	0	0
2	-319.436516	-323.652199	-323.726817	-324.678773	-62186.25	1	0	0	0
3	-319.430726	-323.640837	-323.715394	-324.670311	-62180.94	0	1	0	0
4	-319.435722	-323.647065	-323.721514	-324.673274	-62182.80	0	0	1	0
5	-416.886880	-422.484233	-422.588080	-423.734273	-124364.38	1	1	0	1
6	-416.895038	-422.496333	-422.599849	-423.742341	-124369.45	1	0	1	0
7	-416.885453	-422.478192	-422.581895	-423.728003	-124360.45	0	1	1	1
8	-514.341708	-521.322185	-521.455150	-522.792127	-186543.99	1	1	1	2

^a 1 Hartree = 627.5095 kcal mol⁻¹.

All these data can be analyzed using an additive model, but we will discuss only the MP2/6-311G** fifth column. For this, we have first transformed the Hartrees in kcal mol⁻¹ with regard to pyrazole itself, ΔE (MP2/6-311G** in kcal mol⁻¹) = [E(flouropyrazole) - E(**1**)] x 627.5095. The model matrix corresponding to the additive model has four columns, the first three ones correspond to the presence (1) or absence (0) of fluorine atoms [from **1** (000) to **8** (111)] and the last one corresponds to the presence or absence of two adjacent fluorine atoms [**1-4** and **6** (0), **5** and **7** (1), **8** (2)]. The result of the regression (n = 8, r² = 1.000, no intercept) yields very large values for the coefficients because of the large values of the ΔE column. Therefore, it is convenient to take the 3-fluoro effect as 0.00 by definition, the other effects being then 4-fluoro = 5.6 kcal mol⁻¹, 5-fluoro = 3.7 kcal mol⁻¹ and the destabilizing interaction between two adjacent fluorine substituents = 3.1 kcal mol⁻¹. Consequently, the order of stability of monofluoropyrazoles is 3-F > 5-F > 4-F. In the case of difluoropyrazoles, the order is 3,5-diF > 3,4-diF > 4,5-diF although the differences are larger due to the absence of F/F interaction in compound (**6**). The results of the MNDO calculations¹ are qualitatively consistent with this picture: 3-F > 5-F > 4-F and 3,5-diF > 3,4-diF > 4,5-diF.

The most interesting aspect concerns the annular tautomerism^{8,9} of 3(5)-flouropyrazole and 3(5),4-difluoropyrazole. We have summarized in Table 2 the differences in energy according to the different computations.

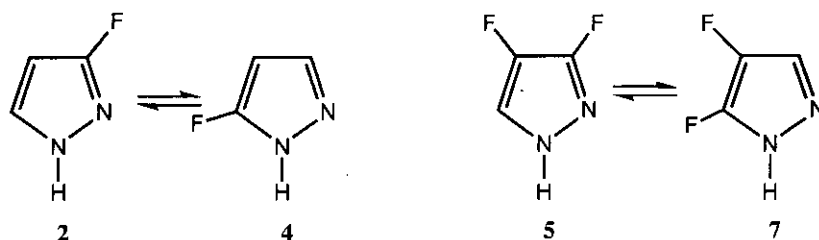


Table 2. Relative energies (in kcal mol⁻¹) for pairs of tautomers (the most stable tautomer between brackets)

Tautomeric pairs	MNDO ¹	STO-3G	6-31G**	6-311G**	MP2/6-311G**
3-F/5-F (2/4)	0.2 [2]	0.50 [2]	3.22 [2]	3.33 [2]	3.45 [2]
3,4-diF/4,5-diF (5/7)	0.3 [5]	0.90 [5]	3.79 [5]	3.88 [5]	3.94 [5]

It is clear that if the MNDO Hamiltonian predicts correctly the predominance of 3-fluoro tautomers (2) and (5), but the difference is so small that the authors concluded that there is "no guarantee which tautomer would be preferred in the gas-phase equilibrium".¹ The same problem arises with the STO-3G calculations, which are clearly insufficient, but the three other approximations yield very consistently that 3-fluoro tautomers are about 3.5-4.0 kcal mol⁻¹ more stable than the 5-fluoro ones, an important result for methods such as MS (mass spectrometry), ICR (ion cyclotron resonance spectrometry), MW (microwave spectroscopy), ED (electron diffraction spectroscopy) and gas-phase NMR.

