VOLUME 112, NUMBER 4
FEBRUARY 14, 1990

JOURNAL
OF THE
AMERICAN
CHEMICAL
SOCIETY

A Theoretical and Experimental Study of the Intrinsic Basicities of Methyldiazoles

J. Catalán,*,† J. L. G. de Paz,† M. Yáñez,† R. M. Claramunt,‡ C. López,‡ J. Elguero,§ F. Anvia,‖ J. H. Quian,‖ M. Taagepera,‖ and R. W. Taft*,‖

Contribution from the Departamento de Quimica, Facultad de Ciencias, C-XIV, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain, Departamento de Química Orgánica, UNED, Ciudad Universitaria, 28040 Madrid, Spain, Instituto de Química Médica, CSIC, Juan de la Cierva 3, 28006 Madrid, Spain, and Department of Chemistry, University of California, Irvine, California 92717. *Received February 7, 1989*

Abstract: The gas-phase basicities of pyrazole, all possible methylpyrazoles (13 derivatives), imidazole, and a selected set of methylimidazoles (8 derivatives) have been determined by ICR. These experimental values and literature data on methylpyrroles and methylpyridines are discussed with the aid of ab initio calculations. STO-3G fully optimized geometries of neutral molecules and their corresponding cations are found to be necessary for proper quantitative evaluation of the effects of the methyl substituents. An examination of the 4-31G//STO-3G energies shows that azolium ions are more sensitive than azoles to substituent effects. Of the four available positions for methyl substitution, those α to the basic center shown an extra stabilization due to methyl hydrogen–nitrogen lone-pair interactions. When the substituent is at position 1 (*N*-methyl derivatives) the effect is quite different, due to a partial loss of hyperconjugation. As predicted earlier from preliminary theoretical calculations, the corresponding gas-phase and aqueous basicities are linearly related within four separate families (that is, for *N*-H and *N*-CH_3 pyrazoles and imidazoles). The aqueous solution attenuation factors are fixed (4.1), having a value similar to that for methylpyridines (3.5). Tautomerism of 3(5)-methylpyrazoles and 4(5)-methylimidazoles is discussed by use of theoretical and experimental values. The proton affinities of pyrazole, imidazole, and their methyl derivatives cover a 25 kcal mol^{-1} range (from 212.7 to 237.6). The latter value is for 1,2,4,5-tetramethylimidazole, which is only 5 kcal mol^{-1} less basic than 1,8-bis(dimethylamino)naphthalene (proton sponge). This illustrates the utility of polyalkyl substitution to obtain very strong gas-phase basicity.

1. Introduction

The understanding of the behavior of organic bases in aqueous solution requires a knowledge of their inherent (gas-phase) basicities.[1-3] For this reason, in previous papers[4] we devoted attention to investigating the intrinsic basicity of the five-membered heteroaromatic azoles from a theoretical point of view. Thus, we previously estimated[4e] the intrinsic basicity of methylpyrazoles and methylimidazoles and discussed their solution properties, in particular, the behavior of N-methylated derivatives.

Recently, we carried out careful studies on the acid–base properties of C-unsubstituted *N*-H and *N*-methylazoles (parent compounds), both in the gas phase and in solution. From the experimental values of these equilibria interesting information about structural effects, such as proximity electrostatic effects[5]

† Universidad Autónoma de Madrid.
‡ UNED.
§ Instituto de Química Médica.
‖ University of California.

(1) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.
(2) Headley, A. D. *J. Org. Chem.* **1988**, *53*, 312.
(3) Abboud, J. L. M.; Catalán, J.; Elguero, J.; Taft, R. W. *J. Org. Chem.* **1988**, *53*, 1137.
(4) (a) Catalán, J.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1869. (b) Catalán, J.; Pérez, P.; Elguero, J. *Heterocycles* **1983**, *20*, 1717. (c) Catalán, J.; de Paz, J. L. G.; Yañez, M.; Elguero, J. *Chem. Scr.* **1984**, *24*, 84. (d) Catalán, J.; de Paz, J. L. G.; Yañez, M.; Elguero, J. *J. Am. Chem. Soc.* **1984**, *106*, 6552. (e) Catalán, J.; Mó, O.; de Paz, J. L. G.; Pérez, P.; Yañez, M.; Elguero, J. *J. Org. Chem.* **1984**, *49*, 4379. (f) Mó, O.; de Paz, J. L. G.; Yañez, M. *J. Phys. Chem.* **1986**, *90*, 5577. (g) Taagepera, M.; Summerhays, K. D.; Hehre, W. J.; Topsom, R. D.; Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1981**, *46*, 891. (h) Hehre, W. J.; Taagepera, M.; Taft, R. W.; Topsom, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 1344.

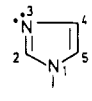
0002-7863/90/1512-1303$02.50/0

and annelation effects,[6] were obtained.

In the present work, we have endeavored to build up the intrinsic basicities of the azoles using simple methyl substitution. Both pyrazole and imidazole are monocentric bases that protonate on N_2 and N_3, respectively.[4c,7] Their basic center should be sensitively enhanced by the effects of successive systematic methyl substitution.

The knowledge of the electronic effects of substituents[1] allows us to conclude that the methyl substituent will act only by predominant hyperconjugative (R) and polarizability (P) effects in the cationic forms, without any base weakening F effects (σ_F = 0), which accompany heteroatom substituent effects. Among alkyl substituents the methyl group has the lowest polarizability value (σ_α = −0.35), but it nevertheless will be indicative of alkyl substituent P effects. According to theoretical calculations,[4e] it ought to be possible, through successive methylations, to cover a range of basicities of ca. 17 kcal mol^{-1} for each diazole. This range would then partially overlap the basicity difference for the parent azoles [PA(pyrazole **1**) = 212.7 kcal mol^{-1}; PA (imidazole **15**) = 223.6 kcal mol^{-1}], giving a very substantial overall range in inherent basicity. Accordingly, we have synthesized and studied all of the possible methylpyrazole (**1–14**) as well as a selected subset of methylimidazoles (**15–23**). Simultaneously, we undertook a theoretical investigation of the problem.

1-14



15-23

With theoretical techniques, mainly SCF calculations, partitioning of substituent effects into components arising from protonated and neutral forms is possible. Actually, these analyses have already been performed for a great variety of organic bases: pyridines,[4g] phenols,[8] benzoic acids,[9] and anilines,[4g] but only standard or partially optimized geometries were employed.

Since the methyl substituent has a moderate effect on the gas-phase basicity of an aromatic compound, the use of fully optimized geometries should be important and this is one of the points that will be illustrated in this paper. The partitioning of the substituent basicity effects between the charged and neutral forms for pyrazoles and imidazoles is also of particular interest and has been carried out here for the first time.

Combined theoretical and experimental data have frequently led to new insights. For this reason, we present in this paper an analysis based upon theoretical and experimental data for the effects of methyl groups on the intrinsic basicities of pyridines, pyrazoles, and imidazoles. As model compounds, the monomethyl-substituted pyridines (picolines), all the monomethyl-substituted pyrazoles and imidazoles, and all the disubstituted compounds that involve *N*-methyl substitution have been selected.

To summarize, our aim has been to answer questions such as the following:

(i) As with many other organic bases, does the effect of the substituent on gas-phase proton affinities arise primarily from interactions in the cationic form?

(ii) How sensitive are the theoretical results to the quality of the basis set used to expand the molecular wave function? In this respect, it is clear that the basis set used and the level of accuracy in the SCF calculations (inclusion or not of correlation effects) are crucial when one attempts to obtain absolute values of the gas-phase proton affinities. However, it is not clear whether this requirement must be fulfilled when attempting to obtain relative proton affinities. Actually, our experience[10,15] shows that a minimal basis set is often good enough for this purpose. Therefore, to investigate this point, we have carried out ab initio calculations using a minimal STO-3G and a split-valence 4-31G basis set.

(iii) How much do theoretical results depend on the use of fully optimized structures instead of standard geometries?

(iv) When the number of methyl groups increases (from one to four), does the basicity increase additively or is a saturation (or enhancement) effect observed?

(v) Finally, we wish also to gain some insight into the influence on the behavior of pyrazoles and imidazoles as bases, resulting in some cases from accompanying tautomeric equilibria.

