FLUOROAZOLES. AN MNDO SCF MO STUDY

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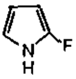
Abstract – MNDO calculations are reported for 43 fluorine-containing nitrogenated five-membered rings. The available experimental data, on fluoropyrazoles **10-15** and other fluoroazoles, correlate quite well with the calculated energies and charge distributions. In the light of such results, some properties of interesting fluoroazoles not yet synthesized may be predicted.

In the past recent years one of us has been involved in the evaluation of the more reliable semiempirical SCF MO methods (MNDO and AM1) as far as the description of several heterocyclic systems is concerned.[1] The results, taken as a whole, point out that the MNDO method[2] is very suitable for predicting the heats of formation of five-membered nitrogenated aromatic rings (azoles), far better than the AM1 method,[3] whereas the last one gives theoretical results that agree much better than MNDO with the available experimental data regarding six-membered nitrogenated aromatic rings (azines).

In this context we wish to report here our most significant MNDO results on the C-fluorinated azoles **1-35** and to compare the thermodynamic stabilities of the different sets of isomers and tautomers. MNDO was selected by the reasons indicated above and because a former work of Dewar and Rzepa[4] showed an excellent agreement between experimental and MNDO energy values of fluorinated benzenes.[5]

The heats of formation and dipole moments, as calculated by MNDO using the MOPAC package,[6] are shown in Table I. According to these values, 2-fluoropyrrole (**1**) is predicted to have a lower energy content and smaller dipole moment than 3-fluoropyrrole (**2**).[7] Among the four difluoropyrroles, 2,5-difluoropyrrole (**5**) appears to be thermodynamically the most stable. The energy difference between 3-fluoropyrazole (**10**) and 5-fluoropyrazole (**12**) is too small to guarantee which tautomer would be preferred in the gas-phase equilibrium, but the difference between the dipole moments of these two tautomers indicates that **10** may be largely favored in polar media.[8] 3,5-Difluoropyrazole (**14**) shows a heat of formation lower than that of its 3,4-difluoro and 4,5-difluoro isomers (**13** and **15**, respectively); both tautomers **13** and **15** may be present in the gas-phase equilibrium, but the higher dipole moment of **13** suggests that it may largely predominate in polar solvents or concentrated solutions.[8] Regarding their relative energies, no significant differences are predicted for monofluoroimidazoles **17**, **18**, and **19**, nor for difluoroimidazoles **20** and **21**, but it is expected that polar solvents will favor 4-fluoro derivative **18** with regard to 5-fluoro derivative **19**, and analogously 2,4-difluoro derivative **20** with respect to 2,5-difluoro derivative **21**. It is also worth noting that all fluoroimidazoles and difluoroimidazoles have ΔH_f values lower than those of their isomeric fluoropyrazoles and difluoropyrazoles, respectively. As far as triazoles are concerned, MNDO predicts that 3-fluoro-1,2,5-triazole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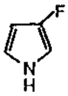
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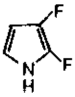
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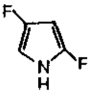
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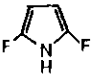
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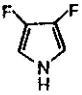
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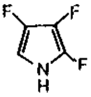
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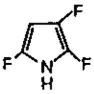
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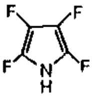
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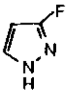
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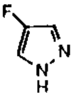
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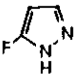
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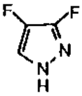
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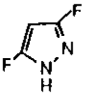
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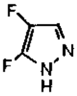
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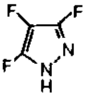
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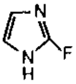
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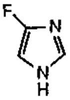
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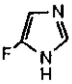
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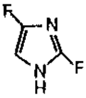
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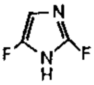
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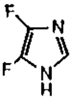
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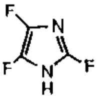
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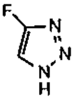
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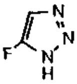
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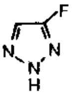
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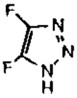
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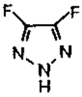
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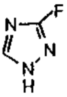
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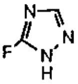
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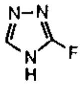
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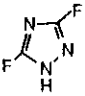
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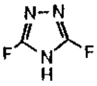
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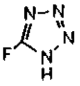
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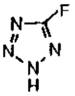
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Table I. Heats of Formation[a] (kcal/mol) and Dipole Moments (D) of **1-35**

