Basicity of Azoles. 6. Calculated Intrinsic Basicities for Methyl-Substituted Pyrazoles and Imidazoles. Comparison to Aqueous Solution Data: N-Methylation Effect

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We have done ab initio calculations, using an STO-3G minimal basis set, for all possible methyl derivatives of pyrazoles and imidazoles in order to predict theoretically their gas-phase basicities, since there is an almost complete lack of experimental information regarding these magnitudes. A comparative study between these predicted gas-phase basicities and those measured in aqueous solution has also been carried out. The calculated proton affinities are analyzed by means of different linear correlations involving N_{1s} orbital energies, HOMO energies, and the energy of the nitrogen lone pair orbital. In general, the correlations obtained show that α-substitution and β-substitution effects are quantitatively distinct. Similar conclusions were reached for methyl-substituted pyridines when employing experimental proton affinities and N_{1s} ionization energies. A considerable attenuation of the basicity in aqueous solution with respect to that predicted for the gas phase is found for both pyrazoles and imidazoles. This attenuation effect is much greater than that observed for other nitrogen-containing cyclic bases as pyridines. Although, in solution, the basicity of N-methylated compounds is always smaller than that of the corresponding non-N-methylated parent compound, in the gas phase, methylation always causes an increase of the intrinsic basicity. Moreover, the attenuation of the solution basicity upon N-methylation varies inversely with the intrinsic basicity, reflecting a parallel weakening of the hydrogen bonds between the protonated molecule and the solvent.

Introduction

In the last few years we have devoted some effort to investigating,[1] from a theoretical point of view, those factors which affect the gas-phase basicity of organic compounds, including carbon, nitrogen, and oxygen bases.

Quite frequently, the corresponding experimental gas-phase proton affinities were readily available[2,3] and useful correlations between them and some theoretical magnitudes such as 1s orbital energies,[1a,b,e,4] lone pair orbital energies,[1b,e,5] calculated protonation energies,[1k,1,6] electrostatic molecular potentials,[1a,c,7,8] charge densities,[1d,f,9,10] etc., could be established. These correlations were then employed to predict relative proton affinities in those cases where experimental measurements were not possible or had not yet been carried out.[1a] As a consequence, the assignment of the preferred protonation site, difficult from an experimental point of view, was possible not only in those cases, but in general.

The analysis of these correlations often led to a better understanding, at the molecular level, of those phenomena involved in the protonation process: resonance stabilization,[1d] intramolecular charge migrations,[1f,j] valence-shell orbital interactions,[1g] etc. In particular, methylindoles[1d] and 7-methyl-7-azaindole and its tautomer 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine[1j] are illustrative examples.

In this paper we shall obtain, within an ab initio SCF scheme, similar correlations for methylpyrazoles and methylimidazoles. Regarding these kinds of compounds, some theoretical papers,[7,11-13] mainly devoted to explaining the considerable gap observed between the basicity in solution of the two parent compounds, have been published. Recently (part 2 of this series),[1h] we carried out a preliminary study, at the semiempirical level, of the basicity of some methylpyrazoles and methylimidazoles. Some of the conclusions reached there suggest the necessity of performing a more exhaustive study of this problem. Even though the information on the basicity of these compounds in aqueous solution is abundant,[14-18] there is, surprisingly, an almost complete lack of experimental information regarding their gas-phase basicities. To our knowledge, only the proton affinities of imidazole[2] and *N*-methylimidazole[19] have been reported. The lack of experimental gas-phase proton affinities prevents either obtaining the kind of correlations indicated above or application of those which

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hold for analogous compounds. Hence, to have a reliable systematization of our theoretical results, which cannot be tested against experimental evidence for the gas phase, we have included in the present study all possible methylpyrazole and methylimidazole derivatives (amounting to 32 different compounds).

On the other hand, a comparative study between the predicted gas-phase basicities and those observed in aqueous solution would be feasable, since all compounds are monocyclic aromatic systems which do not present the problems which arise when comparing pK_a and PA values of monocyclic and bicyclic systems.[20] The substituents do not present special conformational problems (as, for example, methoxy[21] or acyl groups).[22] They are usually classified as "chemically inert" in hydroxylic solvents,[23] and the dipole moment is almost constant[1h] within each family (around 2.3 D for pyrazoles and 3.8 D for imidazoles).

The systematic attenuation of the basicity in aqueous solution with respect to that in the gas phase and the specific effect of the *N*-Me substitution on it, will be discussed.

Simultaneously, a parallel study of the basicity of methylpyridines, whose gas-phase PA's have been reported in the literature[24,25] will be carried out in order to extend our conclusions on methylpyrazoles and methylimidazoles.

Computations

We have carried out ab initio calculations using a STO-3G minimal basis set for all possible methylpyrazole and methylimidazole derivatives and all mono- and disubstituted methylpyridines.