2. Experimental Section

Among the compounds of Table 1, the solids were purified by sublimation (subl:) and the liquids by column chromatography (CC) or preparative gas-phase chromatography (GPC): **1** [commercial (comm)], **2**,[16] **3** (comm), **4** (comm), **5**,[16] **6**,[16] **7**,[16] **8**,[16] **9** (comm), **10**,[16] **11**,[16] **12**,[16] **13**,[16] **14**,[16] **15** (comm), **16** (comm), **17** (comm), **18** (comm), **19** (comm), **20**,[17] **21**,[17] **22**,[18] and **23**.[19]

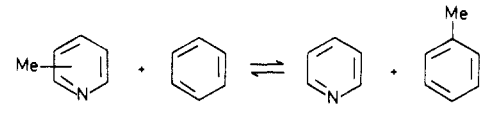
The gas-phase basicities were determined from equilibrium proton-transfer reactions conducted in an FTICR spectrometer under conditions similar to those already described.[6,20] Table 1 presents the results of proton-transfer equilibria (1) obtained in this study along with the standard bases used (B_{ref}):

$$BH^+ + B_{ref} \underset{}{\overset{K}{\rightleftharpoons}} B + B_{ref}H^+ \qquad (1)$$

In this equilibrium, B is a neutral heterocyclic base. The proton affinities of B are obtained according to $PA = PA_{ref} + R \ln K - T\Delta S°$, where $\Delta S°$ for reaction 1 is estimated satisfactorily by methods previously discussed.[20]

3. Computational Details

In order to carry out the partitioning of substituent effects into components arising from each form, the protonated and the nonprotonated one, it is necessary to evaluate the following: (i) The substituent interaction energies, $\Delta E°$, for the neutral species as the change in the ground-state energy for the hypothetical reaction 2 (where pyridines have been taken as an example).



(2)

To study these effects it will be necessary to know the ground-state energy not only of the substituted pyridine, but also of pyridine, benzene, and toluene. For the case of pyrazoles and imidazoles, reaction 2 will involve the methyl-substituted pyrazole

(5) Taft, R. W.; Anvia, F.; Taagepera, M.; Catalán, J.; Elguero, J. *J. Am. Chem. Soc.* **1986**, *108*, 3237.
(6) Catalán, J.; Claramunt, R. M.; Elguero, J.; Laynez, J.; Menéndez, M.; Anvia, F.; Quian, J. H.; Taagepera, M.; Taft, R. W. *J. Am. Chem. Soc.* **1988**, *110*, 4105.
(7) Meot-Ner (Mautner), M.; Liebman, J. F.; Del Bene, J. E. *J. Org. Chem.* **1986**, *51*, 1105.
(8) Pross, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1980**, *45*, 818.
(9) Reynolds, W. F.; Modro, T. A.; Mezey, P. G.; Skorupowa, E.; Maron, A. *Can. J. Chem.* **1980**, *58*, 412.
(10) Catalán, J.; Yañez, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 741; *J. Am. Chem. Soc.* **1984**, *106*, 421.
(11) Catalán, J.; Mõ, O.; Pérez, P.; Yañez, M. *J. Am. Chem. Soc.* **1979**, *101*, 6520.
(12) Catalan, J.; Pérez, P.; Yañez, M. *Tetrahedron* **1982**, *38*, 3693.
(13) Catalán, J.; Mõ, O.; Pérez, P.; Yañez, M. *J. Mol. Struct.: THEOCHEM.* **1983**, *94*, 143.
(14) Catalán, J.; Mõ, O.; Pérez, P.; Yañez, M.; Amat-Guerri, F. *Nouv. J. Chim.* **1984**, *8*, 87.
(15) Catalán, J.; de Paz, J. L. G.; Yañez, M.; Amat-Guerri, F.; Houriet, R.; Rolli, E.; Zehringer, R.; Delhafen, P.; Taft, R. W.; Anvia, F.; Quian, J. H. *J. Am. Chem. Soc.* **1988**, *110*, 2699.
(16) Elguero, J.; Jacquier, R.; Tien Duc, H. C. N. *Bull. Soc. Chim. Fr.* **1966**, 3727.
(17) Hubball, W.; Pyman, F. L. *J. Chem. Soc.* **1928**, 21.
(18) Theilig, G. *Chem. Ber.* **1953**, *86*, 96.
(19) Lions, F.; Ritchie, E. *J. Proc. R. Soc. N.S. Wales*, **1941**, *74*, 365.
(20) (a) Wolf, J. F.; Staley, R. H.; Koppel, I.; Taagepera, M.; McIver, R. T.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5417. (b) Aue, D. H.; Bowers, M. T. In *Gas Phase Ion Chemistry*; Bowers, M. T., Ed.; Academic Press: New York, 1979; Vol. 2, Chapter 9.
(21) Lias, S. G.; Liebman, J. F.; Levin, R. D. *J. Phys. Chem. Ref. Data* **1984**, *13*, 695.
(22) Meot-Ner (Mautner), M. *J. Am. Chem. Soc.* **1988**, *110*, 3071.

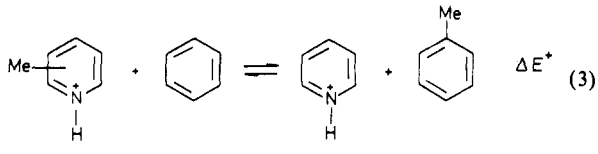
Table I. Gas-Phase Basicity Results Obtained with Standard Bases (in kcal mol^{-1})

	heterocycle	standard base	$\Delta G°$(std)[a]	$\delta\Delta G°$(obs)[b]	$\Delta G°$[c]	$\Delta G°$(bv)[d]	PA
1	pyrazole[e]					9.1 ± 0.2	212.7[e] (212.8)[f]
2	1-methylpyrazole[e]					13.2 ± 0.2	216.4[e]
3	3(5)-methylpyrazole	2-chloropyridine	11.0	−1.5 ± 0.1	12.5		
		3-chloropyridine	11.5	−0.8 ± 0.1	12.3		
		n-butylamine	14.6	2.2 ± 0.4	12.3	12.4 ± 0.1	215.6
4	4-methylpyrazole	2-chloropyridine	11.0	−1.0 ± 0.1	12.0		
		3-chloropyridine	11.5	−0.4 ± 0.2	11.9		
		ethylamine	12.6	0.3 ± 0.2	12.3	12.1 ± 0.1	215.7
5	1,3-dimethylpyrazole	pyridine	17.6	0.2 ± 0.1	17.4		
		2-methoxypyridine	18.2	0.6 ± 0.1	17.6	17.5 ± 0.1	220.7
6	1,4-dimethylpyrazole	neopentylamine	16.3	−0.8 ± 0.1	17.1		
		pyridine	17.6	0.7 ± 0.1	17.0	17.1 ± 0.1	220.3
7	1,5-dimethylpyrazole	pyridine	17.6	−1.0 ± 0.1	18.6		
		tert-butylamine	17.8	−0.7 ± 0.2	18.5		
		2-methoxypyridine	18.2	0.2 ± 0.1	18.0	18.4 ± 0.2	221.6
8	3(5),4-dimethylpyrazole	neopentylamine	16.3	−1.1 ± 0.2	17.4		
		pyridine	17.6	0.2 ± 0.1	17.4	17.4 ± 0.1	220.6
9	3,5-dimethylpyrazole	pyridine	17.6	−0.8 ± 0.1	18.4		
		tert-amylamine	19.2	0.9 ± 0.1	18.3	18.3 ± 0.1	221.9
10	1,3,4-trimethylpyrazole	3-methylpyridine	20.3	−0.9 ± 0.1	21.2		
		trimethylamine	22.0	0.4 ± 0.2	21.6	21.4 ± 0.2	224.6
11	1,3,5-trimethylpyrazole	3-methylpyridine	20.3	−1.9 ± 0.1	22.2		
		4-methylpyridine	21.1	−0.8 ± 0.1	21.9	22.1 ± 0.1	225.3
12	1,4,5-trimethylpyrazole	*tert*-amylamine	19.2	2.1 ± 0.2	21.3		
		trimethylamine	22.0	0.5 ± 0.2	21.5	21.4 ± 0.1	224.6
13	3,4,5-trimethylpyrazole	3-methylpyridine	20.3	−0.7 ± 0.1	21.0		
		pyrrolidine	21.3	0.2 ± 0.1	21.0		
		4-(trifluoromethyl)quinuclidine	21.5	1.2 ± 0.1	20.3	20.8 ± 0.3	224.4
14	1,3,4,5-tetramethylpyrazole	*N*-methylpiperidine	26.6	0.6 ± 0.3	26.0	26.0 ± 0.3	229.2
15	imidazole[e]					19.9 ± 0.2	223.5[e] (222.3)[f]
16	*N*-methylimidazole[e]					23.8 ± 0.2	227.0[e] (228.0)[g]
17	2-methylimidazole	piperidine	22.3	−1.7 ± 0.2	24.0		
		hexamethylenimine	23.1	−1.5 ± 0.1	24.6		
		ethyldimethylamine	24.3	−0.1 ± 0.1	24.4	24.3 ± 0.2	227.9
18	4(5)-methylimidazole	piperidine	22.3	−0.6 ± 0.1	22.9		
		ethyldimethylamine	24.3	1.2 ± 0.3	23.1	23.0 ± 0.1	226.2 (224.8)[g]
19	1,2-dimethylimidazole	triethylamine	29.3	−0.3 ± 0.1	29.6		
		quinuclidine	29.8	0.4 ± 0.2	29.4		
		tri-*n*-propylamine	31.3	2.1 ± 0.2	29.7	29.4 ± 0.1	232.6
20	1,4-dimethylimidazole	diisopropylamine	26.4	−1.5 ± 0.2	27.9		
		cyclohexyldimethylamine	29.3	1.5 ± 0.2	27.8	27.8 ± 0.1	231.0
21	1,5-dimethylimidazole	diisopropylamine	26.4	−1.5 ± 0.1	27.9		
		cyclohexyldimethylamine	29.3	1.2 ± 0.2	28.1	28.0 ± 0.1	231.2
22	2,4,5-trimethylimidazole	triethylamine	29.3	−0.4 ± 0.1	29.7	29.7 ± 0.1	233.0
23	1,2,4,5-tetramethylimidazole	4-*N*-dimethylpyridine	33.2	−1.2 ± 0.1	34.4	34.4 ± 0.1	237.6

[a] Gas-phase basicities relative to ammonia, positive values denoting greater basicity. [b] Differential basicity obtained by measuring proton-transfer equilibrium (1). [c] Basicity of the heterocycle relative to ammonia. [d] Best value of gas-phase basicity relative to ammonia (PA = 204.0 kcal mol^{-1}).[21] [e] Value reported in ref 6. [f] Value reported by Mautner.[22] [g] Value reported by Mautner et al.[7]

or imidazole, the corresponding parent compound, pyrazole **1** or imidazole **15**, pyrrole **28**, and the corresponding substituted pyrrole.

