The interaction of 2-(2-furyl)pyrroles 1–6 with HSO_3F and CF_3COOH was carried out at −80 °C by mixing in the NMR tube 0.02 g of pyrrole with 5–10-fold acid excess in equal (0.2 mL) volumes of CD_2Cl_2. The reactions with hydrogen halides were also performed in the NMR tube, by passing dry HCl (or HBr) through the pyrrole solution in CD_2Cl_2 at −80 or −30 °C.

The methods of synthesis of the compounds studied have been described.[10]

Quantum-chemical (MNDO) calculations of 2-(2-furyl)pyrrole and its protonated forms were performed on an EC-1061 computer.

Registry No. 1, 126476-04-8; 1a·SO_3F, 126475-81-8; 1b, 138667-36-4; 1c, 138667-41-1; 2, 126475-82-9; 2a·SO_3F, 126475-83-0; 2a·Cl, 126475-89-6; 2a·Br, 126475-90-9; 2b (R^3 = CHClMe), 138667-37-5; 2b (R^3 = CHBrMe), 138667-38-6; 2c, 138667-42-2; 2d, 138667-45-5; 3, 138693-70-6; 3a·SO_3F, 126475-85-2; 3b, 138667-39-7; 4, 126475-86-3; 4a·SO_3F, 126475-87-4; 4a·Cl, 126545-35-5; 4b, 138667-40-0; 4c, 138667-43-3; 5, 138667-34-2; 5a·Cl, 126475-88-5; 5a·Cl (R^3 = CHClMe), 126475-91-0; 5a·Br (R^3 = CHBrMe), 126475-90-9; 5d, 138667-46-6; 6, 138667-35-3; 6a·Br, 126475-93-2; 6c, 138667-44-4.

Supplementary Material Available: Tables I–VI and VIII (8 pages). Ordering information is given on any current masthead page.

Basicity of C-Substituted Pyrazoles in the Gas Phase: An Experimental (ICR) and Theoretical Study

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The experimental gas-phase proton affinities (PAs) of 32 *N*-H and *N*-methyl pyrazoles have been determined by means of Fourier transform ion cyclotron resonance spectroscopy (FTICR). Together with the previously reported PAs for 12 *C*-methyl-substituted pyrazoles, they provide a set of 57 data (counting each tautomer separately). The remarkably large spread of PAs, ca. 55 kcal·mol^{-1}, makes this set most suitable for structural analyses. In a few cases, ab initio 6-31G//6-31G protonation energies were calculated and found to be linearly related to the experimental PAs to a very high degree of precision. A simple additive model of substituent effects on PAs (including substitutions at positions 3, 4, and 5) was found to hold, even for very crowded derivatives such as 1,4-dimethyl-3,5-di-*tert*-butylpyrazole (27). The only significant interaction appears between phenyl groups at positions 3 and 5. The statistically averaged substituent effects on PAs were successfully analyzed in terms of polarizability and field and resonance contributions, according to the Taft–Topsom model. Both positions 3 and 5 behave in a way similar to that of position 2 in the pyridines. From this interesting result it follows that, with the exception of 3-aminopyrazole, the tautomerism of pyrazoles is not very dependent of the nature of the 3(5)-substituent.

1. Introduction

To understand the nature of substituent effects, it is necessary to use intrinsic properties, i.e., properties of the isolated molecules. A comparison with the same properties in solution will shed light on solvent effects. In this way, two of the main topics in physical organic chemistry, namely, substituent and solvent effects, can be approached. We have chosen to study the effects of seven substituents (X) on the basicity of NH and *N*-methylpyrazoles.

We expected, through the determination of the effect of X on the basicity of pyrazoles, to attain the position of the tautomeric equilibrium 3-X ⇄ 5-X, for which only solution data are available (the case of 3(5)-methylpyrazole, X = CH_3, has already been discussed).[1]

Differences in energy between 3- and 5-tautomers are often small, and so these kinds of studies need a careful theoretical determination of the protonation energies, ΔE_P. As we have shown previously,[2] linear correlations between ΔE_P and proton affinities, PA, need ab initio calculations of a relatively high level. Although INDO,[3a,3b] AM1,[3c] STO-3G,[3d] and 3-21G[3e] calculations were previously carried out, in this discussion we will use exclusively 6-31G data. At this level, we can calculate only monosubstituted molecules. Even then, the best one can expect is a linear relationship between ΔE_P and PA. To obtain absolute values, calculations at much higher levels are necessary; this has been done only on pyrazole itself.[4]

Substituent effects (SEs) in a six-membered heteroaromatic ring, e.g., pyridine, can be compared to those in

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benzene. In aromatic five-membered rings, e.g., imidazoles and pyrazoles, the question arises of the relationship between the position of the substituent and the equivalent position in a six-membered ring. With regard to pyrazole basic center, N_2, to which position in pyridines can be compared pyrazole positions 3, 4, and 5? Are the substituent effects very different at position 3, in some formal way an "ortho" position, and at position 5, which can be considered a "meta" position? Taking into account that the most basic tautomer is the less abundant, a large difference in these effects would then correspond to a largely shifted tautomeric equilibrium.[5]

To summarize, the aims of this work are as follows:

(1) To determine the effects of seven substituents (methyl, ethyl, *tert*-butyl, phenyl, amino, nitro, ethoxycarbonyl) at positions 3 and 5 on the proton affinities of NH and *N*-methylpyrazoles.

(2) To compare these effects with theoretically calculated protonation energies in order to determine whether the N-methylation effect is constant.

(3) To statistically calculate the SEs from the analysis of the PAs for a series of 57 pyrazoles (counting each tautomer separately).

(4) To discuss empirically these effects using pyridines as reference compounds and multiparametric LFER.[6]

(5) To approach the tautomerism of NH-pyrazoles in the gas phase using SEs both experimentally determined and theoretically calculated.

2. Experimental Section

(A) Materials. Compounds **1–16** were described previously,[2] and the remaining 32 pyrazoles were purified, by sublimation (in the case of some solids), by column chromatography (CC), or preparative gas-phase chromatography (GPC) (in the case of liquids and some solids): **17**,[7] **18** (**19**),[8] (**20**) (this work), **21** (this work), **22**,[8] **23** (this work), **24** (**25**),[9] **26**,[8b] **27** (this work), **28** (**29**),[10] **30**,[11] **31**,[11] **32**,[10] **33**,[12] **34** (**35**),[10] **36**,[11] **37**,[11] **38** (**39**),[13] **40** (**41**),[14] **42**,[15] **43**,[15] **44**,[16] **45**,[17] **46** (**47**),[18] **48**,[18] **49**,[18] **50** (**51**),[19] **52**,[8a] **53**,[8a] **54**,[20] **55**,[20] **56**,[19] and **57**.[19]

1-Methyl-3-*tert*-butyl- (**20**) and 1-methyl-5-*tert*-butylpyrazole (**21**) were prepared by the reaction of hydroxymethylenepinacolone[8b] and methylhydrazine. The mixture (67% yield) was separated by CC. ^{1}H NMR ($CDCl_3$): **20** (90%) δ 1.32 (s, 9 H, tBu), 3.79 (s, 3 H, Me), 6.05 (d, 1 H, H_4), 7.21 (d, 1 H, H_5, J_{45} = 2.1 Hz); **21** (10%) δ 1.26 (s, 9 H, tBu), 3.94 (s, 3 H, Me), 6.05 (d, 1 H, H_4), 7.33 (d, 1 H, H_3, J_{34} = 1.8 Hz). (**20**) Anal. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.73; H, 10.33; N, 19.99. ^{13}C (DMSO-d_6): 161.8 (C_3), 101.4 (C_4), 128.9 (C_5), 31.7 (C), 30.4 (CH_3), 38.2 ppm (NCH_3). (**21**) Anal. Calcd for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.56; H, 9.97; N, 20.48.