The corresponding protonation energies were obtained as the energy difference between the protonated and the nonprotonated forms. As we have indicated elsewhere,[1g,k] the use of optimized structures for this kind of study can be almost crucial. Unfortunately, a geometry optimization at the ab initio level of the 42 compounds included in this study is far beyond our computational capacity. Consequently, we have adopted, for our STO-3G calculations, fully optimized INDO geometries, where the N–H and C–H bond lengths have been adequately scaled, as discussed elsewhere.[1d] An indication of the goodness of the geometries adopted here is the agreement between our calculated structures and those obtained by microwave spectroscopy for the parent compounds, pyrazole[26] and imidazole.[27]

Another problem is the evaluation of the corresponding charge distributions. It is well-established that the most widely used technique in quantum chemistry, the Mulliken population analysis, fails to adequately reproduce[28] the effect of alkyl substituents on the corresponding charge distribution. Moreover, very recently, Stutchbury et al.[29] have shown, using the zero-flux surface criterion of Bader,[30]

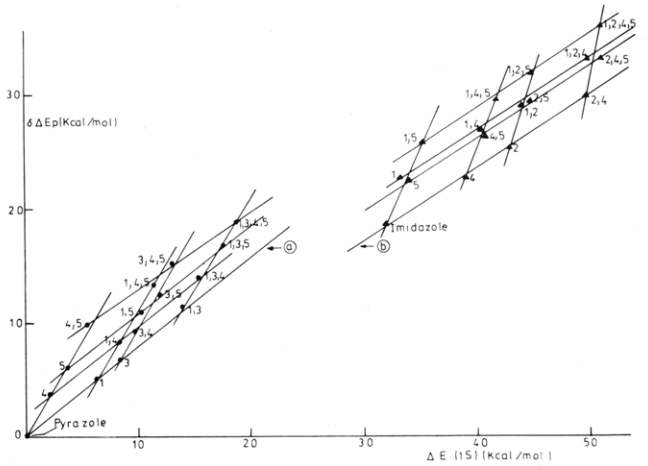

Figure 1. Protonation energies for methylpyrazoles and methylimidazoles vs. the corresponding N_{1s} orbial energies. All values relative to pyrazole: (●) methylpyrazoles; (▲) methylimidazoles.

that the replacement of a hydrogen atom by a methyl group in a charged molecule is accompanied by a charge dispersal over the methyl hydrogens which is not reproduced by the Mulliken population analysis. Therefore, we shall use a different partitioning technique of the total molecular electronic density, the so-called YSP population analysis.[31] This procedure has the advantage of being practically insensitive[31] to the quality of the basis set used to expand the corresponding wave function and reproduces adequately the delocalization of charge over the hydrogen atoms in cations.[32] In all cases, the standard density basis sets defined in ref. 31 were used.

Results and Discussion

We present in Table I the calculated protonation energies for methylpyrazoles and methylimidazoles. It can be noticed that imidazoles are systematically predicted to be stronger bases than pyrazoles, in the gas phase. This is in agreement with the experimental finding of Flammang et al.[33] for the parent compounds. Further, the Me substituent effects on the basicity are almost additive for each family. Actually, there is a reasonably good agreement between the calculated protonation energies and those predicted assuming constant increments of 5.1, 6.6, 3.7, and 6.0 kcal/mol for *N*-, 3-, 4-, and 5-methyl substitution of pyrazoles and of 4.0, 6.7, 4.1, and 3.9 kcal/mol for *N*-, 2-, 4-, and 5-methyl substitution of imidazoles, respectively. The quality of this additive model slightly decreases as the number of methyl substituents increases. It must be indicated that the only experimental gas-phase PA's available [those of imidazole (222.7 kcal/mol[2] and 223.3 kcal/mol[34]) and its N-methyl derivative (228.2 kcal/mol[19])] show an increase in the basicity of about 5 kcal/mol upon N-methylation. Our theoretical results predict an increase of 4.0 kcal/mol, in reasonably good agreement with that experimental finding.

We have previously shown[1a,b] that there exist good linear correlations between the experimental gas-phase proton

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Table I. Calculated Magnitudes for Methylpyrazoles and Methylimidazoles[a]