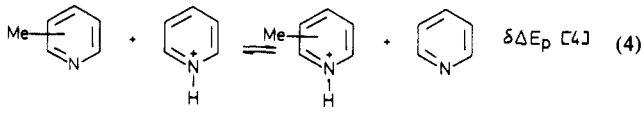
(ii) The substituent interaction energies for the protonated forms, ΔE^+, as the change in the ground-state energy for the hypothetical reaction 3.



(3)

The evaluation of ΔE^+ requires the knowledge of the energies of the protonated parent compounds (pyridinium, pyrazolium, or imidazolium ions, respectively) as well as the protonated forms of the substituted compounds under investigation. The sign convention employed for all these substituent interaction energies is the one reported elsewhere.[4g]

It is evident that the calculated substituent effect on the gas-phase basicity, $\delta\Delta E_p$, defined as the energy change for the reaction



(4)

is equal to the difference $\Delta E° - \Delta E^+$ and can be obtained experimentally.

Since this study was carried out at two levels (STO-3G and 4-31G), to save computation time in view of the considerable number of compounds under study, we have adopted the following procedure. For all compounds needed in the previous schemes (benzene, toluene, **1**–**31**), and their corresponding protonated species, we have carried out a full geometry optimization at the STO-3G level, using a gradient optimization procedure.[23] Then, single-point 4-31G energy calculations were performed on the STO-3G fully optimized structure. The first type of calculations will be denoted hereafter by STO-3G//STO-3G and the second type by 4-31G//STO-3G. In Table II the corresponding total energies are given.

Obviously, the use of STO-3G fully optimized structures at the 4-31G level implies certain limitations regarding the 4-31G//STO-3G results. Nevertheless, we can reasonably assume that these limitations would have small effects since it has been shown[25] that the difference obtained by using 4-31G basis on STO-3G

(23) Murtagh, B. A.; Sargent, R. W. H. *Comput. J.* **1970**, *13*, 185. Pulay, P. In *Applications of Electronic Structure Theory*; Schaefer, H. F., Ed.; Plenum Press: New York, 1977; p 153.
(24) Kao, J.; Hinde, A. L.; Radom, L. *Nouv. J. Chim.* **1979**, *3*, 473.
(25) Del Bene, J. E. *J. Comput. Chem.* **1984**, *5*, 381.

Table II. Calculated Total Energies (Hartrees) for Pyrazoles, Pyrazolium Ions, Imidazoles, Imidazolium Ions, Pyrroles, Benzene, and Toluene and Protonation Energies of Pyrazoles and Imidazoles

compound	STO-3G//STO-3G	$-\Delta E_p$	4-31G//4-31G	$-\Delta E_p$
	(a) Pyrazoles and Pyrazolium Ions			
pyrazole (**1**)	−221.97726	265.1	−224.44663	235.3
pyrazole-H^+ (**1**-H^+)	−222.39962		−224.81678	
1-methylpyrazole (**2**)	−260.56092	271.3	−263.42076	237.5
1-methylpyrazole-H^+ (**2**-H^+)	−260.99313		−263.79917	
3-methylpyrazole (**3a**)	−260.56449	271.2	−263.43131	238.1
5-methylpyrazole (**3b**)	−260.56514	271.6	−263.43152	238.0
3(5)-methylpyrazole-H^+ (**3**-H^+)	−260.99723		−263.81063	
4-methylpyrazole (**4**)	−260.56230	267.9	−263.42759	235.0
4-methylpyrazole-H^+ (**4**-H^+)	−260.98904		−263.80193	
1,3-dimethylpyrazole (**5**)	−299.14769	276.9	−302.40510	242.0
1,3-dimethylpyrazole-H^+ (**5**-H^+)	−299.58889		−302.79068	
1,4-dimethylpyrazole (**6**)	−299.14592	273.8	−302.40135	240.1
1,4-dimethylpyrazole-H^+ (**6**-H^+)	−299.58204		−302.78390	
1,5-dimethylpyrazole (**7**)	−299.14891	275.4	−302.40511	241.5
1,5-dimethylpyrazole-H^+ (**7**-H^+)	−299.58772		−302.78988	
	(b) Imidazoles and Imidazolium Ions			
imidazole (**15**)	−221.98799	283.5	−224.46752	246.8
imidazole-H^+ (**15**-H^+)	−222.43955		−224.86064	
1-methylimidazole (**16**)	−260.57046	288.2	−263.43912	252.0
1-methylimidazole-H^+ (**16**-H^+)	−261.02961		−263.84054	
2-methylimidazole (**17**)	−260.57760	290.6	−263.45531	252.3
2-methylimidazole-H^+ (**17**-H^+)	−261.04060		−263.85731	
4-methylimidazole (**18a**)	−260.57475	288.2	−263.45229	250.4
5-methylimidazole (**18b**)	−260.57509	288.0	−263.45030	251.6
4(5)-methylimidazole-H^+ (**18**-H^+)	−261.03391		−263.85117	
1,2-dimethylimidazole (**19**)	−299.15887	294.7	−302.42554	256.9
1,2-dimethylimidazole-H^+ (**19**-H^+)	−299.62836		−302.83489	
1,4-dimethylimidazole (**20**)	−299.15718	292.8	−302.42377	255.3
1,4-dimethylimidazole-H^+ (**20**-H^+)	−299.62357		−302.83056	
1,5-dimethylimidazole (**21**)	−299.15639	291.4	−302.42071	255.2
1,5-dimethylimidazole-H^+ (**21**-H^+)	−299.62057		−302.82719	
	(c) Pyridines and Pyridinium Ions			
pyridine (**24**)	−243.63861	277.1	−246.32858	241.6
pyridine-H^+ (**24**-H^+)	−244.08014		−246.71352	
2-methylpyridine (**25**)	−282.22495	282.7	−285.31301	245.7
2-methylpyridine-H^+ (**25**-H^+)	−282.67527		−285.70446	
3-methylpyridine (**26**)	−282.22354	279.9	−285.30960	244.2
3-methylpyridine-H^+ (**26**-H^+)	−282.66938		−285.69869	
4-methylpyridine (**27**)	−282.22404	281.8	−285.31064	246.1
4-methylpyridine-H^+ (**27**-H^+)	−282.67292		−285.70278	
	(d) Pyrroles and Benzenes			
pyrrole (**28**)	−206.22712[a]		−208.50542	
1-methylpyrrole (**29**)	−244.80869		−247.47557	
2-methylpyrrole (**30**)	−244.81433[a]		−247.48914	
3-methylpyrrole (**31**)	−244.81158[a]		−247.48642	
benzene	−227.89136		−230.37726	
toluene	−266.47566		−269.35751	

[a] See: Reference 24.

geometries and 4-31G basis on 4-31G geometries are never greater than ~1.0 kcal mol^{-1}.

In several particular cases to complete our discussion we have also carried out a localization of the canonical molecular orbitals using the procedure of Foster and Boys,[26] which has been implemented by us in the framework of the Gaussian 80 series of programs.

4. Results and Discussion

Geometries. For the sake of brevity, the STO-3G optimized geometries of all the compounds listed in Table II will not be reported here but will be given as supplementary material. For azoles existing in two tautomeric forms, 3(5)-methylpyrazole 3- and 4(5)-methylimidazole **18**, both tautomers have been calculated (for each there is only one corresponding cation, **3H**$^+$ and **18H**$^+$, respectively). For pyrrole **28**, imidazole **15**, and imidazolium ion **15H**$^+$, our results are identical with those reported in the literature,[24,27] but they have been included in the corresponding tables to facilitate comparison (see supplementary material). It should also be indicated that previous workers[28a] had also carried out complete STO-3G geometry optimizations on methyl-substituted pyridines, but by optimizing bond lengths and bond angles cyclicly and independently. As a consequence, their ring geometries differ from ours by ~0.01 Å for some bond lengths and by ~1° for some bond angles.