In a first approximation, the influence of the solvent on the tautomeric equilibrium is related to the dipole moment, the higher the dipole moment the more stable the corresponding tautomer in polar solvents. In this case, tautomers (2) and (5) have higher dipole moments than tautomers (4) and (7) respectively (Table 3). Therefore, the conclusions reached for the gas phase will be reinforced in polar solvents. This corresponds to experimental results in CDCl₃ using ¹³C-¹⁹F coupling constants for the (2)/(4) equilibrium⁶ and ¹⁹F-¹⁹F coupling constants for the (5)/(7) equilibrium.¹⁰

Table 3. Dipole moments (μ in D)

Compound	MNDO ¹	STO-3G	6-31G**	6-311G**
Pyrazole (1) ^a	---	2.15	2.37	2.39
3-Fluoropyrazole (2)	4.06	3.15	4.03	4.08
4-Fluoropyrazole (3)	2.55	2.12	2.46	2.50
5-Fluoropyrazole (4)	0.23	1.27	0.97	0.88
3,4-Difluoropyrazole (5)	4.40	3.12	4.09	4.18
3,5-Difluoropyrazole (6)	2.19	2.28	2.58	2.57
4,5-Difluoropyrazole (7)	1.83	1.40	1.49	1.55
3,4,5-Trifluoropyrazole (8)	2.99	2.35	2.89	2.95

^a The experimental value for pyrazole in the gas phase is $\mu = 2.21$ D (by MW).^{9,11}

Dipole moments are not a severe test for computations.⁹ Thus, MNDO values are reasonably good and correlate quite well with 6-311G** ones ($\mu_{\text{MNDO}} = -0.4 + 1.1 * \mu_{6-311G^{**}}$; $n = 7$, $r^2 = 0.957$). Selecting these last values as the most representative, a presence/absence analysis led to: 3-fluoro, +1.6 D, 4-fluoro, +0.3 D and 5-fluoro, -1.3 D ($n = 8$, $r^2 = 0.986$). Although dipole moments are a vectorial property, this simple additive model works reasonably well.

Theoretical calculations: chemical shifts

There are no experimental results concerning energies, nor absolute (heats of formation) neither relative (tautomeric equilibrium constants), or dipole moments for fluoroazoles. On the other hand, some chemical shifts have been reported for these compounds. Consequently, we decided to calculate using the GIAO perturbation method¹² at the RHF/6-311G** level the ¹H, ¹³C, ¹⁵N and ¹⁹F chemical shifts for compounds (1)-(8). Computations provide isotropic shifts (absolute shielding, σ) which to be converted into chemical shifts (δ) need the calculation, at the same computational level, of the usual references: TMS for ¹H and ¹³C, nitromethane for ¹⁵N and fluorotrichloromethane for ¹⁹F. These references contain atoms (Si, O, Cl) that are predicted with large errors using GIAO calculations,¹³ that is the reason why in the present case we have preferred to adjust the calculations to the experimental data by simple regression which provides a set of predicted values for the remaining compounds. The four regressions are:

$$\delta^1\text{H} = 29.7 - 0.893 \sigma^1\text{H}, n = 7, r^2 = 1.000 \quad (1)$$

$$\delta^{13}\text{C} = 184 - 0.882 \sigma^{13}\text{C}, n = 6, r^2 = 0.988 \quad (2)$$