Me–pyrazoles						
substituent	ΔE_p	ΔE(1s)	ΔE(HOMO)	$\Delta\epsilon_n$	Δq_{N2}	$\Delta\alpha$
H	0.0	0.0	0.0	0.0	0	0.0
1-Me	5.1	6.3	3.4	5.2	−33	+1.7
3-Me	6.6	8.4	6.8	7.5	−28	+2.0
4-Me	3.7	2.2	5.5	3.3	−6	−0.4
5-Me	6.0	3.7	9.9	4.3	−1	+0.1
1,3-Me	11.3 (11.7)[b]	14.0	10.9	12.3	−58	+3.6
1,4-Me	8.2 (8.8)	8.4	8.3	8.3	−36	+1.3
1,5-Me	10.8 (11.1)	10.3	13.5	9.3	−41	+1.6
3,4-Me	9.2 (10.3)	9.7	9.8	10.1	−33	+1.6
3,5-Me	12.4 (12.6)	11.9	15.7	11.7	−36	+1.7
4,5-Me	9.8 (9.7)	5.5	16.4	7.1	−12	−0.4
1,3,4-Me	13.9 (15.4)	15.3	13.1	14.8	−61	+3.3
1,3,5-Me	16.7 (17.7)	17.6	18.7	16.3	−64	+3.4
1,4,5-Me	13.2 (14.8)	11.4	18.3	11.7	−41	+1.1
3,4,5-Me	15.0 (16.3)	12.9	19.3	13.9	−37	+0.8
1,3,4,5-Me	18.8 (21.4)	18.6	21.9	18.3	−65	+3.1
Me–Imidazoles						
substituent	ΔE_p	ΔE(1s)	ΔE(HOMO)	$\Delta\epsilon_n$	Δq_{N3}	$\Delta\alpha$
H[c]	0.0	0.0	0.0	0.0	0	0.0
	(18.6)	(31.9)	(7.4)	(15.2)	(−156)	
1-Me[e]	4.0	1.2	1.7	1.5	−7	−0.5
2-Me[e]	6.7	10.8	9.5	9.4	−31	+2.6
4-Me	4.1	7.1	7.0	6.9	−26	+2.1
5-Me	3.9	2.1	9.3	2.2	−3	−0.7
1,2-Me	10.4 (10.7)[d]	12.1	11.0	10.8	−37	+2.3
1,4-Me	8.3 (8.1)	8.3	9.1	8.5	−33	+1.6
1,5-Me[e]	7.3 (7.9)	3.3	11.8	3.4	−6	+1.2
2,4-Me[e]	11.2 (10.8)	17.6	15.5	15.8	−56	+4.4
2,5-Me	10.8 (10.6)	12.8	18.2	11.3	−33	+1.8
4,5-Me	7.8 (8.0)	8.9	15.8	8.6	−29	+1.5
1,2,4-Me	14.5 (14.8)	17.9	20.8	16.8	−59	+4.1
1,2,5-Me	13.3 (14.6)	12.8	20.1	11.7	−33	+1.4
1,4,5-Me	11.0 (12.0)	9.7	18.3	9.7	−32	+1.0
2,4,5-Me	14.6 (14.7)	19.1	23.7	17.4	−57	+3.8
1,2,4,5-Me	17.2 (18.7)	18.9	25.1	17.7	−57	+3.4

[a] Protonation energies (ΔE_p), N1s orbital energies (ΔE(1s)), HOMO energies (ΔE(HOMO)), nitrogen lone pair orbital energies ($\Delta\epsilon_n$) (all values in kcal/mol), and YSP charge densities of the basic center (Δq_{N2} or Δq_{N3} in millielectrons) referred to those of the corresponding parent compounds. For each family of compounds the last column presents the varition ($\Delta\alpha$, in degrees) of the endocyclic bond angle centered on the basic nitrogen (N1N2C3 or C2N3C4) upon methyl substitution. [b] Values in parentheses were predicted assuming constant increments of 5.1, 6.6, 3.7, and 6.0 kcal/mol for 1-, 3-, 4-, and 5-methyl substitution, respectively. [c] Within parentheses we have given those values for imidazole relative to pyrazole. [d] Values in parentheses were predicted assuming constant increments of 4.0, 6.7, 4.1, and 3.9 kcal/mol for 1-, 2-, 4-, and 5-methyl substitutions, respectively. [e] The corresponding 4-31G values are ΔE_p = 4.4, ΔE(1s) = 2.6, ΔE(HOMO) = 2.6, and $\Delta\epsilon_n$ = 2.7 for 1-Me. ΔE_p = 4.6, ΔE(1s) = 8.8, ΔE(HOMO) = 9.7, and $\Delta\epsilon_n$ = 8.7 for 2-Me. ΔE_p = 8.8, ΔE(1s) = 4.4, ΔE(HOMO) = 13.1, and $\Delta\epsilon_n$ = 5.1 for 1,5-Me. ΔE_p = 7.1, ΔE(1s) = 14.2, ΔE(HOMO) = 16.5, and $\Delta\epsilon_n$ = 14.3, for 2,4-Me.

affinity and the 1s orbital energy of the corresponding basic center within a given family of compounds. In the present case, due to the lack of experimental information on the gas-phase proton affinities of methylpyrazoles and methylimidazoles, we shall limit ourselves to the analysis of the relationship shown in Figure 1 between the corresponding calculated magnitudes: protonation energies (ΔE_p) and N1s orbital energies (ΔE(1s)) (See Table I).

Several facts should be singled out for comment: (a) The correlations obtained for pyrazoles and imidazoles are different, i.e., according to these indices, pyrazoles and imidazoles are not homologous bases. (b) Within each family of compounds there are two different kinds of linear correlations, ones with slope close to unity and others with a greater slope. (c) It can also be noticed that the first ones correspond to an α-effect, while the second ones represent a β-effect. That is, the correlations with smaller slope give the variation of the protonation energy (relative to the compound of smaller basicity) produced when one or two substituents are introduced at the α-positions relative to the basic center. For instance, in both pyrazoles and imidazoles, the lower line involves the parent compound, the α-monosubstituted derivatives, and the α,α'-dimethyl derivative. The second and the third line correspond to a β-monomethyl derivative and the corresponding dimethyl- and trimethyl-substituted compound obtained by introducing at the α-positions of the former, one or two methyl groups, respectively. Finally, the upper line involves the β,β'-dimethyl compound and those trimethyl and tetramethyl derivatives obtained by Me substitution at one or the two α-positions of the former.