Some interesting features should be noticed. First, the equilibrium geometry of the ring of the free bases is almost unaffected by the substituent, and it is practically insensitive to its position in the ring. In fact, the most significant change is one that affects the endocyclic angle centered on the position that undergoes substitution. This angle closes ~0.5–1° due to a slight increase of the "p" character of the two hybrids involved in this endocyclic angle and centered on the substituted atom. Second, the most dramatic changes take place upon protonation. Here the endocyclic angle centered on the basic nitrogen opens ~7° or more

(26) Boys, S. F. In *Quantum Theory of Atoms, Molecules, and Solid State*; Lõwdin, P. O., Ed.; Academic Press: New York, 1966; p 253.

(27) Kollmann, P. A.; Hayes, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 2955.

(28) (a) Del Bene, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 5285; *Ibid.* **1979**, *101*, 6184. (b) Sunko, D. E.; Hehre, W. J. *Prog. Phys. Org. Chem.* **1983**, *14*, 208–214.

Table III. Substituent Interaction Energies in Pyridines, Imidazoles, and Pyrazoles, and Their Corresponding Cations (kcal mol^{-1})

	STO-3G//STO-3G			4-31G//4-31G			
	ΔE^0	ΔE^+	$\delta\Delta E_p$	ΔE^0	ΔE^+	$\delta\Delta E_p$	δPA
pyridines							
2-methyl (**25**)	1.3	6.8	−5.5	2.6	6.7	−4.1	−3.8
3-methyl (**26**)	0.4	3.1	−2.7	0.4	3.1	−2.7	−2.7
4-methyl (**27**)	0.7	5.2	−4.5	1.1	5.5	−4.4	−3.5
imidazoles							
1-methyl (**16**)	0.6	5.3	−4.7	0.9	6.1	−5.2	−3.5
2-methyl (**17**)	1.5	8.7	−7.2	2.6	8.1	−5.5	−4.4
4-methyl (**18a**)	1.4	6.2	−4.8	2.4	6.0	−3.6	
5-methyl (**18b**)	−0.1	4.5	−4.6	−0.6	4.3	−4.9	
1,2-dimethyl (**19**)			−11.3			−10.2	−9.1
1,4-dimethyl (**20**)			−9.3			−8.6	−7.5
1,5-dimethyl (**21**)			−7.9			−8.4	−7.7
pyrazoles							
1-methyl (**2**)	1.3	7.5	−6.2	2.5	7.7	−5.2	−3.7
3-methyl (**3a**)	1.7	8.2	−6.5	2.3	8.1	−5.8	
5-methyl (**3b**)	0.4	6.5	−6.1	0.7	6.3	−5.6	
4-methyl (**4**)	0.4	3.2	−2.8	0.0	2.6	−2.6	−3.0
1,3-dimethyl (**5**)			−11.8			−9.7	−8.0
1,4-dimethyl (**6**)			−8.6			−7.8	−7.6
1,5-dimethyl (**7**)			−10.3			−9.2	−8.9

in pyridine and ~5° in azoles, as a consequence of the change from a σ-lone orbital to a σ-bonding orbital. Accordingly, the whole structure of the ring changes considerably. These effects have been analyzed elsewhere[13,14] and will not be discussed here in more detail. Third, it should be emphasized that the geometrical changes upon protonation affect both sides of the equilibria 3 and 4. Consequently, one must expect the substituent interaction energies, ΔG^+ and $\delta\Delta E_p$, to change little when not using fully optimized structures. However, as we shall discuss later, if one desires to have a *quantitative* estimation of the substituent effects on these energies, the use of fully optimized geometries becomes unavoidable, since although these effects are small in absolute value (~1.5 kcal mol^{-1}), they become relatively important when the total energy change is of a few kilocalories per mole.

As indicated in the introduction, we have employed in previous ab initio calculations[4c,d,f,12-14] scaled INDO fully optimized geometries (STO-3G//INDO). It is interesting to know the most important deviations of this economical approach with respect to those based on ab initio fully optimized structures.

For instance, for methylpyrazoles and methylimidazoles[4f] the agreement between both sets of values is fairly good. However, there are some geometry differences that result in STO-3G//INDO energies that are ~4 kcal mol^{-1} higher than the corresponding STO-3G//STO-3G ones for monomethyl derivatives and ~7 kcal mol^{-1} for dimethyl derivatives. The most important point is the systematic character of these deviations. The substitution and protonation effects discussed above are equally well reproduced by the INDO method, implying that calculations at the STO-3G//INDO level are valid whenever one is interested in *relative* values of protonation energies.

Finally, it must be indicated that for those compounds considered here, the methyl group shows distinct conformational preferences.[15,24] Therefore, the geometrical parameters listed in the supplementary material always correspond to the minimal energy conformation (for methyl groups α to the basic nitrogen, this conformation has one hydrogen in the ring plane and near to the nitrogen).

Protonation Energies and Theoretical Estimation of Substituent Interaction Energies. Table III shows the substituent interaction energies, $\Delta E°$, ΔE^+, and $\delta\Delta E_p$, defined in the previous section for monosubstituted methylpyridines, methylimidazoles, and methylpyrazoles.

Several facts should be singled out for comment:

(i) The largest interaction energies always correspond to the stabilization of the cationic form by the substituent, in agreement with previous findings.[4e] However, it should be noticed that the present results qualify those obtained previously for the same systems by using standard geometries. For instance, while calculations employing standard geometries predict a stabilization of 2.3 and 5.7 kcal mol^{-1} of the pyridinium ion upon 3- and 4-methyl substitution, respectively, the new results, using fully optimized geometries, are unavoidable when attempting an accurate estimation (better than 1 kcal mol^{-1}) of these effects.

(ii) The interaction energies for neutral molecules, $\Delta E°$, are small when compared with the corresponding quantities for the cations (ΔE^+). This implies for pyrazoles and imidazoles as well as pyridines that the effect of methyl groups on proton affinities comes primarily (>70%) from interactions in the charged form. Again, there are some quantitative differences between the new results and those obtained by using standard geometries.[4e] For instance, while with standard geometries a slight destabilization of pyridine upon β substitution is predicted, the new calculations predict a slight stabilization (see Table IV).

(iii) As we shall show later, pyrazoles and imidazoles (see Figure 1) accumulate π charge at the α position to the basic center. Therefore, a greater stabilization of imidazoles substituted in C_2 and C_4 in relation to those substituted on C_5 or N_1 is expected

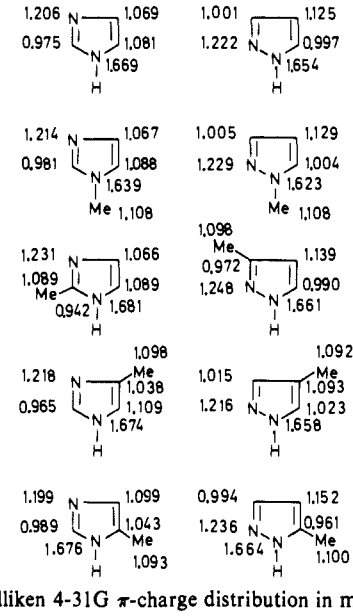


Figure 1. Mulliken 4-31G π-charge distribution in methylazoles.

Scheme I

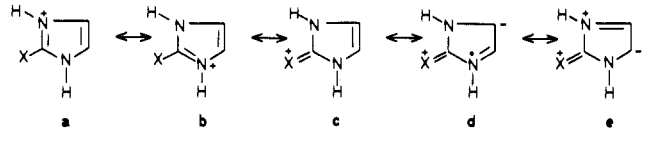


Table IV. Thermochemistry of Isodesmic Reactions of Pyridines (eq 2 and 3) (kcal mol^{-1})

compound	$\Delta H_f°(B)_g$[a]	PA[b]	$\Delta H_f°(BH^+)_g$[c]	$\Delta H°$[d]	$\Delta E°$[e]	ΔH^+[f]	ΔE^+[g]
benzene	19.81 ± 0.07[h]						
toluene	11.97 ± 0.07[h]						
pyridine (**24**)	33.50 ± 0.28[i]	220.8	178.4				
2-methylpyridine (**25**)	23.71 ± 0.17[h]	224.6	164.8	2.0	2.6	5.8	6.7
3-methylpyridine (**26**)	25.43 ± 0.12[h]	223.5	167.6	0.3	0.4	3.0	3.1
4-methylpyridine (**27**)	24.80 ± 0.22[j]	224.3	166.2	0.9	1.1	4.4	5.5

[a] Enthalpies of formation of B in the gas phase [$\Delta H_f°(H^+)$ = 365.7 kcal mol^{-1}].[21] [b] Experimental proton affinities. [c] Enthalpies of formation of BH^+ in the gas phase, $\Delta H_f°(BH^+) = \Delta H_f(H^+) + \Delta H_f(B) - PA$. [d] Experimental variation of enthalpy corresponding to eq 2. [e] From 4-31G//STO-3G values of Table III. [f] Experimental variation of enthalpy corresponding to eq 3. [g] From 4-31G//STO-3G values of Table III. [h] From ref 30. [i] From ref 31. [j] From ref 32.