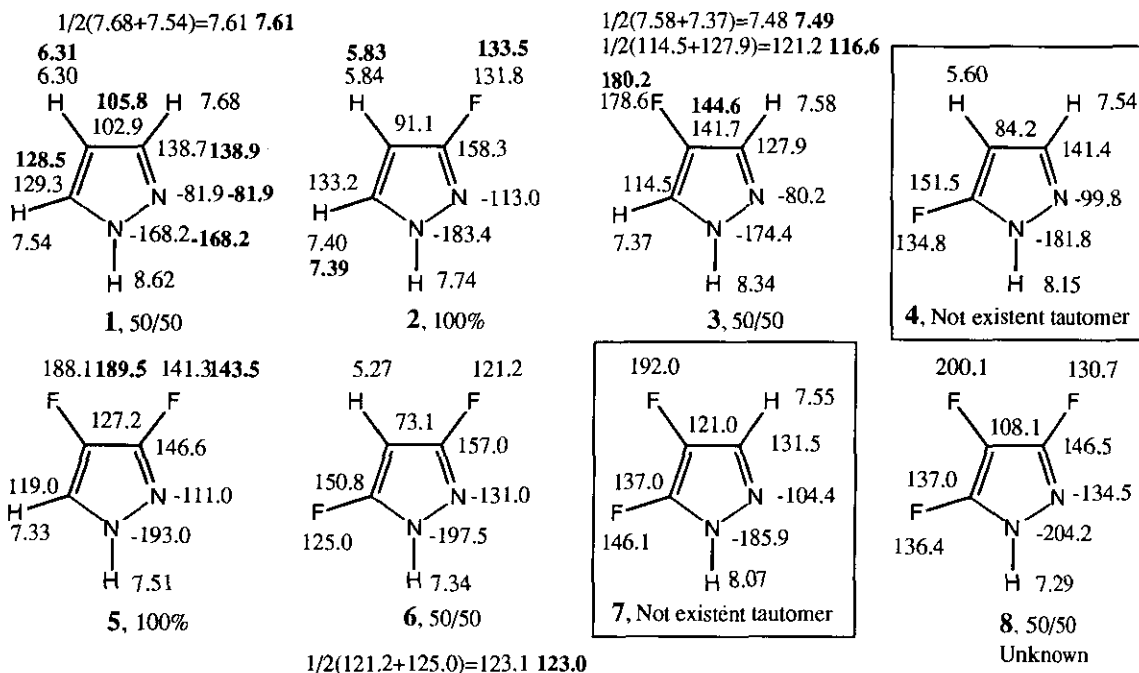
$$\delta^{15}\text{N} = -128 - 0.605 \sigma^{15}\text{N}, n = 2 \quad (3)$$

$$\delta^{19}\text{F} = 152 - 0.798 \sigma^{19}\text{F}, n = 12, r^2 = 0.999 \quad (4)$$

The intercept corresponds to the references whose experimental shieldings are: ¹H (TMS) = 31.4, ¹³C (TMS) = 188.1, ¹⁵N(CH₃NO₂) = -117.5 and ¹⁹F(CFCl₃) = 196, which are in reasonable good agreement with the values obtained by regression taking into account that they are far away from the experimental domain.

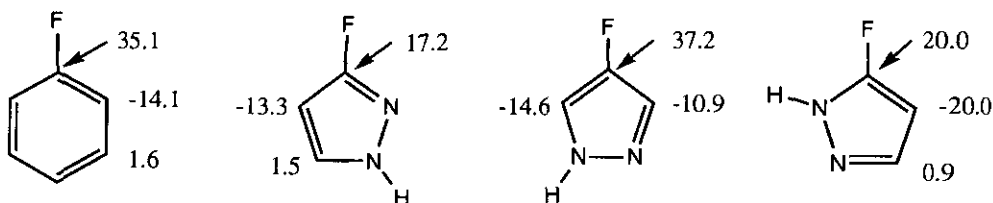
Experimental values (Scheme 1 in bold) are from the following sources: (1), ¹H (only the average value for H3 and H5 is known),⁹ ¹³C,¹⁴ ¹⁵N;¹⁵ (2), ¹H,¹⁶ ¹⁹F;¹⁷ (3), ¹H (only the average value for H3 and H5 is known),¹⁸ ¹³C (only the average value for C3 and C5 is known);¹⁴ ¹⁹F;¹⁸ (5), ¹⁹F;^{10,16} (6), ¹⁹F (only the average value for F3 and F5 is known).^{10,16}

The complete set of calculated values of Scheme 1 can be used to determine the average effect of the fluorine substituents on the ¹³C chemical shifts (SCS) assuming that they are additive (Scheme 2). In sign and importance, these SCS are similar to those reported for *ipso*, *ortho* and *meta* positions of fluorobenzene,¹⁹ although the case of pyrazoles is more complicated since the effect depends on the position of the fluorine atom and on the carbon atom considered.



Bold: Experimental values

Scheme 1



Scheme 2

The results summarized in Scheme 1 are an additional proof that the predominant tautomers are **2** and **5** while tautomers **4** and **7** are virtually non-existent.

COMPUTATIONAL DETAILS

The SPARTAN program²⁰ has been used to build and optimize the structures of the pyrazoles at the RHF/STO-3G,²¹ RHF/6-31G**,²² RHF/6-311G**,²³ and MP2/6-311G** computational levels.²⁴ No symmetry restriction has been imposed in the optimization process. The NMR shieldings have been calculated using the GIAO perturbation method¹² as implemented in the Gaussian-94 package.²⁵ The GIAO calculations have been carried out at the RHF/6-311G** level on the MP2/6-311G** optimized geometries.

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