The straight lines of higher slope, on the contrary, give the variation in the protonation energy (relative to the compound of smaller basicity) when introducing one or two methyl substituents on β-positions. For example, the first line of this group involves the parent compound (pyrazole or imidazole) and the mono- and di-β-substituted derivatives. The different slopes of these correlations imply that compounds with analogous basicity present a greater variation of their N1s orbital energies upon α-substitution than upon β-substitution. The explanation of this behavior will be given later.

One may wonder, however, whether the conclusions indicated above might be an artifact of our calculations; in other words, one may wonder whether similar effects would be observed when dealing with experimental proton affinities and 1s binding energies.

To clarify this matter we have carried out similar calculations on mono- and dimethylpyridines, whose gas-phase PA's are known.[24,25] Our calculated ΔEp's, relative

Table II. Calculated ($\delta\Delta E_p$) and Experimental (ΔPA_{exp}) Protonation Energies for Mono- and Disubstituted Methylpyridines. ΔE(1s) Symbolizes the Calculated N_{1s} Orbital Energies. All Values in kcal/mol Relative to the Parent Compound

substituent	$\delta\Delta E_p$	ΔPA_{exp}[a]	ΔE(1s)
H	0	0	0 (0)[d]
2-Me	5.4	3.7 (3.7)[b] [4.1][c]	8.9 (7.2)[d]
3-Me	2.6	2.8 (2.8)[b]	2.6 (4.4)[d]
4-Me	4.1	3.7 (4.3)[b]	3.5 (6.0)[d]
2,3-Me	8.3	6.6	10.9
2,4-Me	9.5	7.4	12.0
2,5-Me	8.3	6.6	11.2
2,6-Me	10.9	7.6 [7.8][c]	17.1 (13.7)[e]
3,4-Me	6.6	6.6	5.2 (8.86)[e]
3,5-Me	5.5	5.4	4.4 (7.5)[e]

[a] Values taken from ref 24, corrected according to the criterion of Bromilow; see ref 25. [b] Values taken from ref 25. For 4-methylpyridine we use the average value obtained from those given in Table I. [c] Values taken from ref 35. [d] Experimental N_{1s} binding energies, relative to pyridine, taken from ref 37. [e] N_{1s} binding energies estimated from the corresponding N_{1s} orbital energies.

to the parent compound, together with the experimental ones, and the corresponding N1s orbital energies, are presented in Table II.

In agreement with our findings for pyrazoles and imidazoles, the substituent effects are practically additive. Moreover, when the calculated protonation energies (ΔEp) are plotted against the calculated N1s orbital energies (See Figure 2, Part a) a similar behavior to that discussed for pyrazoles and imidazoles is found. For the sake of clarity, exclusively ortho-substituted and nonortho-substituted compounds were included in that figure. Both sets of compounds follow different linear correlations, being the slope smaller for ortho-substituted compounds.

It can also be observed, from Table II, that there exists a good agreement between our calculated ΔEp's and the experimental ones. Actually, for those derivatives with meta and/or para substituents, the relationship between both magnitudes obeys a linear equation[36] of slope very close to 1. When the substituent is ortho the calculated proton affinity slightly overestimates the experimental one.

Unfortunately, the corresponding N1s binding energies are only known for the parent compound and the monosubstituted derivatives,[37] but to complete our discussion we have estimated (from the corresponding N1s orbital energies) those of 2,6-, 3,4-, and 3,5-dimethyl derivatives. In Figure 2 Part b, we have represented the experimental PA's vs. the corresponding N1s binding energies for the same compounds included in Figure 2 Part a. A similar behavior to the one discussed when employing calculated values is observed, though clearly attenuated; i.e., the difference between the corresponding slopes is smaller than that obtained when using calculated values.

We can conclude, therefore, that the α- and β-effects discussed for methylpyrazoles and methylimidazoles are not artifacts of our calculations, though, very likely, they would appear somewhat attenuated if experimental gas-phase PA's and 1s ionization potentials were employed.

We can come back now to the possible explanation of these α- and β-effects.

It is well-known[38,39] that the 1s orbital energy of a given center acts as a probe of the electrostatic potential near the corresponding nucleus. This implies that the 1s orbital

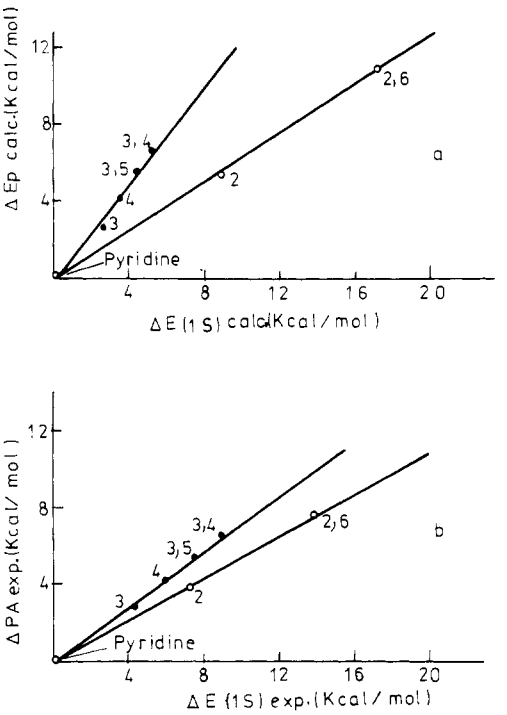

Figure 2. Linear correlations between (a) calculated protonation energies and N_{1s} orbital energies and (b) experimental proton affinities and N_{1s} binding energies for some methyl-substituted pyridines. See text for details. Values relative to pyridine.