(the same situation holds for the corresponding pyrazoles).

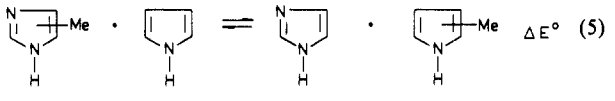
Moreover, there is an extra stabilization of the 2-substituted imidazolium ion because this cation is highly symmetric, and consequently, the resonance stabilization by π donation is most effective through the contribution of the canonical structures c, d, and e, shown in Scheme 1.

The stabilization of *N*-methylimidazolium **16H$^+$** is greater than that obtained for 5-methylimidazolium ion **18H$^+$** (both β-substituted compounds). This is an indication that, besides the π donation from the methyl to the imidazolium ring, structures involving polarization of the π electrons (forms a and b of Scheme 1) must be, in this case, important contributors. This seems to be confirmed by the 0.8 kcal mol^{-1} increase (to be compared with the 0.2 kcal mol^{-1} decrease in the 5-methylimidazolium case) in the stabilization of the *N*-methyl-substituted compound when enlarging the basis set (see Table III). That is, it is shown best using a basis set that describes polarization effects better than a minimal one. Similar trends are observed for pyrazoles, where the least stable pyrazolium ion is the C_4-substituted one (β with respect to the basic center) while the most stable one is the C_3-substituted derivative (α with respect to the basic center).

(iv) Some significant changes occur when enlarging the basis set that require a closer analysis. The substituent interaction energies for the protonated forms (ΔE^+) for all families under consideration are almost insensitive to the change in the basis set, the greatest variation (~0.8 kcal mol^{-1}) being observed for *N*-methylimidazole (**16**) (see above). A similar finding applies to the substituent interaction energies for neutral forms ($\Delta E°$), with the exception of those compounds where the substituent is at the α position. In these cases, the larger basis set predicts an extra stabilization of ~1 kcal mol^{-1}.

This change in the value of $\Delta E°$ is of great importance since it implies a parallel decrease in the corresponding protonation energy and, as we shall discuss later, a better agreement with our experimental results. Therefore, we think that this basis set effect deserves the following discussion. For this purpose imidazoles have been chosen as a suitable example, since in this regard they are completely similar for pyrazoles and only slightly different for pyridines.

Reaction 2 for imidazoles becomes



28 15

Two compounds, **28** and **15**, one on each side of the reaction, remain unchanged. Consequently, the changes in $\Delta E°$ that are found upon enlarging the basis set come from the other two species, the substituted pyrrole and the substituted imidazole. Therefore, we have studied how the theoretical description of these compounds is affected by the basis set. To do this we have chosen as the reference system, the *N*-methyl-substituted derivative, which is for both families the less stable isomer. The relative stability of the remaining isomers is represented in Figure 2.

Two main effects are observed: in effect (a) the stabilities of all isomers with respect to the N-methylated one are considerably increased when enlarging the basis set; with effect (b) this stabilization is quantitatively greater for the α-substituted imidazoles, but is qualitatively the same for methylpyrroles. As a consequence

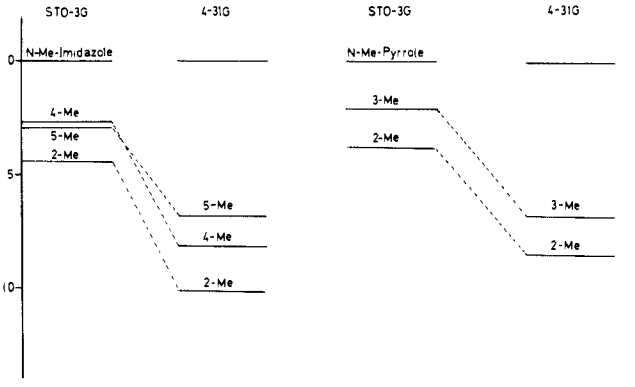


Figure 2. Basis set effect on methylazole energies (kcal mol^{-1}).

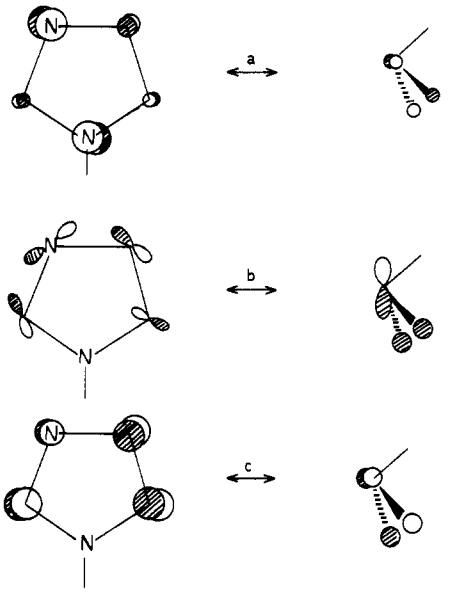


Figure 3. Most significant interaction between MOs of the aromatic imidazole system and those of the methyl group (see Chart I and the text).

Chart I

of effect b, the stability in methylimidazoles changes from *N*-Me < 4-Me < 5-Me < 2-Me (STO-3G//STO-3G) to *N*-Me < 5-Me < 4-Me < 2-Me (4-31G//STO-3G).

It is well documented that hyperconjugation is an important contributor to stabilization provided by the methyl group, and this is usually accompanied by π donation to the aromatic ring. However, a methyl group may act either as a π-electron donor or as a P-electron acceptor since it possesses two degenerate π orbitals (occupied) as well as two vacant π^* orbitals (see Chart I).[28b]

Scheme II

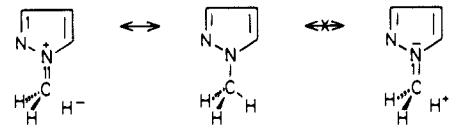
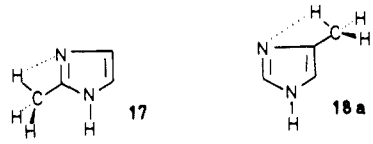


Chart II



The three most important interactions between MOs of the aromatic system and those of the methyl group have been schematized in Figure 3. Interaction a involves an occupied MO of the imidazole ring with a vacant orbital of the methyl group, while interactions b and c involve a vacant MO of imidazole and an occupied MO of the methyl group. It is easy to see that interaction a (where the methyl group would behave as a π acceptor) must be very important for *N*-methyl-substituted compounds, because the overlap is much greater at the N_1 position than at the remaining positions of the ring. To the contrary, interactions b and c (where the methyl group behaves as a π donor) must be very small for N-substituted compounds in comparison with other methyl derivatives.

These interactions are well reflected by the corresponding π-electron distribution (see Figure 1). It is clear that while all substituted *C*-methylimidazoles present a π charge of the ring greater than six electrons (π donation from methyl), the aromatic ring of *N*-methylimidazole (**16**) presents a π charge smaller than six electrons. Accordingly, the π charge of the methyl group is greater in **16** than in the remaining methyl derivatives.

This confirms that azoles differ from azines in two ways: (i) they are π-excessive heterocycles, whereas azines are π-deficient; (ii) the substitution on the nitrogen of azoles is without parallel in six-membered heteroaromatic compounds. Moreover, our results are compatible with the usually accepted resonance structures that can be drawn for *N*-methylazoles (see Scheme II) and which are clearly corroborated by the available experimental evidence.[29]

A second consequence is that the hyperconjugative interaction is much smaller for *N*-methyl-substituted compounds than for the other derivatives. A split-valence basis set would be expected to describe better than a minimal one for this kind of effect. This is due, among other things, to the fact that a split-valence basis allows a better dispersal of the positive charge on the hydrogens of the methyl group, since the outer and the inner shell populates independently. Furthermore, as indicated above, there are also π-polarization effects that are also better described by the more flexible basis set. Consequently, all methyl derivatives appear more stabilized with respect to the *N*-methyl compound when using the larger basis set.

The π-polarization effect, however, is quantitatively different for the different isomers. In particular, there is an additional effect in the bases of 2-methylimidazole (**17**) and 4-methylimidazole (**18a**), which is not present in 5-methylimidazole (**18b**) and in methylpyrroles **30** and **31**. This additional effect involves a "non-bonding interaction between N_3 and the hydrogens of the methyl group (see Chart II). The effect is better described by a 4-31G basis than by a minimal one, because once more, the greater flexibility of the former allows a better description of the charge density far from the nucleus of N_3. Consequently, the centroid of charge of the corresponding localized nitrogen lone-pair orbital is further from the nucleus (0.72 au) when using a 4-31G basis than when employing a STO-3G basis set (0.65 au). Moreover, the overlap population between N_3 and the methyl hydrogen, although small, is higher at the 4-31G level than at the STO-3G level, indicating a stronger nonbonding interaction between both atoms when the former basis is used. Finally, the total net charges of both N_3 (negative) and the methyl hydrogen (positive) are much greater at the 4-31G level, implying a greater Coulombic interaction.