	ΔH_f		μ_D		ΔH_f		μ_D		ΔH_f		μ_D
1	-16.7	(-17)	2.03	**13**	-47.7	(-45)	4.40	**24**	4.0	(14)	4.74
2	-15.2	(-15)	3.62	**14**	-50.4	(-50)	2.19	**25**	4.4	(14)	2.25
3	-62.8	(-60)	3.94	**15**	-47.4	(-45)	1.83	**26**	10.5	(10)	1.80
4	-63.6	(-64)	2.61	**16**	-93.1	(-88)	2.99	**27**	-39.9	(-27)	3.41
5	-65.2	(-65)	0.16	**17**	-14.8	(-15)	3.93	**28**	-33.9	(-31)	2.56
6	-61.6	(-59)	4.96	**18**	-15.3	(-15)	5.08	**29**	-3.3	(-3)	4.65
7	-108.2	(-103)	4.46	**19**	-14.7	(-15)	2.71	**30**	-1.9	(-2)	1.98
8	-110.3	(-108)	2.12	**20**	-62.1	(-62)	4.79	**31**	-5.6	(2)	5.08
9	-154.0	(-147)	3.25	**21**	-61.6	(-62)	2.23	**32**	-48.8	(-49)	3.42
10	-3.1	(-3)	4.06	**22**	-60.9	(-58)	4.69	**33**	-50.9	(-43)	4.20
11	-1.0	(-1)	2.55	**23**	-106.8	(-104)	3.66	**34**	10.2	(28)	3.98
12	-2.9	(-3)	0.23					**35**	13.5	(24)	3.00

[a] Corrected values within parentheses: correction terms of 8-10 kcal/mol per each pair of neighboring pyridine-like nitrogens (see ref. 1b) and of 2.5 kcal/mol per each pair of ortho fluoro substituents (see ref. 5) have been added to the MNDO values. MNDO may also underestimate the lone pair repulsions between the vicinal pyridine-like nitrogens and fluorine substituents, so that structures **10**, **13**, **14**, **16-18**, **20-24**, and **26-35** would probably need a small additional correction, but the lack of experimental data precludes to evaluate it.

(2H-4-fluoro-1,2,3-triazole, **26**) is the less stable tautomer of the set constituted by **24**, **25**, and **26**, but it is just in the triazole and tetrazole cases where MNDO results may be unreliable[1b] since these heterocycles may contain two or three neighboring pyridine-like nitrogens, so that the so-called corrected values shown in Table I must be compared. The same comment can be applied to the 4,5-difluoro-1,2,3-triazole/3,4-difluoro-1,2,5-triazole equilibrium (**27** ⇄ **28**). In the 1,2,4-triazole series, taking into account the corrected ΔH_f values, it may be expected that 3-fluoro-1,2,4-triazole (**29**) and 3,5-difluoro-1,2,4-triazole (**32**) are the predominant tautomers in the **29** ⇄ **30** ⇄ **31** and **32** ⇄ **33** equilibria, respectively, either in the gas phase or in diluted solutions in apolar solvents; in the first equilibrium, polar media should further favor **29** (and obviously **31** as well) in relation to **30**. Comparison of the energies of 5-fluoro-1,2,3,4-tetrazole (**34**) with 4-fluoro-1,2,3,5-tetrazole (**35**) suggests that the last one may be more stable.