1-Methyl-3,5-di-*tert*-butylpyrazole (**23**) was prepared by refluxing 2,2,6,6-tetramethyl-3,5-heptanedione and methylhydrazine in ethanol. The product was purified by column chromatography (chloroform–ethanol (8:2)). Yield: 88%. ^{1}H NMR ($CDCl_3$): 1.25 (s, 9 H, 3-tBu), 1.33 (s, 9 H, 5-tBu), 3.96 (s, 3 H, Me), 5.93 (s, 1 H, H_4). ^{13}C (DMSO-d_6): 159.3 (C_3), 99.4 (C_4), 150.9 (C_5), 31.5 and 30.4 (C), 30.8 and 29.5 (CH_3), 38.55 ppm (NCH_3). (**23**) Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.98; H, 11.67; N, 14.37.

1,4-Dimethyl-3,5-di-*tert*-butylpyrazole (**27**) was prepared by reacting 2,2,4,6,6-pentamethyl-3,5-heptanedione[8b] and methylhydrazine in ethanol under reflux. The product was purified by column chromatography (chloroform–ethanol (8:2)). Yield: 60%. ^{1}H NMR ($CDCl_3$): 1.37 (s, 9 H, 3-tBu), 1.46 (s, 9 H, 5-tBu), 2.20 (s, 3 H, 4-Me), 3.93 (s, 3 H, 1Me). (**27**) Anal. Calcd for $C_{13}H_{24}N_2$: C, 74.94; H, 11.61; N, 13.45. Found: C, 75.11; H, 11.47; N, 13.43.

(B) Gas-Phase Basicities and Proton Affinities. The gas-phase basicities were determined from equilibrium proton-transfer reactions conducted in a modified Bruker CMS 47 FTICR mass spectrometer under conditions similar to those already described.[21] Table I presents the results of proton-transfer equilibria (1) obtained in this study along with the standard bases used (B_{ref}):

$$B_{ref}H^+ + B \rightleftarrows BH^+ + B_{ref} \quad K_P \tag{1}$$

In this equilibrium, B is a neutral pyrazole. The reversibility of reaction 1 was systematically confirmed by means of double-resonance experiments. At least two reference bases were used in each case. Their gas-phase proton basicities (GB) are mostly published[22] values from Taft's laboratory. Recent work by Meot-Ner (Mautner) and Sieck[21d] suggests that Taft's data were determined at 360 K, somewhat above the initially accepted value of 320 K. The ICR scale of gas-phase proton basicities is built from a ladder of equilibrium constants, K_p, through eq 1. Thus, the original values from Taft's laboratory have been multiplied by a factor of 1.125 (360/320 = 1.125), following Meot-Ner and Sieck's advice.[21d] This correction has been applied to all the reference values, $\Delta G°$(std), given in Table I.

The values of $\Delta G°$ (obs) given in Table I are defined as

$$\Delta G°(\text{obs}) = -RT \ln K_P \tag{1a}$$

The GBs determined against each reference ($\Delta G°$) as well as the average values ΔG_H (g) are taken with respect to ammonia, reaction 2:

$$B(g) + NH_4^+(g) \rightleftarrows BH^+(g) + NH_3(g) \tag{2}$$

Proton affinities (PA) relative to ammonia are the negative of the standard enthalpy change for reaction 2.

ΔS, the entropy change for reaction 2, can be calculated by means of the symmetry numbers, σ, of the species involved.[23] $\sigma(NH_3)$ = 3 and $\sigma(NH_4^+)$ = 12, so that eq 3 obtains for ΔS

$$\Delta S = R \ln 4 + R \ln [\sigma(B)/\sigma(BH^+)] \tag{3}$$

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Table I. Gas-Phase Basicity Results Obtained with Standard Bases (in kcal mol^{-1}) at 333 K