Table V. Relative N_{1s} Orbital Energies for Imidazoles and Pyrazoles (kcal mol^{-1})

	STO-3G//STO-3G	4-31G//4-31G
imidazoles		
unsubstituted (**15**)	0.0	0.0
1-methyl (**16**)	3.34	3.20
2-methyl (**17**)	8.30	5.07
4-methyl (**18a**)	5.09	3.94
5-methyl (**18b**)	2.86	3.07
pyrazoles		
unsubstituted (**1**)	0.0	0.0
1-methyl (**2**)	6.31	5.15
3-methyl (**3a**)	8.20	6.80
4-methyl (**4**)	1.40	1.64
5-methyl (**3b**)	5.23	5.13

In conclusion, since effect a is in the same direction, for both methylpyrroles (right side of reaction 5 and methylimidazoles (left side of reaction 5), no significant changes are observed in the value of $\Delta E°$ for those derivatives where the substituent is not α with respect to the basic center. However, for α-substituted compounds, effect b is also present, and accordingly, the left side of reaction 5 is more stabilized than the right side when enlarging the basis set and $\Delta E°$ increases.

Similar arguments can be used for pyrazoles. For pyridines, the situation is simpler because in reaction 2 only methylpyridines (on the left side) change, and the changes observed when enlarging the basis set are only those affecting them. These are identical with those described above for imidazoles, i.e., both 2- and 4-methylpyridines slightly stabilize with regard to 3-methylpyridine due to effect a, but the α-substituted derivative **25** undergoes an extra stabilization due to effect b.

It should be noticed that the values of $\Delta E°$ and ΔE^+ obtained at the 4-31G//STO-level are in very good agreement with the corresponding experimental standard enthalpy changes for methylpyridines and methylpyridinium ions (see Table IV). Further, the agreement between the values for $\delta\Delta E_p$ evaluated at the 4-31G//STO-3G level and the experimental ones is better than those obtained at the STO-3G//STO-3G level. Actually, the STO-3G results always overestimate $\delta\Delta E_p$ (due to the underestimation of $\Delta E°$) for α-substituted compounds.

Table III also contains the protonation energies (obtained as the energy difference between the protonated and the unprotonated forms and relative to the parent compound) for those dimethyl derivatives indicated at the end of the previous section.

The particular behavior of α-substituted compounds when enlarging the basis set poses an additional problem. We have previously show, for a great variety of bases,[4,11] that there is a linear relationship between protonation energies (both calculated and measured) and 1s orbital energies evaluated at the STO-3G level. Since our calculated protonation energies for α-substituted derivatives decrease $\sim$1.5 kcal mol^{-1} in going from a STO-3G to a 4-31G basis, one wonders whether the correlation indicated above still holds when using the larger basis set. To answer this question we have evaluated the corresponding N_{1s} orbital energies (relative to the parent compound), which have been summarized in Table V. It is evident that these *relative* orbital energies are practically insensitive to the change in the basis set, except for α-substituted compounds, where the split-valence basis set predicts a value 1.0–2.5 kcal mol^{-1} lower than that obtained at the STO-3G level. This result indicates that the linear relationship between

(29) Begtrup, M.; Elguero, J.; Faure, R.; Camps, P.; Estopã, C.; Ilavský, D.; Fruchier, A.; Marzin, C.; de Mendoza, J. *Magn. Reson. Chem.* **1988**, *26*, 134.

(30) Pedley, J. B.; Rylance, J. *Sussex-N.L.P. Computer Analyzed Thermochemical Data; Organic and Organometallic Compounds*; 1977.

(31) Skinner, H. A. In *Thermochemistry and Its Applications to Chemical and Biochemical Systems*; Riveiro da Silva, M. A. V., Ed.; Reidel: Dordrecht, The Netherlands, 1984; p 592.

(32) Good, W. D. *J. Chem. Eng. Data* **1972**, *1*, 28.

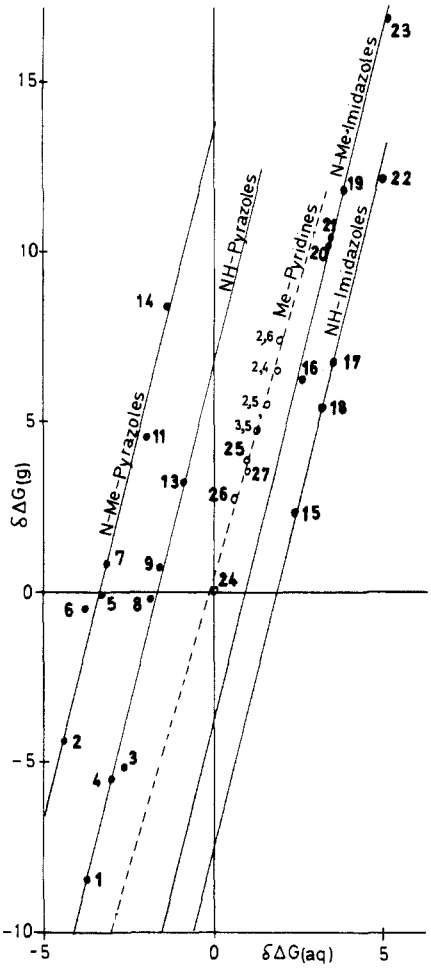


Figure 4. Gas-phase basicity, $\delta\Delta G_{(g)}$, vs aqueous basicity, $\delta\Delta G_{(aq)}$, of azoles and pyridines referred to pyridine (**24**) itself (0,0). Pyridine data for the gas phase are from ref 21 and those for the aqueous solution from ref 36 in units of kcal mol^{-1}.

protonation energies and 1s orbital energies is practically basis set independent.

The variation observed in the N_{1s} orbital energies of α-substituted derivatives when enlarging the basis set has the same origin as the stabilization of the neutral form discussed above. In fact, the 1s orbital energy of a given center acts as a probe of the electrostatic potential near the corresponding nucleus.[33,34] Therefore, the 1s orbital energy depends not only on the total electron population at the host atom (which changes with the basis about the same for all derivatives), but also on the charge of those atoms physically close to it. In this respect, α-methyl derivatives constitute a special case, since close to the basic center there are positively charged hydrogens of the methyl group, which obviously affect the electrostatic potential experienced by the N nucleus. The better description of these electrostatic effects at the 4-31G level (more realistic charge density on the methyl hydrogens) is reflected by a corresponding variation of the N_{1s} orbital energy.

3(5)-Methylpyrazole and 4(5)-Methylimidazole Tautomerism. An interesting problem related to the basicity of azoles is the existence in some cases of tautomeric equilibria. Such is the case of 3(5)-substituted pyrazoles and 4(5)-substituted imidazoles. Our theoretical results (both STO-3G//STO-3G and 4-31G//STO-3G) indicate in both cases that the two tautomers are almost equally stable when the substituent is a methyl group. However, as indicated in the previous section, the relative stability of these compounds may change with the basis set. Actually, 5-methylimidazole (**18b**) is predicted to be 0.2 kcal/mol^{-1} more stable than 4-methylimidazole (**18a**) at the STO-3G//STO-3G level, while at the 4-31G//STO-3G level **18a** is found to be 1.25 kcal mol^{-1} more stable than **18b**. The explanation of these findings (due to α substitution) has been given in the preceding section.

In the case of 3(5)-methylpyrazole, the 5-methyl tautomer **3b** is calculated to be more stable at both the STO-3G//STO-3G level (0.4 kcal mol^{-1}) and the 4-31G//STO-3G level (0.1 kcal mol^{-1}), but a 6-31G*//6-31G calculation[35] favors the 3-methyl tautomer **3a** by 0.4 kcal mol^{-1}, showing that polarization effects can be very important.

Gas-Phase vs Aqueous Basicity of Pyrazoles, Imidazoles, and Pyridines. Figure 4 gives the gas-phase basicities of diazoles plotted vs the corresponding aqueous ones. To make the discussion easier, the values are referred to pyridine itself, which lies at the origin. Thus, the reported $\Delta G°$ values correspond to the equilibrium

$$AzH^+ + \text{pyridine (24)} \rightleftarrows Az + \text{pyridinium (24H}^+) \quad \delta\Delta G° \quad (6)$$

where positive $\delta\Delta G$ values mean that the azole (Az) is more basic than pyridine. Both in the gas phase and in solution it is always the case that imidazoles are more basic ($\delta\Delta G°$ positive). Pyrazoles, on the other hand, can be more basic than pyridine in the gas phase but never in aqueous solution. The dashed line in Figure 4 corresponds to methylpyridines.