To gain insight into the effect of electron-donating and electron-withdrawing substituents at N1 on different properties of fluoroazoles, the following pairs of structures have been also calculated: 2,5-difluoro-1-methylpyrazole (**36**) and 3,4-difluoro-1-methylpyrazole (**37**); 2,5-difluoro-1-formylpyrazole (**38**) and 3,4-difluoro-1-formyl pyrazole (**39**); 3,4,5-trifluoro-1-methylpyrazole (**40**) and 2,4,5-trifluoro-1-methylimidazole (**41**); and 3,4,5-trifluoro-1-formylpyrazole (**42**) and 2,4,5-trifluoro-1-formylimidazole (**43**). Their heats of formation and dipole moments are shown in Table II. When pairs **36**/**37** and **38**/**39** are compared to **5**/**6**, it turns out that: (i) **36** and **38** are relatively destabilized by 1.5 and 1.9 kcal/mol; (ii) the dipole moments of both **36** and **37** increase slightly, whereas those of **38** and **39** are leveled. The first point indicates that the methyl and formyl groups cause the same effect, presumably a small steric effect. The second result is explained by the contribution, of opposite sign, of the methyl and formyl groups to the total dipole moment. When pairs **40**/**41** and **42**/**43** are compared with the N-unsubstituted trifluoropyrazole/trifluoroimidazole pair (**16**/**23**), the same conclusions can be reached: since these pyrazoles have only one fluorine atom vicinal to N1-R (R = H, Me, CHO), whereas in these imidazoles there are two, the small, relative destabilization of **41** and **43** with regard to **23** may be attributed to a steric effect; furthermore, it is reasonable that the dipole moments of **40** and **41** increase, while those of **42** and **43** undergo a leveling effect, as observed before in the formyl derivatives **38**/**39**.

Table II. Heats of Formation (kcal/mol) and Dipole Moments (D) of **36**-**43**

	ΔH_f	μ_D		ΔH_f	μ_D
36	-63.7	0.65	**40**	-94.7	3.64
37	-61.6	5.24	**41**	-106.0	4.31
38	-93.3	2.27	**42**	-122.7	3.28
39	-91.9	3.67	**43**	-134.9	3.34

At last, to expand the predictive value of the present calculations, we have considered any possible relationship between the available ^{19}F chemical shifts[8,9] and the MNDO-calculated electron densities. The best correlation has been found when the δF values of the N-methylated fluoroazoles,[10] in $CDCl_3$ with respect to and at higher field than external trifluoroacetic acid, are represented, as shown in Figure 1, against the π-electron densities at the fluorine-linked carbon atoms (see Table III). Bearing in mind that the effect on δF of the interaction among the in-plane nitrogen and fluorine lone pairs cannot be reliably evaluated and is therefore neglected, we recognize

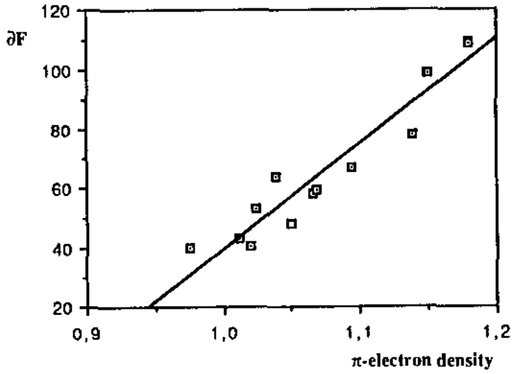

Figure 1. ^{19}F chemical shifts of *N*-methyl analogues of **10-15**, **17-19**, and **29** vs. MNDO-calculated π-electron densities at the fluorine-linked carbon atoms.

Table III. π-Electron Densities on the Fluorine-Linked Carbon Atoms

1	1.116	**10**	1.023	**17**	1.019	**24**	1.093	**38**	1.070(C2)
2	1.117	**11**	1.150	**18**	1.065	**25**	1.082		1.114(C5)
3	1.143(C2)	**12**	1.068	**19**	1 139	**26**	1.052	**39**	1.130(C3)
	1.144(C3)	**13**	1.039(C3)	**20**	1.001(C2)	**27**	1.118(C4)		1.108(C4)
4	1.097(C2)		1.179(C4)		1.056(C4)		1.115(C5)	**40**	1.029(C3)
	1.109(C4)	**14**	1.011(C4)	**21**	1.015(C2)	**28**	1.074		1.209(C4)
5	1.112		1.049(C5)		1.139(C5)	**29**	0.975		1.074(C5)
6	1.141	**15**	1.179(C3)	**22**	1.087(C4)	**30**	0.974	**41**	0.993(C2)
7	1.125(C2)		1.094(C5)		1.174(C5)	**31**	1.028		1.081(C4)
	1.169(C3)	**16**	1.028(C3)	**23**	0.997(C2)	**32**	0.962(C3)		1.176(C5)
	1.132(C4)		1.209(C4)		1.081(C4)		0.956(C5)	**42**	1.014(C3)
8	1.140(C2)		1.074(C5)		1.175(C5)	**33**	1.028		1.186(C4)
	1.136(C3)					**34**	0.972		1.070(C5)
	1.092(C5)					**35**	0.995	**43**	0.949(C2)
9	1.121(C2)					**36**	1.109		1.058(C4)
	1.162(C3)					**37**	1.138		1.186(C5)