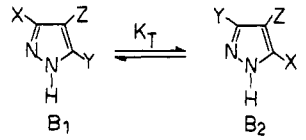
pyrazole	standard base	$\Delta G°$(std)	$\Delta G°$(obs)	$\Delta G°$	ΔG_{H^+}(g)
3(5)-methyl (3), (4)	cyclopropylamine	−12.6	−0.80	−13.40	−13.5 ● 0.1
	pyridazine	−14.3	0.72	−13.58	
4-methyl (7)	cyclopropylamine	−12.6	−0.60	−13.20	−13.3 ● 0.1
	pyridazine	−14.3	0.86	−13.44	
3,5-dimethyl (9)	*tert*-butylamine	−20.0	−0.07	−20.07	−20.2 ± 0.1
	pyridine	−19.8	−0.43	−20.23	
	tert-amylamine	−21.6	1.40	−20.20	
3(5),4-dimethyl (11), (12)	pyridine	−19.8	0.78	−19.02	−18.9 ± 0.1
	neopentylamine	−18.3	−0.52	−18.82	
3,5-diethyl-4-methyl (17)	4-methylpyridine	−23.7	−0.76	−24.46	−24.6 ± 0.1
	4-ethylpyridine	−24.5	−0.15	−24.65	
3(5)-*tert*-butyl (18), (19)	butylamine	−17.1	−0.97	−18.07	−17.9 ± 0.1
	neopentylamine	−18.3	0.51	−17.79	
1-methyl-3-*tert*-butyl (20)	3-methylpyridine	−22.8	−0.23	−23.03	−23.0 ± 0.1
	4-methylpyridine	−23.7	0.68	−23.02	
1-methyl-5-*tert*-butyl (21)	*tert*-amylamine	−21.6	−0.61	−22.21	−22.2 ± 0.1
	1,5-dimethylpyrazole	−20.7	−1.43	−22.13	
3,5-di-*tert*-butyl (22)	4-ethylpyridine	−24.5	−0.26	−24.76	−24.8 ● 0.1
	4-isopropylpyridine[21b]	−25.5	0.60	−24.90	
1-methyl-3,5-di-*tert*-butyl (23)	diisopropylamine	−29.7	0.24	−29.46	
	diethylmethylamine	−30.0	0.70	−29.30	−29.3 ± 0.1
	dipropylamine[25a]	−27.4	−1.66	−29.06	
	tert-amylamine	−21.6	−1.36	−22.96	23.1 ● 0.2
3(5)-methyl-5(3)-*tert*-butyl (24), (25)	4-ethylpyridine	−24.5	1.17	−23.33	
3,5-di-*tert*-butyl-4-methyl (26)	diisopropylamine	−29.7	1.12	−28.58	
	dipropylamine	−27.4	−1.04	−28.44	−28.5 ● 0.1
	2,6-dimethylpyridine	−28.0	−0.57	−28.57	
1,4-dimethyl-3,5-di-*tert*-butyl (27)	diisopropylamine	−29.7	−2.19	−31.89	−32.1 ± 0.2
	triethylamine	−33.0	0.78	−32.22	
3(5)-phenyl (28), (29)	propylamine	−15.9	0.30	−15.60	−15.9 ± 0.3
	butylamine	−17.1	0.97	−16.13	
1-methyl-3-phenyl (30)	*tert*-butylamine	−20.0	−0.46	−20.46	−20.2 ± 0.3
	neopentylamine	−18.3	−1.50	−19.80	
1-methyl-5-phenyl (31)	*tert*-butylamine	−20.0	−0.37	−20.37	−20.6 ● 0.2
	tert-amylamine	−21.6	0.83	−20.77	
3,5-diphenyl (32)	*tert*-amylamine	−21.6	−1.49	−23.09	
	4-methylpyridine	−23.7	0.12	−23.58	−23.3 ● 0.2
	3-methylpyridine	−22.8	−0.38	−23.18	
1-methyl-3,5-diphenyl (33)	4-*tert*-butylpyridine	−26.2	−0.53	−26.73	−26.7 ● 0.1
	dipropylamine	−27.4	0.74	−26.66	
3(5)-methyl-5(3)-phenyl (34), (35)	*tert*-butylamine	−20.0	−0.17	−20.17	−20.1 ● 0.1
	1,5-dimethylpyrazole	−20.7	0.65	−20.05	
1,3-dimethyl-5-phenyl (36)	4-ethylpyridine	−24.5	−1.16	−25.66	
	4-*tert*-butylpyridine	−26.2	0.10	−26.10	−25.8 ± 0.2
	4-isopropylpyridine	−25.5	−0.22	−25.72	
1,5-dimethyl-3-phenyl (37)	4-isopropylpyridine	−25.5	0.13	−25.37	−25.2 ± 0.2
	4-ethylpyridine	−24.5	−0.56	−25.06	
3(5)-ethyl-5(3)-phenyl (38), (39)	*tert*-butylamine	−20.0	−1.39	−21.39	
	tert-amylamine	−21.6	0.36	−21.24	−21.3 ● 0.1
	pyridine	−19.8	−1.43	−21.23	
3(5)-nitro (40), (41)	acetone	+8.7	−1.38	+7.32	+7.2 ± 0.1
	tetrahydrofuran	+5.9	1.23	+7.13	
1-methyl-3-nitro (42)	cyclohexanone	+1.8	−1.05	+0.75	+0.7 ● 0.1
	diisopropyl ketone	−0.5	1.24	+0.74	
1-methyl-5-nitro (43)	cyclohexanone	+1.8	−1.74	+0.06	0.0 ● 0.1
	dipropylketone[25b]	+0.9	−0.88	+0.02	
	tetrahydrothiophene	−0.6	0.54	−0.06	
3,5-dinitro (44)	methanol	+23.3	−0.89	+22.41	+22.6 ± 0.2
	benzene	+22.8	−0.01	+22.79	+22.6 ± 0.2
1-methyl-3,5-dinitro (45)	ethylbenzene	+14.3	0.83	+15.13	
	propionaldehyde	+16.2	−0.82	+15.38	+15.3 ± 0.1
	toluene	+15.3	0.12	+15.42	
3(5)-amino (46), (47)	butylamine	−17.1	−0.62	−17.72	−17.6 ± 0.1
	neopentylamine	−18.3	0.81	−17.49	
1-methyl-3-amino (48)	*tert*-amylamine	−21.6	−0.16	−21.76	−21.7 ± 0.1
	3-methylpyridine	−22.8	1.09	−21.71	
1-methyl-5-amino (49)	3-methylpyridine	−22.8	−1.38	−24.18	−24.2 ± 0.1
	4-ethylpyridine	−24.5	0.31	−24.19	
3(5)-methyl-5(3)-ethoxycarbonyl (50), (51)	4-methylpyrazole	−13.3	0.53	−12.77	−12.7 ± 0.1
	3-methylpyrazole	−13.5	0.96	−12.54	
	propylamine	−15.9	3.11	−12.79	
1,3-dimethyl-5-ethoxycarbonyl (52)	neopentylamine	−18.3	−0.04	−18.34	−18.4 ± 0.2
	tert-butylamine	−20.0	1.31	−18.69	
	butylamine	−17.1	−1.15	−18.25	
1,5-dimethyl-3-ethoxycarbonyl (53)	*tert*-butylamine	−20.0	−0.49	−20.49	−20.4 ± 0.1
	1,5-dimethylpyrazole	−20.7	0.34	−20.36	

Table I (Continued)

pyrazole	standard base	$\Delta G°$(std)	$\Delta G°$(obs)	$\Delta G°$	ΔG_{H^+}(g)
3,5-diethoxycarbonyl (54)	propargylamine[25c]	-8.9	1.08	-7.82	-7.8 ± 0.1
	2-fluoropyridine	-8.3	0.50	-7.80	
1-methyl-3,5-diethoxycarbonyl (55)	4-acetylpyridine	-15.5	0.18	-15.32	-15.3 ± 0.1
	pyridazine	-14.3	-0.94	-15.24	
3(5)-phenyl-5(3)-ethoxycarbonyl (56), (57)	cyclopropylamine	-12.6	0.34	-12.26	-12.1 ● 0.1
	di-*tert*-butylsulfide	-11.3	-0.70	-12.00	
4-fluoro	diisopropyl ether	-2.3	-0.17	-2.47	-2.5 ± 0.1
	acetylacetone	-4.2	1.65	-2.55	

3. The Problem of Tautomeric Equilibria in the Gas Phase

There is evidence[5,23] indicating that in the gas and liquid phases equilibrium (4) takes place:



Frequently, the activation barriers for this reaction are low and interconversion is fast.[24a] The thermodynamic stabilities of both tautomers being quite close, vapors and liquids are made up in most cases of inseparable mixtures of tautomers.

Under the low total pressures prevailing in these experiments, the ratio of the relative pressures, $P(B_2)/P(B_1) = K_T$, is essentially independent of the pressure. Theoretical calculations (vide infra) and the available experimental evidence indicate that the standard enthalpy change for reaction 4 is small (in absolute value), so that K_T is little affected by moderate temperature changes.

Consider now a reservoir holding a liquid sample in equilibrium with its vapor under a pressure of, say, a few Torr. A small amount of this vapor is allowed to suddenly expand into the high-vacuum section of the ICR spectrometer, where the pressure is reduced by a factor of ca. 10^{-7}. In light of the previous discussion, it seems safe to assume that the actual ratio $P(B_2)/P(B_1)$ in the ICR cell will remain "frozen" at the value of K_T for the vapor in the reservoir.

The case of solid samples is very important, for all the new NH pyrazoles studied in this work are solids, often having such low vapor pressures that the use of a direct insertion probe is required.

It is known that in solid pyrazoles, equilibrium (4) is frequently shifted strongly in either direction (only one of the tautomers is observed by X-ray diffraction and by solid-state NMR[24b]). The problem of assessing the composition of the gaseous phase is then more difficult.

Let us consider the solid sample to be made out of only one of the isomers, say B_1(s). In a closed vessel, reactions

Table II. Calculated Total Energies (Hartrees) for Pyrazoles and Their Cations and Protonation Energies (kcal mol^{-1})

compd	6-31G//6-31G	$-\Delta E_p$
pyrazole (1)	-224.70975[3e]	232.6 (H)[3e]
pyrazole-H$^+$ (1H$^+$)	-225.06030	
3-methylpyrazole (3)	-263.71674	238.1 (3-Me)
5-methylpyrazole (4)	-263.71573	238.7 (5-Me)
3(5)-methylpyrazole-H$^+$ (3H$^+$ ≡ 4H$^+$)	-264.09607	
4-methylpyrazole (7)	-263.71166	237.3 (4-Me)
4-methylpyrazole-H$^+$ (7H$^+$)	-264.08962	
3-nitropyrazole (40)	-428.03355	207.1 (3-NO_2)
5-nitropyrazole (41)	-428.03269	207.1 (5-NO_2)
3(5)-nitropyrazole-H$^+$ (40H$^+$ ≡ 41H$^+$)	-428.36343	
3-aminopyrazole (46)	-279.70170	243.8 (3-NH_2)
5-aminopyrazole (47)	-279.69860	245.8 (5-NH_2)
3(5)-aminopyrazole-H$^+$ (46H$^+$ ≡ 47H$^+$)	-280.09015	
3-ammoniopyrazole (46A$^+$)	-280.0555	222.1
5-ammoniopyrazole (47A$^+$)	-280.026323	205.7

4a and 4b occur that ensure the full equilibration of the system.

$$B_1(s) \rightleftarrows B_1(g) \quad (4a)$$

$$B_1(g) \rightleftarrows B_2(g) \quad (4b)$$

The case is then similar to that of a liquid sample. However, the real problem arises when the sample is in the direct insertion probe and not in a closed vessel. In the immediate neighborhood of B_1(s) (contained in a semicapillary tube), the concentration of gaseous species is relatively high, thus helping the attainment of the thermodynamic equilibrium. *At this point we lack, however, the certainty* that the composition of the gaseous mixture [B_1(g), B_2(g)] in the ICR cell is equal or close to that imposed by K_T. In what follows, we shall assume as a working hypothesis that this is the case and, as we shall see, a number of very consistent results, both theoretical and experimental are strongly supportive of this concept.