energy depends primarily on the total electron population at the host atom. The YSP charge distribution obtained for the compounds under study (see Table I) reveals that β-substitution induces a very small variation on the charge density located at the basic center, while this variation is significant when the substituent is introduced at α. Moreover, similar to what has been observed regarding the charge distribution of amino-substituted pyridines and pyrimidines,[40] the charge density of the basic center also reflects additivity of the substituent effects. Hence, a greater variation of the N1s orbital energy for α-substitution than for β-substitution should be expected.

Besides, N1s orbital energies are also affected by variations in the local bonding at the host atom.[41] These variations are almost negligible for β-substitution but significant upon α-substitution, as revealed by the opening of the endocyclic angle centered on the basic nitrogen (see Table I). This endocyclic angle varies very little upon β-substitution, while single α-substitution causes openings of about 2° or more and α,α'-disubstitution of about 4.5 degrees, in both, pyrazoles and imidazoles.

These changes can be related, using simple valence shell electron pair repulsion arguments[1g,42] to variations in the hybridization at the basic center. The opening of this endocyclic angle implies an increase in the p character of the corresponding N σ-lone pair orbital, which, as a consequence, becomes less tightly bound and so the N1s orbital.

Both factors (charge density variations and hybridization changes) yield a greater variation of the 1s orbital energy upon α-substitution than upon β-substitution, reflected

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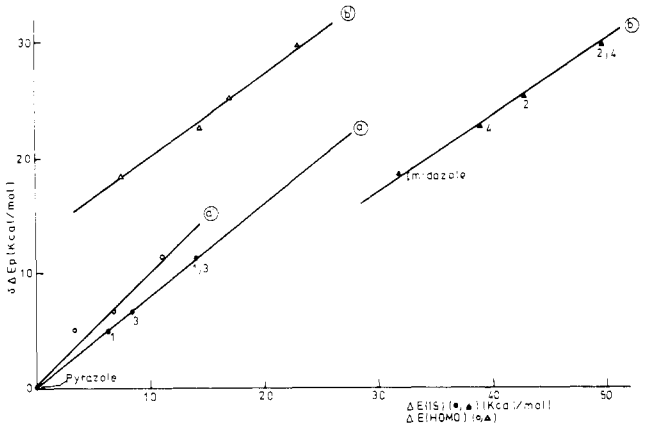

Figure 3. Lines a′ and b′ correspond to the linear correlations between protonation energies and HOMO energies for those compounds included in lines a and b of Figure 1. To facilitate the discussion, lines a and b have been repeated here.

in the slopes of the corresponding ΔEp vs. ΔE(1s) linear correlations.

We have shown above that methylpyrazoles and methylimidazoles follow different protonation energy (ΔEp) vs. 1s orbital energy (ΔE(1s)) correlations. Let us consider, for instance, lines a and b in Figure 1. It can be seen that the correlation ΔEp vs. ΔE(1s) for α-substituted imidazoles (line b) is shifted about 6 kcal/mol (in the protonation energies scale) with respect to that corresponding to α-substituted pyrazoles (line a). Accordingly, imidazoles present a ΔEp *smaller* than what should be expected from their 1s orbital energies, if the relationship obtained for pyrazoles were valid for imidazoles.

This result is not surprising, since it has been shown[1a,b] that, in general, this kind of correlation holds only for homologous series of compounds.

We have previously shown[1e] that multivariant linear correlations: experimental gas-phase PA's vs. 1s binding energies and the first ionization potentials of the molecules exist for carbon, nitrogen, and oxygen bases. We have also proved[1e] that similar correlations can be obtained by using orbital energies, calculated by using a STO-3G basis instead of experimental ionization energies. Hence, in the discussion which follows we shall employ N1s orbital and HOMO energies (see Table I) instead of 1s binding energies and first ionization potentials, respectively.

For the sake of simplicity we shall discuss exclusively those compounds belonging to lines a and b of Figure 1, i.e., α-substituted pyrazoles and imidazoles. In Figure 3 lines a and b of Figure 1 are repeated and, for the same compounds, the protonation energy (ΔEp) vs. the energy of the HOMO [ΔE(HOMO)] (all values relative to pyrazole) is also plotted. The behavior of the correlations found is opposite to that observed for the ΔEp vs. ΔE(1s) correlations: Imidazoles (line b′) present a basicity *greater* than what should be expected from their HOMO energies, if the correlation obtained for pyrazoles were valid for imidazoles. It is then reasonable to expect the multivariant correlations ΔEp vs. ΔE(1s) and ΔE(HOMO), to be unique for both families. Such a correlation, obtained by a least-squares tecnique, obeys the equation:

$$\Delta E\text{p} = -193.29\Delta E(1\text{s}) - 166.04\Delta E(\text{HOMO}) + 4816.73 \quad (1)$$

$$\sigma = 0.4 \text{ kcal/mol}$$

Equally good multivariate correlations are obtained for the other three groups of compounds included in Figure 1.