Since the slopes of the regression lines for the four families of azoles are not significantly different, we have carried out an unbalanced analysis of the variance.[29] Assuming the four slopes to be identical, we have obtained the following regression results for the 21 compounds: $R^2 = 0.994$. The $\delta\Delta G_{(aq)}$ data for 1,4-dimethylimidazole (**20**), 1,2,5-tetramethylimidazole (**23**), and 2,4,5-trimethylimidazole (**22**), used in the calculation, were obtained from estimated pK_a values.[4e]

N-methylpyrazoles:

$$\delta\Delta G_{(g)} = 13.66\ (\pm 0.53) + 4.08\ (\pm 0.15)\delta\Delta G_{(aq)} \quad n = 6 \quad (7)$$

N-H-pyrazoles:

$$\delta\Delta G_{(g)} = 6.66\ (\pm 0.39) + 4.08\ (\pm 0.15)\delta\Delta G_{(aq)} \quad n = 6 \quad (8)$$

N-methylimidazoles:

$$\delta\Delta G_{(g)} = -3.74\ (\pm 1.08) + 4.08\ (\pm 0.15)\delta\Delta G_{(aq)} \quad n = 5 \quad (9)$$

N-H-imidazoles:

$$\delta\Delta G_{(g)} = -7.64\ (\pm 1.08) + 4.08\ (\pm 0.15)\delta\Delta G_{(aq)} \quad n = 4 \quad (10)$$

For methylpyridines, eq 11 was obtained:

$$\delta\Delta G_{(g)} = 0.22\ (\pm 0.20) + 3.45\ (\pm 0.15)\delta\Delta G_{(aq)} \quad n = 8,\ r^2 = 0.989 \quad (11)$$

The main conclusions that can be drawn from Figure 4 or from eq 7–11 are as follows:

(i) The attenuation effect experienced by the basicity of methylazoles in going from gas phase to water solution, 4.08, is quite large. However, it is not very different from that of pyridines (3.45; eq 11). This similarity was not detected previously[4e] since we used for pyridines different kinds of substituents and not exclusively methyl groups. To compare attenuation effects, (i.e., the slopes of $\delta\Delta G_{(g)}$ vs. $\delta\Delta G_{(aq)}$ linear relationships) obtained by using different kinds of substituents, it is necessary to carry out a previous dissection of the different effects produced by the substituents.[3] The observed attenuation values, 3.5–4.1, correspond to the essential loss of the methyl substituent polarizability effect in water.[3]

(ii) Going from the gas phase to the water solution the N-methylation effect is larger in pyrazoles than in imidazoles; the parallel lines are separated by −1.7 and −1.0 kcal mol^{-1}, respectively, along the $\delta\Delta G_{(a)}$ axis. This is consistent with, and was

(33) Martin, R. L.; Shirley, P. A. *J. Am. Chem. Soc.* **1974**, *96*, 5259.
(34) Davis, D. W.; Rabalais, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 5305.
(35) Catalán, J.; Sanchez-Cabezudo, M.; de Paz, J. L. G.; Elguero, J.; Taft, R. W.; Anvia, F. *J. Comput. Chem.* **1989**, *10*, 426.
(36) Perrin, D. D. *Dissocation Constants of Organic Bases in Aqueous Solutions*; Butterworths: London, 1965.

Table VI. N-Methylation Effect on Basicity of Pyrazoles

substitutent position	gas	water	water[a]
1-methyl	4.1	−0.9	
3-methyl	4.2	1.1	1.0
4-methyl	3.4	0.6	0.6
5-methyl	4.7	1.2	1.0

[a] Calculated by using the model for pyridines.[3]

anticipated by, our previous theoretical findings.[4e]

(iii) In the case of pyridines, we have proposed a model to correct gas-phase values by removing the methyl group polarizability.[3] By use of this model, a figure similar to Figure 4 was obtained, with small slopes, and, what is more important, with the same N-methylation effect, ~−1.8 kcal mol^{-1}, for pyrazoles and imidazoles.

(iv) It is worth noticing in Figure 4 a relationship for which we presently do not have an explanation. The lines corresponding to *N*-H pyrazoles and to *N*-H imidazoles are almost equidistant from the methylpyridines line (~1.8 kcal mol^{-1}). The *N*-H pyrazoles line is displaced in the direction of smaller solution basicities and that for the *N*-H imidazoles toward greater solution basicities.

A comparison of the values of $\Delta G_{(g)}$ (Table I), excluding tautomeric compounds, leads to the conclusion (Table VI) that the base-enhancing effect produced by the methyl group on intrinsic pyrazole basicity diminishes in the order 5-methyl ≫ 3-methyl > 1-methyl ≫ 4-methyl.

It is noticeable that *C*-methylpyrazoles follow, in water, a behavior similar to that described for the gas phase. Moreover, the values for the aqueous solution are in excellent agreement with those deduced from the model established for pyridines (see right column of Table VI).[3]

Experimental Study of the Tautomerism of Methylpyrazoles and Methylimidazoles. As we noted earlier, theoretical calculations of tautomeric equilibria of methylazoles are basis set dependent. Since the difference in energy is so small, any variation in the energy of individual tautomers may result in the inversion of the equilibrium position. The effect of solvation (two water molecules) on the tautomeric equilibrium of 3(5),4-dimethylpyrazole **8** has been studied by Hodošček, Kocjan, and Hadži:[37] 4,5-dimethyl tautomer **8b** is always the most stable, but the difference in energy takes the values 1.2 (free molecule, STO-3G), 0.9 (dihydrate, STO-3G), 0.26 (free molecule, 3-21G) and 0.4 kcal mol^{-1} (dihydrate, 3-21G).

For compound **8**, the gas phase $\Delta G°$ value of Table I is 17.4 kcal mol^{-1}, and those of 1,3,4-trimethylpyrazole (**10**) and 1,4,5-trimethylpyrazole (**12**) are both 21.4 kcal/mol^{-1}, i.e., both model compounds are 4.0 kcal mol^{-1} more basic than the N-methylation effect of Table VI. The apparent conclusion is that 3(5),4-dimethylpyrazole is about a 50:50 mixture ($\Delta E_t = 0$) of tautomers **8a** and **8b**. However, an error of 0.1–0.2 kcal mol^{-1} in the measurement of $\Delta G°$ for **10** and **12** and/or a difference of 0.1–0.2 kcal mol^{-1} in the N-methylation effects, could explain the 3-21G results of Hodošček et al.[37] Since the pK_a of **10** and **12** are not known,[36] we cannot discuss the equilibrium position in water.

The case of 4(5)-methylimidazole **18** is also clear. Assuming that, both in the gas phase and in water solution, the N-methylation effect is constant, the 4-methyl tautomer **18a** is 0.2 kcal mol^{-1} more stable than the 5-methyl tautomer **18b** (N-methylation effect, 4.9 kcal mol^{-1}). Calculations yield 0.2 kcal mol^{-1} in favor of **18a** (4-31G). In water, the pK_a of the *N*-methyl derivatives, **20** and **21**, have been determined by Takeuchi, Kirk, and Cohen.[38] 1,4-Dimethylimidazole (**20**) is reported to have a pK_a of 7.20 and 1,5-dimethylimidazole (**21**) of 7.70. This corresponds to a difference in ΔG_t of 0.68 kcal mol^{-1} in favor of the 4-methyl tautomer **18a** (N-methylation effect, −0.3 kcal mol^{-1}). However, this result must be considered with some caution as the 7.70 value has been doubted.[4e]

(37) Hodošček, M.; Kocjan, D.; Hadži, D. *J. Mol. Struct.: THEOCHEM.* **1988**, *165*, 115.
(38) Takeuchi, T.; Kirk, L.; Cohen, L. A. *J. Org. Chem.* **1978**, *43*, 3570.

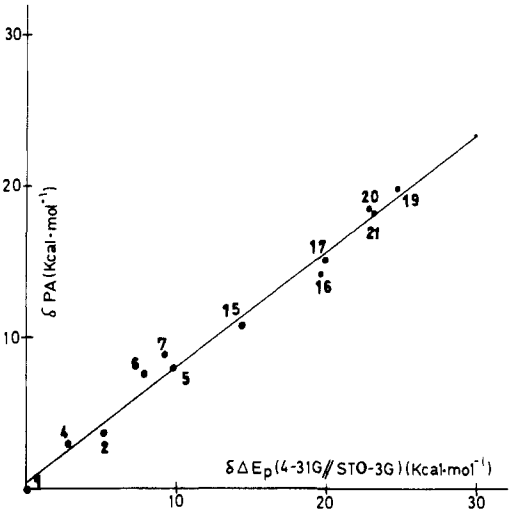


Figure 5. Experimental relative proton affinities, δPA, vs corresponding protonation energies, $\delta\Delta E_p$, calculated at the 4-31G/STO-3G level.

The last example to discuss is the less satisfactory case of 3(5)-methylpyrazole **3**. From the gas-phase $\Delta G°$ values of Table I the *N*-methyl derivatives **5** and **7**, with the hypothesis of a constant N-methylation effect, indicate that the 3-methyl tautomer **3a** should be 0.9 kcal mol^{-1} more stable than 5-methyl tautomer **3b**. However, this would correspond to an N-methylation effect of 5.3 kcal mol^{-1}, which appears to be unreasonably large. In water, from the pK_a values of compounds **3**, **5**, and **7**,[36] it appears that the 3-methyl tautomer is slightly more stable than the 5-methyl one (ΔG_t = 0.09 kcal mol^{-1}) with an N-methylation effect of −0.64 kcal mol^{-1}. It is our opinion that the value of the gas-phase basicity difference obtained for compound **5** and **7** is too large. In Table I, using the result for 2-methoxypyridine with both **5** and **7**, the difference in basicity is only 0.4 kcal mol^{-1}.