In the ICR experiments we measure the pressure ratios $P(BH^+)/P(B_{ref}H^+)$ and $P(B_{ref})/[P(B_1) + P(B_2)]$. Thus, the equilibrium constants K determined for reaction 1 are actually "apparent" values, related to the constants K_{B_1} and K_{B_2} (eq 5):

$$B_1(g) + B_{ref}H^+ \overset{K_{B_1}}{\rightleftharpoons} BH^+ \overset{K_{B_2}}{\rightleftharpoons} B_2(g) + B_{ref}H^+(g) \quad (5)$$

It can be shown[23] that, for a given tautomer, say B_1, the "true" constant (K_{B_1} in this case) is given by eq 6

$$K_{B_1} = K(1 + K_T) \quad (6)$$

(notice that $K_T = K_{B_2}/K_{B_1}$).

This implies a correction of ΔG_{H^+}(g) by a term $-RT \ln (1 + K_T)$. For these compounds, $\sigma(B_1) = \sigma(B_2) = \sigma(BH^+) = 1$. Thus $PA(B_1)$ is given by eq 7:

$$PA = -\Delta G_{H^+}(g) - RT \ln [4/(1 + K_T)] \quad (7)$$

The PA values given in Table II were calculated using $K_T = 1$. This choice is discussed later on.

(24) (a) The tautomerization does not necessarily imply an intramolecular process (Catalán, J.; de Paz, J. L. G.; Cabezudo, M. S.; Elguero, J. *Bull. soc. Chim. Fr.* **1986**, 429–435) but may involve associations (pyrazoles are strongly associated even in the gas phase: Zecchina, A.; Cerruti, L.; Coluccia, S.; Borello, E. *J. Chem. Soc. B* **1967**, 1363–1368). (b) Smith, J. A. S.; Wehrle, B.; Aguilar-Parrilla, F.; Limbach, H. H.; Foces-Foces, M. C.; Cano, F. H.; Elguero, J.; Baldy, P.; Pierrot, M.; Khurshid, M. M. T.; Larcombe-McDouall, J. B. *J. Am. Chem. Soc.* **1989**, *111*, 7304–7312.

(25) Measured in this work: (a) (n-C_3H_7)$_2$ NH was found to be 1.1 kcal·mol^{-1} more basic than 4-*tert*-butylpyridine [$\Delta G°$(std) = -26.2 kcal·mol^{-1}] and 0.5 kcal·mol^{-1} less basic than 2,6-dimethylpyridine [$\Delta G°$(std) = -28.0 kcal·mol^{-1}]. (b) (C_3H_7)$_2$CO was found to be 0.8 kcal·mol^{-1} more basic than cyclohexanone [$\Delta G°$(std) = 1.8 kcal·mol^{-1}] and 1.4 kcal·mol^{-1} less basic than tetrahydrothiophene [$\Delta G°$(std) = 0.6 kcal·mol^{-1}]. (c) Propargylamine was found to be 0.1 kcal·mol^{-1} less basic than DMF [$\Delta G°$(std) = -9.0 kcal·mol^{-1}] and 0.6 kcal·mol^{-1} more basic than 2-fluoropyridine [$\Delta G°$(std) = -8.3 kcal·mol^{-1}].

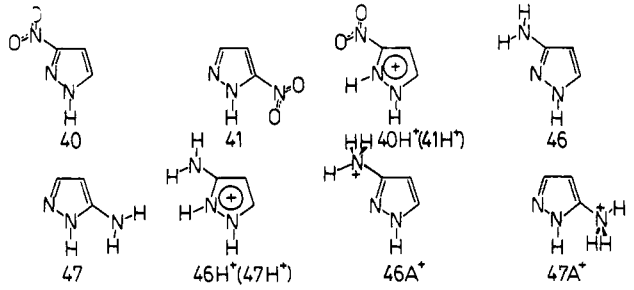
In cases wherein no tautomeric equilibria are involved, only entropy terms, as given by eq 3, are to be considered.

4. Computational Methodology

The total energies of pyrazoles **1**, **3**, **4**, **7**, **40**, **41**, **46**, **47**, and their corresponding conjugated acids have been calculated at the 6-31G level after complete optimization of the geometry at the same level (6-31G//6-31G calculations; only the planarity of the pyrazole ring was assumed.[26] All the calculations were carried out with program packages GAUSSIAN 80 modified by one of us (J.L.G de P.) and Hondo.[27] The results are gathered in Table II.

5. Results and Discussion

Geometries. The geometries of pyrazole and its methyl derivatives have already been discussed.[1,2] The nitro group in compounds **40**, **41**, and **40H$^+$** and **40H$^+$** ≡ **41H$^+$** lies in the plane of the pyrazole ring.



In this work, aminopyrazoles **46** and **47**, the cation resulting from their protonation on N_2, as well as the two tautomeric cations **46A$^+$** and **47A$^+$** protonated on the amino group were studied. An examination of the 6-31G geometries of these derivatives shows that the hybridization of the amino group is much closer to sp^2 than to sp^3, the hydrogen atoms being nearly coplanar with the ring in compounds **46**, **47**, and **46H$^+$**. Compounds **46A$^+$** and **47A$^+$** adopt the same conformation as methyl derivatives **3**, **4**, and **3H$^+$**,[1] i.e., with one N^+–H (or C–H) bond directed toward the N_2 lone pair in compound **46A$^+$** (and **3**). The conjugation between the amino group and the pyrazole ring explains the sp^2 character of the nitrogen and will disfavor protonation on the amino group.

Comparison of Calculated Protonation Energies ($-\Delta E_p$) with Experimental Proton Affinities (PAs). We have gathered in Figure 1 all the information necessary for this discussion.

The calculated (6-31G//6-31G), ΔE_p values, taken from Table II and the corresponding experimental PAs (obtained using K_T = 1 for all tautomeric couples), for eight pyrazoles are presented in Tables II and III. An excellent linear relationship between these magnitudes (eq 8a) is found to hold for the following species 3-nitro- (**40**), 5-nitro- (**41**), unsubstituted (**1**), 4-methyl- (**7**), 3-methyl- (**3**), 5-methyl- (**4**), 3-amino- (**46**), and 5-aminopyrazole (**47**)

$$-\Delta E_p = (218.52 \pm 0.52) + (1.511 \pm 0.039)\mathrm{PA} \quad (8a)$$

in kcal·mol^{-1}, where $n = 8$, $r^2 = 0.9967$, and sd = 0.82 kcal·mol^{-1}. This relationship is portrayed in Figure 1.