An alternative analysis of substituent effects in methyl-substituted pyrazoles and imidazoles can be performed

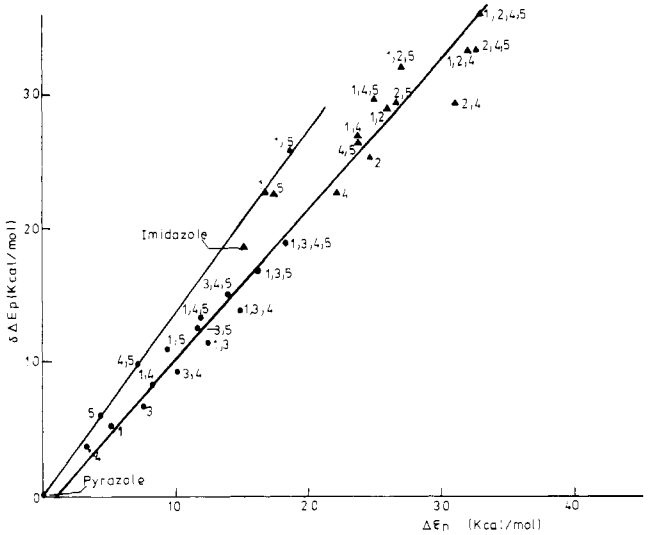

Figure 4. Protonation energies vs. the energy of the nitrogen lone pair for methylpyrazoles (●) and methylimidazoles (▲). All vallues relative to pyrazole.

by means of the corresponding ionization potentials of the nitrogen lone pair[4,43] or, alternatively, the energy of the nitrogen lone pair orbital.[1b,5,44] Similarly, linear relationships between pK_a values measured in aqueous solution for N-containing heterocycles and vertical lone pair ionization potentials have also been reported.[45,46]

Since one of our goals is to analyze the solution basicity of the compounds under consideration, the analysis of the behavior of the nitrogen lone pair orbital energies seems quite important.

The corresponding calculated STO-3G values have been summarized in Table I. Figure 4 presents calculated protonation energies (ΔEp) vs. lone pair orbital energies ($\Delta\epsilon$n), all relative to pyrazole.

Some facts deserve detailed discussion: (a) Within each family of compounds (pyrazoles and imidazoles) a behavior similar to that discussed for 1s orbital energies, although somewhat attenuated, is observed. (b) There is, however, a noticeable difference with respect to the correlations discussed in previous sections, in the sense that there is not a significnat gap between the variations observed in the protonation energies and those observed in the lone pair orbital energies. This causes imidazoles and pyrazoles to follow roughly the same correlation.[1i] (c) A closer analysis of this rough correlation reveals the existence of two distinct relationships, which have been indicated in the figure. The line with a higher slope includes those pyrazoles and imidazoles which do not present any substituent at the α-position, while that with a smaller slope comprises α-monosubstituted and α,α'-disubstituted derivatives.

According to the arguments of Aue et al.,[24] the proton affinity and the nitrogen lone pair ionization potential of a given base are related to each other by the equation

$$\text{PA(B)} = \text{HA(B}^+\text{)} - \text{IP(B)} + \text{IP(H)}$$

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Table III. Experimental and Predicted pK_a Values for Methylpyrazoles and Methylimidazoles. All Values Relative to the Corresponding Parent Compounds

Me–pyrazoles			Me–imidazoles		
substituent	δpK_a (expt)[b]	δpK_a (calcd)[a]	substituent	δpK_a (expt)	δpK_a (calcd)[a]
H	0 (0)[c]	0	H	0[d,e] (0)[c]	0
1-Me	−0.43 (−1.0)	−0.53	1-Me	0.13 (−0.2)	0.17
3-Me	0.80 (1.1)	0.91	2-Me	0.85[d,e] (1.2)	0.87
5-Me		0.82	4-Me	0.56[d,e] (0.8)	0.53
4-Me	0.57 (0.8)	0.51	5-Me		0.51
1,3-Me	0.30 (0.0)	0.45	1,2-Me	1.00[d] (1.0)	1.04
1,4-Me	−0.04 (−0.1)	−0.04	1,4-Me	0.20[d,g] (−0.1)	0.76[g]
1,5-Me	0.37 (0.1)	0.37	1,5-Me	0.70[d] (0.5)	0.62
3,4-Me	1.39 (1.9)	1.26	2,4-Me	1.41[e] (1.9)	1.46
4,5-Me		1.35	2,5-Me		1.41
3,5-Me	1.60 (2.2)	1.70	4,5-Me		1.02
1,3,4-Me		0.86	1,2,4-Me		1.61
1,3,5-Me	1.28 (1.3)	1.31	1,2,5-Me		1.44
1,4,5-Me		0.75	1,4,5-Me		1.13
3,4,5-Me	2.11 (2.9)	2.06	2,4,5-Me	1.96[f] (2.7)	1.90
1,3,4,5-Me	1.75 (2.0)	1.64	1,2,4,5-Me		1.98

[a] Predicted from eq 3–6. [b] Values from ref 14. [c] $\delta\Delta G$(aq) obtained from the corresponding pK_a (expt) values. See text for details. [d] Values from ref 18. [e] Values from ref 15. [f] Values from ref 16. [g] See text.