A Basicity Scale Based on Azaheteroaromatic Five-Membered Compounds. There are two publications dealing with the effect of multiple alkyl substitution upon the basicity of heteroaromatic compounds. One of them concerns pyridines[20b] and covers only mono- and dimethyl derivatives (see Table IV and Lias' review[21]). According to the available information, this six-membered ring shows a saturation effect, i.e., the values obtained with an additive model are larger than the experimental ones. The second one concerns the work of Houriet et al.[39] on methylfurans. In this case, the study included even the tetramethyl derivative, and although the authors conclude that methyl effects are additive, the fact that furans protonate on different carbon atoms and not on the oxygen makes their conclusion uncertain.

Azoles, on the other hand, maintain the protonation center along a series of derivatives, and as can be observed in Figure 5, they show a good correlation between experimental data and theoretical results for six pyrazoles and six imidazoles without tautomeric problems:

$$\delta PA = 0.58\ (\pm 0.46) + 0.76\ (\pm 0.03)\delta\Delta E_p\ \text{4-31G//STO-3G} \quad n = 12,\ r^2 = 0.985 \tag{12}$$

From a theoretical point of view, the most important fact is that our results at both levels of accuracy (STO-3G//STO-3G and 4-31G//STO-3G) show that the effects of methyl groups upon basicity are almost additive, confirming previous findings at the STO-3G//INDO level.[4e] This conclusion can be supported experimentally by using the data of Tables I and VI. Thus: 1,3,4,5-Tetramethylpyrazole (**14**) − pyrazole (**1**) = 26.0 − 9.1 = 16.5 kcal mol^{-1}; 1-methyl + 3-methyl + 4-methyl + 5-methyl. Table I: (13.2 − 9.1) + 2(12.4 − 9.1) + (12.1 − 9.1) + (12.1 − 9.1) = 13.7, using monomethyl derivatives and a 50:50 mixture

(39) Houriet, R.; Rolli, E.; Bouchoux, G.; Hoppilliard, Y. *Helv. Chim. Acta* **1985**, *68*, 2037.

Table VII. Gas-Phase Basicities for Azoles and Methylazoles Relative to Ammonia

compound	$\Delta G(g)^a$
oxazole	4.8[b]
1*H*-1,2,3-triazole	6.1 ± 0.2[c]
benzoxazole	8.4[d]
pyrazole (**1**)	9.1 ± 0.2[c]
thiazole	10.3 ± 0.1
1*H*-indazole	11.0 ± 0.2[c]
4-methylpyrazole (**4**)	12.1 ± 0.1
3(5)-methylpyrazole **3**	12.4 ± 0.1
1-methylpyrazole (**2**)	13.2 ± 0.2
pyrazolo[1,5-*a*]pyridine	15.0 ± 0.2[d]
1-methylindazole	15.6 ± 0.1[c]
1,4-dimethylpyrazole (**4**)	17.1 ± 0.1
3(5),4-dimethylpyrazole **8**	17.4 ± 0.1
1,3-dimethylpyrazole (**5**)	17.5 ± 0.1
3,5-dimethylpyrazole (**9**)	18.3 ± 0.1
1,5-dimethylpyrazole (**7**)	18.4 ± 0.2
imidazole (**15**)	20.0 ± 0.1[c]
2-methylindazole	20.3 ± 0.1[c]
3,4,5-trimethylpyrazole (**13**)	20.8 ± 0.3
1,3,4-trimethylpyrazole (**10**)	21.4 ± 0.2
1,4,5-trimethylpyrazole (**12**)	21.4 ± 0.1
1,3,5-trimethylpyrazole (**11**)	22.1 ± 0.1
4(5)-methylimidazole **18**	23.0 ± 0.1
imidazo[1,5-*a*]pyridine	23.4 ± 0.1
1-methylimidazole (**16**)	23.8 ± 0.1
2-methylimidazole (**17**)	24.3 ± 0.2
1-methylbenzimidazole	25.6 ± 0.1[c]
1,3,4,5-tetramethylpyrazole (**14**)	26.0 ± 0.3
imidazo[1,2-*a*]pyridine	26.8 ± 0.1[d]
1,4-dimethylimidazole (**20**)	27.8 ± 0.1
1,5-dimethylimidazole (**21**)	28.0 ± 0.1
1,2-dimethylimidazole (**19**)	29.4 ± 0.1
2,4,5-trimethylimidazole (**22**)	29.7 ± 0.1
7-methylpyrrolo[2,3-*b*]pyridine	32.4 ± 0.2[d]
1,2,4,5-tetramethylimidazole (**23**)	34.4 ± 0.1

[a] ΔG^0 (kcal mol^{-1}) for the gas-phase reactions $BH^+ + NH_3 \rightleftharpoons B + NH_4^+$; $\Delta G^\circ_{(NH_3)}$ = 195.6 kcal mol^{-1}. [b] Reference 7. [c] Reference 6. [d] Reference 15.

for 3(5)-methylpyrazole. Table I: (13.2 − 9.1) + (17.5 − 13.2) + (12.1 − 9.1) + (18.4 − 13.2) = 16.6, using dimethyl derivatives. Table VI: 4.1 + 4.2 + 3.4 + 4.7 = 16.4 kcal/mol^{-1}.

1,2,4,5-Tetramethylimidazole (**23**) − imidazole (**15**) = 34.4 − 19.9 = 14.5 kcal mol^{-1}; 1-methyl + 2-methyl + 4-methyl +5-methyl. Table I: (23.8 − 19.9) + (24.3 − 19.9) + 2(23.0 − 19.9) = 14.5, using monoethyl derivatives and a 50:50 mixture for 4(5)-methylimidazole. Table I: (23.8 − 19.9) + (29.4 − 23.8) + (27.8 − 23.8) + (28.0 − 23.8) = 17.7 kcal mol^{-1}, using dimethyl derivatives.

Thus, azoles provide a suitable means to establish intrinsic basicities well beyond the present limit, since they are monocentric bases that apparently do not present saturation problems. In Table VII we show gas-phase basicities for unsubstituted or methyl-substituted azoles. The scale smoothly increases, reaching the level obtained with 1,2,5-tetramethylimidazole (**23**), which is only 4.9 kcal mol^{-1} below the value for proton sponge,[21] 1,8-bis(dimethylamino)naphthalene.

The results obtained in this work point out the likely possibility of stepwise increases in the basicity of azoles carrying well beyond that of the present high for 1,2,4,5-tetramethylimidazole. The fact that polyalkyl substitution has not been previously used to increase the intrinsic basicity of heteroaromatic compounds may be due to the fact that alkyl substituents lose their base-strengthening properties in aqueous solution (solvent attenuation effect), and as a consequence, their usefulness in expanding the basicity scale has escaped notice.

Acknowledgment. We thank the 'Comitê Conjunto Hispano-Norteamericano para la Cooperación Científica y Técnica' for successive grants (CCB 84/02/045 and 86/04/009). All calculations have been performed at the UAB/IBM and CC/UAM centers.

Registry No. **1**, 288-13-1; **1** H^+, 17009-91-5; **2**, 930-36-9; **2** H^+, 30967-43-2; **3**, 1453-58-3; **3** H^+, 30967-44-3; **4**, 7554-65-6; **4** H^+, 30967-45-4; **5**, 694-48-4; **5** H^+, 52287-85-1; **6**, 1072-68-0; **6** H^+, 58333-01-0; **7**, 694-31-5; **7** H^+, 52287-86-2; **8**, 2820-37-3; **9**, 67-51-6; **10**, 15802-99-0; **11**, 1072-91-9; **12**, 15802-97-8; **13**, 5519-42-6; **14**, 1073-20-7; **15**, 288-32-4; **15** H^+, 17009-90-4; **16**, 616-47-7; **16** H^+, 17009-89-1; **17**, 693-98-1; **17** H^+, 114550-92-4; **18**, 822-36-6; **18** H^+, 24378-15-2; **19**, 1739-84-0; **19** H^+, 123431-00-5; **20**, 6338-45-0; **20** H^+, 124512-02-3; **21**, 10447-93-5; **21** H^+, 124512-03-4; **22**, 822-90-2; **23**, 1739-83-9; **24**, 110-86-1; **24** H^+, 16969-45-2; **25**, 109-06-8; **25** H^+, 16969-46-3; **26**, 108-99-6; **26** H^+, 17203-41-7; **27**, 108-89-4; **27** H^+, 16950-21-3; **28**, 109-97-7; **29**, 96-54-8; **30**, 636-41-9; **31**, 616-43-3; C_6H_6, 71-43-2; MePh, 108-88-3; thiazole, 288-47-1; imidazo[1,5-*a*]pyridine, 274-47-5.

Supplementary Material Available: Tables A–D of optimized geometrical parameters for pyridines (**24–27**), pyrroles (**28–31**), imidazoles (**15–21**), and pyrazoles (**1–7**) obtained at the STO-3G computational level (4 pages). Ordering information is given on any current masthead page.