However good the correlation appears, we felt that the slope of our plot was heavily weighted by the values of the nitro points. Thus it would be comforting to have a point in the middle of the plot. 4-Fluoropyrazole was selected, for the following reasons: (i) it is not involved in tautomeric equilibria, (ii) it can be treated at the 6-31G//6-31G level, and (iii) from simple structural considerations, it was expected to occupy a central position in the plot. It is rewarding to see that the corresponding data point ($-\Delta E_p$ = 221.3 kcal·mol^{-1}, PA = 2.0 ± 0.1 kcal·mol^{-1} and $\Delta G_{H^+}(g)$ = −2.5 ± 0.1 kcal·mol^{-1}) falls almost exactly on the line defined by eq 8a; indeed, inclusion of these data in the correlation between $-\Delta E_p$ and PA does not alter the intercept and the slope of the linear relationship to any

Table III. Presence–Absence Matrix and Experimental Responses (in kcal·mol^{-1})

	1	3					4	5							PA	$-\Delta G_{H^+}(g)$	Pyrazole
	H	Me	Et	t-Bu	Ph	NO_2	NH_2	H	Me	Et	t-Bu	Ph	NO_2	NH_2	Ph/Ph			
	-	a	b	c	d	e	f	g	h	i	j	k	l	m	n			
1																9.7	10.2	Itself
2	1															14.0	14.9	1-Me
3		1														13.0	13.5	3-Me
4									1							13.0	13.5	5-Me
5	1	1														18.8	19.7	1,3-di-Me
6	1								1							19.8	20.7	1,5-di-Me
7							1									12.9	13.3	4-Me
8	1						1									18.3	19.2	1,4-di-Me
9		1							1							19.7	20.2	3,5-di-Me
10	1	1							1							24.0	24.9	1,3,5-tri-Me
11		1					1									18.5	18.9	3,4-di-Me
12							1	1								18.5	18.9	4,5-di-Me
13	1	1					1									23.2	24.1	1,3,4-tri-Me
14	1						1	1								23.2	24.1	1,4,5-tri-Me
15		1					1	1								22.9	23.4	3,4,5-tri-Me
16	1	1					1	1								28.4	29.3	1,3,4,5-tetra-Me
17		1					1	1								24.1	24.6	3,5-di-Et-4-Me
18			1													17.5	17.9	3-t-Bu
19									1							17.5	17.9	5-t-Bu
20	1		1													22.1	23.0	1-Me-3-t-Bu
21	1								1							21.3	22.2	1-Me-5-t-Bu
22			1						1							24.4	24.8	3,5-di-t-Bu
23	1		1						1							28.4	29.3	1-Me-3,5-di-t-Bu
24		1							1							22.7	23.1	3-Me-5-t-Bu
25			1					1								22.7	23.1	3-t-Bu-5-Me
26			1				1	1								28.1	28.5	3,5-di-t-Bu-4-Me
27	1		1				1	1								31.1	32.1	1,4-di-Me-3,5-di-t-Bu
28				1												15.4	15.9	3-Ph
29									1							15.4	15.9	5-Ph
30	1		1													19.3	20.2	1-Me-3-Ph
31	1								1							19.7	20.6	1-Me-5-Ph
32			1						1						1	22.8	23.3	3,5-di-Ph
33	1		1						1						1	25.8	26.7	1-Me-3,5-di-Ph
34		1							1							19.7	20.1	3-Me-5-Ph
35			1					1								19.7	20.1	3-Ph-5-Me
36	1	1							1							24.9	25.8	1,3-di-Me-5-Ph
37	1		1					1								24.3	25.2	1,5-di-Me-3-Ph
38		1							1							20.8	21.3	3-Et-5-Ph
39			1					1								20.8	21.3	3-Ph-5-Et
40			1													-7.7	-7.2	3-NO_2
41									1							-7.7	-7.2	5-NO_2
42	1		1													-1.7	-0.7	1-Me-3-NO_2
43	1								1							-0.9	0.0	1-Me-5-NO_2
44			1						1							-23.1	-22.6	3,5-di-NO_2
45	1		1						1							-16.2	-15.3	1-Me-3,5-di-NO_2
46			1													17.2	17.6	3-NH_2
47									1							17.2	17.6	5-NH_2
48	1		1													20.8	21.7	1-Me-3-NH_2
49	1								1							23.3	24.2	1-Me-5-NH_2
50		1								1						12.2	12.7	3-Me-5-E[a]
51			1					1								12.2	12.7	3-E-5-Me
52	1	1								1						17.5	18.4	1,3-di-Me-5-E
53	1		1					1								19.5	20.4	1,5-di-Me-3-E
54			1							1						7.3	7.8	3,5-di-E
55	1		1							1						14.4	15.3	1-Me-3,5-di-E
56		1								1						11.7	12.1	3-Ph-5-E
57			1					1								11.7	12.1	3-E-5-Ph

[a] E stands for $CO_2C_2H_5$.

(26) Hehre, W. J.; Radom, L.; Schleyer, P.v.R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; John Wiley: New York, 1986 and references cited therein.

(27) GAUSSIAN-80: Binkley, J. S.; Whiteside, R. A.; Krishna, R.; Seeger, R.; De Frees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. Department of Chemistry, Carnegie Mellon University. IBM version by: Fluder, E. M.; Kahn, L. R. HONDO. Dupuis, M.; Rys, J.; King, H. F. *J. Chem. Phys.* **1976**, *65*, 111–116. HONDO7. Dupuis, M.; Watts, J. D.; Hurst, G. J. B.; Villar, H. O. QCPE program 544, 1987.

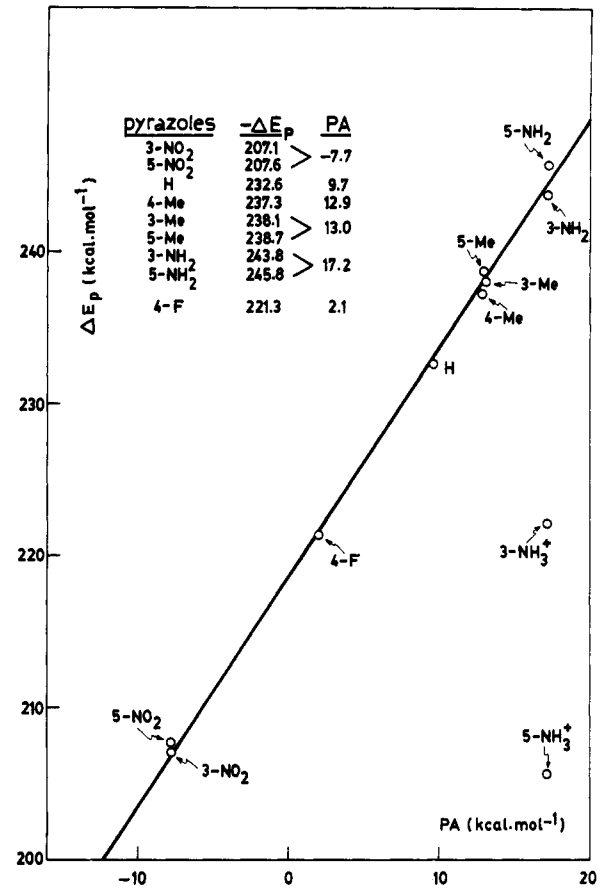
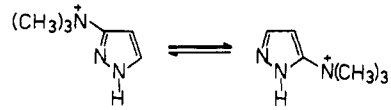


Figure 1. Calculated 6-31G//6-31G protonation energies, ΔE_p, vs proton affinities, PA (calculated from the experimental $\Delta G_{H^+}(g)$ values and $K_T = 1$), for selected NH pyrazoles.

significant extent [they become, respectively, 218.41 ± 0.42 kcal·mol^{-1} and 1.517 ± 0.034 with $n = 9$, $r^2 > 0.9970$, and sd = 0.76 kcal·mol^{-1}].