Therefore, variations in proton affinities would be identical with those in ionization potentials if and only if the hydrogen affinity (HA) (defined as the homolytic bond dissociation energy of the —(=)N$^+$H bond, in the protonated form) is constant.[47]

One can reasonably assume that such a term must be roughly constant when considering methylpyrazoles and methylimidazoles (explaining point b). However, it must be taken into account that HA's are especially sensitive[24,27] to changes in hybridization and geometry at the basic center. This would explain point c. As indicated at the beginning of this section, the endocyclic angle centered on the basic nitrogen of pyrazoles and imidazoles varies upon α-substitution, while it remains practically constant upon β-substitution. One can then conclude that derivatives without substituents at α and α-substituted derivatives must follow different ΔEp vs $\Delta\epsilon$n correlations.

Finally, it must be emphasized that our previous discussion qualifies, in some manner, the implicit assumption, generally accepted,[1h,46] that there is a unique correlation between protonation energies and lone pair ionization potentials within an homologous series of compounds. Our results clearly show that, depending on the position of the substituent and the degree of substitution, the correlations found are slightly different.

Similar analyses regarding the charge density of the basic center and the minima of the electrostatic molecular potentials lead to the same conclusions and have not been included here but can be obtained from any of us.

To check whether our conclusions are basis set independent we have carried out calculations, at the 4-31G level for imidazole, 1-methyl-, 2-methyl-, 1,5-dimethyl-, and 2,4-dimethylimidazole and their corresponding protonated forms, using the same geometries as before. The new relative values (see Table I) for ΔE(HOMO) and $\Delta\epsilon$n are not significantly different from those obtained at the STO-3G level and only for α-substituted compounds do ΔEp and ΔE(1s) become clearly smaller when enlarging the basis set. It can be easily seen, however, that although these differences imply some quantitative changes with regard to the STO-3G results, they do not affect our conclusions.

To compare substituent effects on the basicity of a given family of compounds in the gas phase and in aqueous solution one may plot the variations of the free energy of the protonation process in the gas-phase $\delta\Delta G$ (g) vs. the corresponding quantity in aqueous solution, $\delta\Delta G$(aq). The latter can be calculated from the corresponding pK_a values of the two bases in solution. In our case, since we shall try to compare *N*-methyl- and non-*N*-methyl-substituted compounds, the pK_a values of the non-*N*-methyl-substituted ones must be incremented by 0.3 pK_a units. The former, $\delta\Delta G$(g), will be substituted by the corresponding theoretically calculated protonation energies ($\delta\Delta E$p). These plots for methylpyrazoles and methylimidazoles are given in Figure 5 Part a and b, respectively.

For both families, good linear correlations $\delta\Delta E$p vs. $\delta\Delta G$(aq) are found, though 1,4-dimethylimidazole clearly deviates. In all cases, the slopes of these linear relationships, which obey the equations

$$\delta\Delta E\text{p} = 4.56\delta\Delta G(\text{aq}) + 10.35 \quad (r^2 = 0.987,\ n = 6) \quad (3)$$

$$\delta\Delta E\text{p} = 5.33\delta\Delta G(\text{aq}) + 0.00 \quad (r^2 = 0.991,\ n = 6) \quad (4)$$

for *N*-methyl-substituted and non-*N*-methyl-substituted pyrazoles, respectively, and

$$\delta dE\text{p} = 5.23\delta\Delta G(\text{aq}) + 5.00 \quad (r^2 = 0.975,\ n = 3) \quad (5)$$

$$\delta dE\text{p} = 5.59\delta\Delta G(\text{aq}) + 0.05 \quad (r^2 = 0.996,\ n = 5) \quad (6)$$

for N-methylated and non-N-methylated imidazoles, respectively, are considerably greater than unity, showing a large attenuation of the substituent effect in aqueous solution, which is practically the same for pyrazoles and imidazoles but almost twice that observed for other nitrogen-containing cyclic bases, as pyridines.[25] Equations 3–6 allowed us to predict the pK_a values for those methyl derivatives, whose aqueous basicity has not been measured. Those predicted values have been listed in Table III.

It seems well-established that this partial cancellation of substituent effects in solution is mainly due to the difference between the relative solvation enthalpies of the neutral base and the corresponding ion. It seems also clear[2,48] that the major factor is related to the substituent effect on the solvation of the charged species, via hydrogen