that Figure 1 has only a qualitative value. Nevertheless, certain predictions seem sound. For instance: were **36** and **37** synthesized, one would expect for them δF values of ca. 80 ppm and 90 ppm, respectively; were trifluoroimidazole **41** ever prepared one would expect δF values of ca. 35 ppm (F2), ca. 70 ppm (F4), and ca. 105 ppm (F5).

In conclusion, application of the MNDO method to the fluorine-substituted, nitrogenated five-membered rings affords results that agree quite well with the available experimental data and allow us to guess the relative stabilities, polarities, and approximate fluorine chemical shifts of several unknown compounds.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. (a) S. Olivella and J. Vilarrasa, J. Heterocycl. Chem., 1981, **18**, 1189; (b) E. Fos, J. Vilarrasa, and J. Fernández, J. Org. Chem., 1985, **50**, 4894; (c) J. Fernández, J. Anguiano, and J. Vilarrasa, J. Comput. Chem., in press; (d) J. Anguiano, J. Fernández, and J. Vilarrasa, J. Org. Chem., in press.
2. M. J. S. Dewar and W. Thiel, J. Am. Chem. Soc., 1977, **49**, 4899, 4907.
3. M. J. S. Dewar, E. C. Zoebisch, E. F. Healy, and J. J. P. Stewart, J. Am. Chem. Soc., 1985, **107**, 3902.
4. M. J. S. Dewar and H. S. Rzepa, J. Am. Chem. Soc., 1978, **100**, 58.
5. Nevertheless, the differences between the experimental and calculated heats of formation increase in polyfluorinated benzenes: the calculated heats of formation turn out to be lower than the experimental ones by ca. 9 and 16 kcal/mol for C_6HF_5 and C_6F_6, respectively.[4]
6. The IBM/CMS version (S. Olivella, QCPE Bull., 1984, **4**, 109) of the MOPAC program, with the parameters, was used (J. J. P. Stewart, QCPE Bull., 1983, **3**, 101). All geometries were optimized by minimizing the energy with respect to all geometrical variables (except for dihedral angles since all the rings were assumed to be planar), and can be obtained from the authors on request.
7. Cf. J. Kao, A. L. Hinde, and L. Radom, Nouv. J. Chim., 1979, **3**, 473.
8. In practice, the ^{19}F NMR spectra in $CDCl_3$ and CD_3OD indicate that **10** and **13** are the major tautomers in the **10** $\rightleftharpoons$ **12** and **13** $\rightleftharpoons$ **15** equilibria, respectively: (a) F. Fabra, J. Vilarrasa, and J. Coll, J. Heterocycl. Chem., 1978, **15**, 1447; (b) F. Fabra, E. Fos, and J. Vilarrasa, Tetrahedron Lett., 1979, 3179; (c) F. Fabra, Doctoral Thesis, Universitat de Barcelona, 1980.
9. (a) S. R. Naik, J. T. Witkowski, and R. K. Robins, J. Org. Chem., 1973, **38**, 4353; (b) H. J. C. Yeh, K. L. Kirk, L. A. Cohen, and J. S. Cohen, J. Chem. Soc., Perkin II, 1975, 928; (c) F. Fabra, C. Gálvez, A. González, P. Viladoms, and J. Vilarrasa, J. Heterocycl.Chem., 1978, **15**, 1227; (d) J. Garcia, Graduation Thesis, Universitat de Barcelona, 1980; (e) L. Coderch, Graduation Thesis, Universitat de Barcelona, 1981.
10. In unsubstituted fluoroazoles the observed chemical shifts may often be average values (due to the possible presence of other tautomers). Our experience[8,9c-e] points out that in nonambiguous cases "N-methylation" shifts the δ^{19}F values 2 ppm downfield at most.

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