*An important conclusion to be drawn from Figure 1 and eq 8 is that $K_T = 1$ is a good trial value for the various tautomeric couples, with the exception of **46**/**47**, where calculations show that **46** clearly predominates.*

Another very clear consequence of the representation shown in Figure 1 is that aminopyrazoles protonate on the endocyclic nitrogen and not on the amino group. Structures **46A**$^+$ and **47A**$^+$ are much more acidic than **46H**$^+$ (**47H**$^+$) and will isomerize into the latter. This is consistent with the result in solution.[28] **47A**$^+$ was found to be some 18 kcal·mol^{-1} more stable than **46A**$^+$. Thus, the tautomeric equilibrium **46A**$^+$ ⇄ **47A**$^+$ is heavily shifted to the right, a feature that might be relevant to related quaternary ammonium salts.



Now, we can go one step further and test the hypothesis that the *N*-methyl derivatives are acceptable models for tautomeric studies, i.e., that there is no significant interaction between the substituents at positions 1 and 3 and/or between those at positions 1 and 5.

From eq 8 and the calculated ΔE_p, values of Table II it is possible to *estimate* the PA values for eight NH pyrazoles. In Table IV are collected these values, together

(28) Catalán, J.; Menéndez, M.; Laynez, J.; Claramunt, R. M.; Bruix, M.; de Mendoza, J.; Elguero, J. *J. Heterocycl. Chem.* **1985**, *22*, 997–1000.

Table IV. Calculated (*N*H pyrazoles) and Experimental (*N*-Methylpyrazoles) PA Values (All Values in kcal mol^{-1})

substit	PA(NH)	*N*-methyl homolog	PA(NMe)
3-NO_2	−7.76	42	−1.7
5-NO_2	−7.42	43	−0.9
H	9.51	2	14.0
4-Me	12.69	8	18.3
3-Me	13.23	5	18.8
5-Me	13.64	6	19.8
3-NH_2	17.09	48	20.8
5-NH_2	18.44	49	23.3

with *experimental* PAs for the corresponding *N*-methylpyrazoles. These values are linearly related, eq 9 (in kcal·mol^{-1}, $n = 8$, $r^2 = 0.995$, and sd = 0.8 kcal·mol^{-1}).

$$\text{PA(NMe)} = (5.87 \pm 0.38) + (0.942 \pm 0.029)\ \text{PA (NH)} \quad (9)$$

Thus, we can safely assume that substituent effects determined from the *N*-methyl derivatives can be used to discuss the individual tautomers of NH-pyrazoles.

Quantitative Empirical Analysis of SEs. (A) The Model. It follows from the previous discussion that it is legitimate to assume that the C-substituent effects on the PAs of NH and *N*-methylpyrazoles are very nearly the same. The analysis to follow is based on the experimental GBs and PAs of pyrazole (**1**) and 56 of its derivatives, as summarized in Table III.

Values for compounds **17–57** were determined in this work. Data for pyrazoles **1–16** have already been published.[1] A number of GBs for the latter were measured again, and only in four cases [**3**, **7**, **9**, **11**(**12**)] we found slightly different results (Table I).

The left part of Table III is a matrix of presence–absence (called a Free-Wilson matrix): variable 1 corresponds to the *N*-methyl group, variables 2–8 to substituents at position 3, variable 9 to a substituent at position 4, variables 10–16 to substituents at position 5, and variable 17 to an interaction term for substituents at positions 3 and 5. Tautomeric pyrazoles have been included twice, once for each tautomer. These 57 compounds cover a respectable PA range of 55 kcal mol^{-1} between derivatives **44** and **27**.

The PA values given in Table III are calculated by means of eq 7 with the trial value $K_T = 1$. These PAs are then analyzed by means of the model $\eta = a_0 + \sum a_i x_i$, where η is the theoretical PA value of the model, which differs from the experimental PA since the model is only an approximation of the reality. The x_is take the values 0 and 1, corresponding to the Free-Wilson indexes given in Table III. The difference in energy between tautomers in any given couple is then simply the difference between the corresponding a_i terms in positions 3 and 5. It is also reasonable to assume that this is also the difference in standard free energy between the tautomers. Referring back to equilibrium (4) we have

$$RT \ln K_T = [(a_j)_5 + (a_k)_3 - (a_j)_3 - (a_k)_5]$$

This expression leads to values of K_T that can be inserted into eq 7, thus leading to new sets of a_is. This treatment is repeated until convergence is reached.

The results of the model $\eta = a_0 + \sum a_i x_i$ are collected in Table V. These coefficients can be discussed empirically by comparing them to substituent effects on pyridine intrinsic basicity and by means of the Taft–Topsom model of substituent effects.

It is important that the only statistically significant "interaction term" is a_{17}. In other words, *the PAs of the pyrazoles studied herein can be described by a simple*

Table V. Results of the Multiregression Analysis of the Data Given in Table III (All Variables in kcal mol^{-1})

variables of the model	contribn to PA	variables of the model	contribn to PA
a_0 constant	9.4	a_{11} 5-ethyl	6.0
a_1 *N*-methyl	5.0	a_{12} 5-terbutyl	7.0
a_2 3-methyl	4.8	a_{13} 5-phenyl	5.4
a_3 3-ethyl	5.5	a_{14} 5-nitro	−15.6
a_4 3-terbutyl	7.7	a_{15} 5-amino	9.2
a_5 3-phenyl	4.9	a_{16} 5-ethoxycarbonyl	−1.7
a_6 3-nitro	−16.3	a_{17} 3,5-diphenyl	2.1
a_7 3-amino	6.8	n	57
a_8 3-ethoxycarbonyl	−0.3	r^2	0.9952
a_9 4-methyl	3.6	sd (kcal mol^{-1})	0.87
a_{10} 5-methyl	5.2		

additive model with only one significant interaction; that involving two phenyl groups in positions 3 and 5. In this respect, theoretical (semiempirical) and experimental studies of the electronic spectra of phenylpyrazoles clearly show the nonadditivity of the effects of 3- and 5-phenyl substituents.[29]

(B) The Tautomerism of Pyrazoles in the Gas Phase and in Solution. We have two ways to determine the difference in energy between the tautomer of a 3(5)-X pyrazole: (1) through the use of the 6-31G//6-31G calculations (Tables II and IV) and eq 8a and (2) by means of the a_i values summarized in Table IV (see Discussion).

Table VI shows that these two different approaches yield comparable results for the three substituents that we have been able to calculate at the 6-31G level: predominance of the 3-methyl, 3-nitro, and 3-amino tautomers. For other substituents, we have only the averaged values of Table V; the predominant tautomer should be 3-ethyl, 5-*tert*-butyl, 3-phenyl, and 5-ethoxycarbonyl.

We have collected the experimental evidence on tautomerism in solution in the right side of Table VI. *The agreement between gas phase and solution is surprisingly good.* Reasonably, the main differences are expected for pairs of tautomers whose dipole moments differ considerably. This is the case only for nitro and amino substituents; the 6-31G calculated dipole moments are as follows: 3-NO_2 (**40**), μ = 7.63 D; 5-NO_2 (**41**), μ = 3.08 D; 3-NH_2 (**46**), μ = 2.04 D; and 5-NH_2 (**47**), μ = 4.12 D. Thus, in solution, the predominance of 3-nitro tautomer should be enhanced, whereas the predominance of the 3-amino tautomer in the gas phase would probably be reduced in solution.

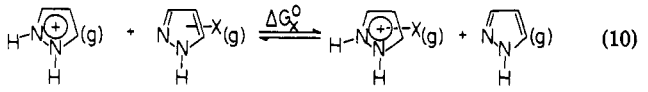
The enhanced stability of the 5-ethoxycarbonyl tautomer is possibly related to an intramolecular hydrogen bonding between the N_1–H and the ester group.

It is worth emphasizing the extremely high degree of self-consistency of these results. Thus, the various PA values for NH pyrazoles obtained through the iterative analysis of the experimental $\Delta G_{H^+}(g)$ values given in Table III by means of the linear model and eq 7 are nicely correlated with the 6-31G//6-31G calculated $-\Delta E_p$ values, eq 8b (n = 9, r^2 = 0.9986, and sd = 0.58 kcal·mol^{-1}).

$$-\Delta E_p = (218.51 \pm 0.25) + (1.479 \pm 0.021)\text{PA} \quad (8b)$$

The regression line defined by this equation is portrayed in Figure 2.

(c) Taft–Topsom Analysis of SEs. This methodology is based on the treatment of SEs on reactivity as linear combinations of polarizability (P), field (F), and resonance (R) contributions, respectively, characterized by the substituent parameters σ_α, σ_F, and σ^+_R and given by P = $\rho_\alpha\sigma_\alpha$, F = $\rho_F\sigma_F$, and R = $\rho_R\sigma^+_R$.[6c] Consider now the proton exchange reaction (10):



(10)

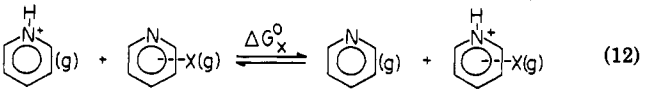
The parameters a_i for i = 2–17 provide an average measure of structural effects on $\Delta G°_x$ (corrected for symmetry and tautomerism contributions).

Thus, an analysis in terms of the Taft–Topsom eq 11 can be undertaken:

$$-\Delta G°_x = \rho_\alpha\sigma_\alpha + \rho_F\sigma_F + \rho_R\sigma^+_R \quad (11)$$

As indicated earlier, a comparison of SEs on the GBs of pyrazoles and pyridines seems worthwhile.

We present in Table VII the results of a treatment of SEs on reactions 10 and 12.



(12)

Relevant conclusions derived therefrom are as follows:

(1) The high quality of all the correlations suggests the general applicability of this method to heterocyclic systems.

(2) All ρ values for pyrazoles are close to those for 2-substituted pyridines. It is particularly important that ρ_R's are much smaller than in the case of 4-substituted pyridines, likely because of the repulsion between the –R substituent and the N–H (or N–Me) group in the pro-

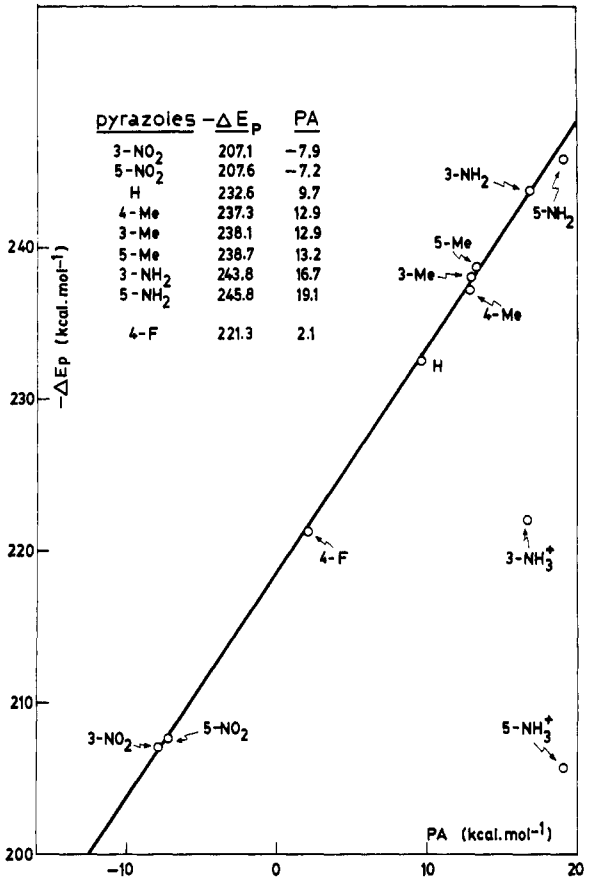


Figure 2. Calculated 6-31G//6-31G protonation energies vs proton affinities, PA (calculated from the experimental $\Delta G_{H^+}(g)$ values and the optimized equilibrium constants K_T), for selected NH pyrazoles.

(29) Cativiela, C.; Garcia-Laureiro, J. I.; Elguero, J.; Elguero, E. *Gazz. Chim. Ital.* 1991, *121*, 477–481.

(30) Cabildo, P.; Claramunt, R. M.; Elguero, J. *J. Magn. Reson.* 1984, *22*, 603–607.

Table VI. Tautomerism of 3(5)-Substituted Pyrazoles

substit	6-31G calcns (Table III)[a,b]	statistical treatment (Table V) $(a_i)_3 - (a_i)_5$[a,b]	results concerning tautomerism in soln	ref
methyl	−0.36	−0.40	54% 3-Me, K_T = 1.17, $\Delta G°$ = −0.10[a] (pK_a, H_2O, 20 °C)	5
ethyl		−0.50	no data	
tert-butyl		0.70	no data	
phenyl		−0.50	80% 3-Ph, K_T = 4, $\Delta G°$ = −0.82[a] (^{13}CNMR, HMPT at −20 °C)	29
nitro	−0.30	−0.70	3-NO_2 tautomer predominates (pK_a, H_2O, 25 °C)	15
amino	−1.21	−2.4	3-NH_2 tautomer predominates	5
ethoxycarbonyl		1.4	5-ethoxycarbonyl tautomer predominates (^{13}CNMR, DMSO-d_6)	30

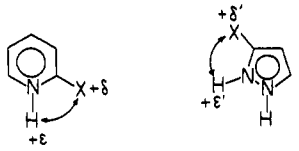
[a] In kcal·mol^{-1}. [b] A negative value corresponds to the 3-X tautomer being more stable than 5-X tautomer.

Table VII. Analysis of Structural Effects on GBs of Pyrazoles and Pyridines

compounds	$-\rho_\alpha$[a]	$-\rho_F$[a]	$-\rho_R$[a]	n[b]	r^2[c]	sd[a]
substd pyrazoles[d]						
3-X	9.4 ± 1.6	28.1 ± 1.6	17.4 ± 2.1	7	0.994	0.9
5-X	7.7 ± 1.0	27.4 ± 1.0	22.1 ± 1.3	7	0.998	0.6
substd pyridines[e]						
2-X	7.2 ± 0.8	30.4 ± 2.0	16.1 ± 2.0			
3-X	4.7 ± 1.4	25.7 ± 1.4	18.3 ± 1.7			
4-X	5.4 ± 2.1	24.2 ± 1.2	29.1 ± 1.4			

[a] In kcal·mol^{-1}. [b] Number of data points. [c] Square of the correlation coefficient. [d] This work. [e] From ref 31.

tonated species. This is a feature common to 3- and 5-substituted pyrazoles and 2-substituted pyridines.



(3) Phenyl groups both in the 3 and the 5 positions are less efficient at stabilizing positive charges than expected from these correlations, the difference being close to 3 kcal·mol^{-1}. Notice that σ^+_R = −0.22 for a phenyl group but reproducing the experimental SE for this substituent only requires $\sigma^+_R \approx -0.0$. This strongly suggests that in the protonated forms the pyrazole and phenyl moieties are not fully coplanar.

(4) We are now in a position to attempt a comparison of gas-phase and solution basicities of pyrazoles and *N*-methylpyrazoles. Table VIII summarizes the available data for these compounds (excluding 4-substituted derivatives).

Inasmuch as tautomeric effects in the gas phase and in aqueous solution are fairly similar, a direct comparison of ΔG_{H^+}(g) and aqueous pK_as seems justified. Taking into account the "N-methylation effect" (the replacement of the N–H hydrogen by a methyl group *decreases* the aqueous basicity and *increases* the gas-phase basicity),[31] the following linear relationship is obtained (eq 13)

$$-\Delta G_{H^+}(g) = (4.98 \pm 0.72) + (2.73 \pm 1.38)pK_a + (6.71 \pm 0.90)X \quad (13)$$

in kcal·mol^{-1}, where n = 10, r^2 = 0.986, and sd = 1.4 kcal·mol^{-1}. X is an indicative variable such that X = 0 for N–H pyrazoles and X = 1 for *N*-methylpyrazoles.

Out of this highly significant correlation, three data points were excluded: 3(5)-*tert*-butylpyrazole, **18(19)**, 3(5)-phenylpyrazole, **28(29)**, and 1-methyl-5-nitropyrazole, **43**. We have no rationale for the behavior of the latter, a compound displaying an unexpectedly high aqueous basicity. On the other hand, **18(19)** and **28(29)** are much more basic in the gas phase than expected on the basis of eq 13. This provides a valuable clue: In a recent comparison of SEs on the gas-phase and solution basicities of pyridines[32] it was shown that the main difference lies in the fact that polarizability effects in aqueous solution are extremely small. This has prompted us to carry out a comparison between $[\Delta G_{H^+}(g)-P]$, given in Table VIII, and the aqueous pK_as. P values were calculated using ρ_α (from Table VII) and the appropriate σ_α values. We then obtain eq 14

$$-[\Delta G_{H^+}(g)-P] = (3.10 \pm 0.47) + (2.79 \pm 0.10)pK_a + (6.63 \pm 0.61)X \quad (14)$$

in kcal·mol^{-1}, where n = 12, r^2 = 0.989, and sd = 1.06 kcal·mol^{-1}.

Equation 14 not only provides a better fit than eq 13, but it also applies to **18(19)** and **28(29)**. This is a phenomenological result that likely reflects several solvation contributions.[33]

Table VIII. Experimental Gas-Phase and Aqueous Basicities of NH and *N*-Methylpyrazoles

pyrazoles	$-\Delta G_{H^+}(g)$[a]	$-[\Delta G_{H^+}(g)-P]$[a,b]	pK_a[c]
1	10.2	10.2	2.48
3/4	13.5	10.5	3.27
18/19	17.9	11.5	3.25
28/29	15.9	9.0	2.09
40/41	−7.2	−9.4	−4.66
46/47	17.6	16.2	4.11
2	14.9	14.9	2.06
5	19.7	16.4	2.77
6	20.7	18.0	2.84
42	−0.7	−3.1	−4.58
48	21.7	20.2	3.81
49	24.2	23.0	4.23
43	0.0	−2.0	−2.35

[a] In kcal·mol^{-1} at 333 K. [b] P = $\rho_\alpha\sigma_\alpha$, see text. [c] From ref 23. Values at 298 K.

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(34) Although our experiments do not constitute a direct proof of an equilibrium between pyrazole tautomers (eq 4), all the data are consistent with such a hypothesis. Either there is an equilibrium or the mixture has proportions of tautomers near those of the equilibrium. This attitude corresponds with that of different authors who have studied tautomeric equilibria in the gas phase using different methods: UV,[35] IR,[35] mass spectrometry,[36–40] photoelectron spectroscopy,[40,41] microwave spectroscopy,[42,43] electron diffraction,[43] and ICR.[1,44,45]

(35) Beak, P. *Acc. Chem. Res.* **1977**, *10*, 186–192 and references cited therein.

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The coefficient of pK_a in eq 14 is 2.79. Recalling that at 298 K one pK_a unit amounts to 1.37 kcal·mol^{-1} in free energy, it follows that with respect to the gas-phase values both field and resonance effects in aqueous solution are attenuated by a factor of (2.79/1.37) = 2.0. This is essentially the value found for 2-substituted pyridines, and is well below the attenuation factors for 3- and 4-substituted pyridines.

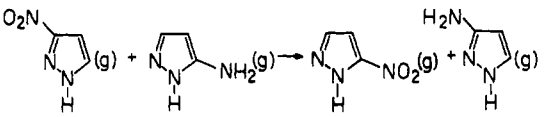
The coefficient of X in eq 14 amounts to 6.6 kcal·mol^{-1}. Its presence indicates that the basicity of *N*-methylpyrazoles in aqueous solution is reduced by (6.6/2.79) = 2.4pK_a units (or 3.2 kcal·mol^{-1}) with respect to the value expected on the basis of their GBs.

The N-methylation is seen to increase the PA of pyrazoles by an average of 5.9 kcal·mol^{-1} (Table V and eq 9). A complete loss of this effect would lower the aqueous pK_a by (5.9/2.79) = 2.1 units. The fact that the actual loss is of the same order of magnitude is a clear example of the "*N*-methyl effect". On the basis of previous discussions, the main contributions to this effect are as follows: (i) the loss of polarizability stabilization in aqueous solution and (ii) the loss of one hydrogen-bonding donor site. A complete analysis of SEs in N-substitution is not yet available, so the first contribution cannot be calculated precisely. A crude order of magnitude is given by the value of P for 3- or 5-methyl substitution: ≈3.0 kcal·mol^{-1} (from $\rho_\alpha = -8.6$ and $\sigma_\alpha(\mathrm{Me}) = -0.35$).

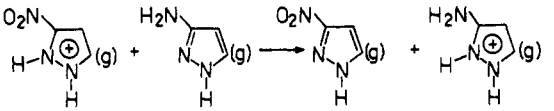
The loss of hydrogen bonding interactions would then amount to 5.9–3.0 = 2.9 kcal·mol^{-1}.

Conclusion

The main objectives of this study, as defined in the introduction, have been reached. Thus, through a combination of experimental, quantum-mechanical, and correlation techniques, the influence of the substituents on the position of equilibria (4) and (10) has been determined and analyzed. Consider reactions 15 and 16:



(15)



(16)

The corresponding $\Delta G°$ values are −1.7 and −24.8 kcal·mol^{-1}. They are representative of the order of magnitude of the structural effects investigated in this work, respectively, in the tautomerism between neutral forms and in the intrinsic basicities of these species.

The fact that the Taft–Topsom formalism performs nicely in the quantitative analysis of $\Delta G°_x$ for reactions 10 and 12 is rewarding in that it shows that we have an excellent tool for the analysis of substituent effects on the intrinsic reactivity of heterocyclic systems. It also highlights the need for more work in this field: The order of magnitude of $\Delta G°$ for reactions 15 and 16 clearly indicates that the leading factor determining the ergonicity of the proton-exchange reactions is the difference in the interactions between the substituents and the positive charge. From this point of view, in the protonated forms of both 3- and 5-substituted pyrazoles the substituent is always in an "ortho" position with respect to one of the NHs. On the basis of simple considerations of aromaticity[46] and topological similarities, this seems in line with the striking resemblance with 2-substituted pyridines revealed by the gas-phase LFERs. This reasoning is obviously too simplistic: in fact, we ignore at this point whether this is happenstance or we are facing a phenomenon rooted at the very basis of chemical reactivity.

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