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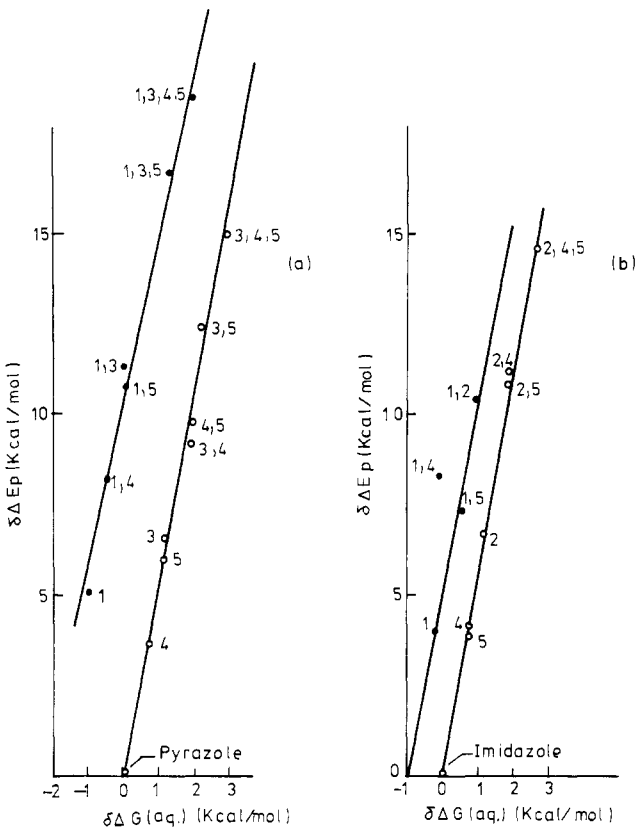

Figure 5. Gas-phase protonation energies vs. aqueous solution protonation energies: (a) methylpyrazoles; (b) methylimidazoles. All values relative to the corresponding unsubstituted parent compounds.

bonds.[49] Correspondingly, only a few water molecules are required to yield the attenuation effect observed in aqueous solution.[49,50] Moreover, this effect varies linearly with the substituent, within homologous series of compounds. It seems then obvious that the relative heats of hydration must depend on the number and kind of protonic sites present in the molecule.

Some other interesting conclusions can be drawn from the correlations seen in Figure 5, Parts a and b.

Within each family of compounds, the *N*-methyl-substituted derivatives follow a correlation different from that which holds for non-N-methylated compounds. In principle, and according to the arguments of the preceding paragraph, this result is not surprising since the former compounds present one fewer protonic site than the latter. This results in a clear contrast between the substituent effects in the gas phase and in solution. In the gas phase, substitution by a methyl group implies an increase in the basicity of about 4.0–5.0 kcal/mol. This increment is more or less the same for N-methyl or C-methyl substitution, almost regardlessly the position which undergoes substitution. However, in aqueous solution and due to the loss of an active center for solvation, the basicity of N-methylated compounds is considerably smaller than that of non-N-methyl-substituted ones.

This effect is usually quantified by comparing the solution bacisity of the *N*-methyl-substituted derivative to that of the parent compound. This leads to an underestimation of the N-methylation effect. As indicated in the previous paragraph, *N*-, 4-, and 5-methylimidazoles present quite similar gas-phase basicities, about 4.0 kcal/mol greater than that of imidazole. In solution, however, *N*-methylimidazole is 0.33 kcal/mol[22] less basic than imidazole but *about 1.0 kcal/mol* (0.7 pK_a units) less basic than those methyl derivatives which present analogous basicity in the gas phase. Therefore, the attenuation of the solution basicity upon *N*-methyl substitution is not actually given by the decrease with respect to the parent compound, but, on the average, by the difference in the $\delta\Delta G$(aq) axis intercepts of the two correlations $\delta\Delta E$p vs. $\delta\Delta G$(aq) (see Figure 5 Part b), which is about 1.0 kcal/mol for imidazoles. Clearly, such a difference is even greater for pyrazoles, [~2.0 kcal/mol (1.40 pK_a units)], while the difference between the solution basicity of pyrazole and *N*-methylpyrazole is only of 1.0 kcal/mol (0.7 pK_a units).

It could also be illustrative to consider this *N*-methyl substitution effect from a different point of view, i.e., by considering the differences in the $\delta\Delta G$(g) axis intercepts. Accordingly, for *N*-methylimidazole to be as basic as imidazole in aqueous solution, the former should have a gas-phase basicity 5 kcal/mol greater than the latter. Similarly, only if *N*-methylpyrazole had a gas-phase basicity 10.3 kcal/mol greater than that of pyrazole would both compounds be equally basic in aqueous solution.

The quantitative difference between N-methylation effect on pyrazoles and imidazoles is easily explained taking into account that in pyrazoles, besides the loss of one active center for solvation, some steric hindrance to solvation of the other protonic center (N2) would also appear.

A closer look to the correlations in Figure 5 Parts a and b reveals that this *N*-methylation effect is not constant. That is, the corresponding straight lines are not parallel, since the slope for N-methylated derivatives is smaller than that for non-N-methylated ones (see eq 3–6). This reveals that the strength of the hydrogen bonds involving the additional active center of non-N-methylated derivatives and the solvent vary inversely with the corresponding basicity. Recently, Meot-Ner[50] showed that the strength of the ionic hydrogen bond $XH^+\cdots Y$ correlates with $\Delta PA = PA(X) - PA(Y)$ and that the ratio of enthalpies of tetramolecular to monomolecular solvation is constant for a wide range of onium ions. In our particular case, Y is always a water molecule, hence PA (Y) = constant and the strength of the corresponding hydrogen bond must correlate with PA(X), in agreement with our findings. Moreover, for strong positive ion hydrogen bonds, Desmueles and Allen[51] have shown that there is a linear correlation between the calculated dimerization energies and the charge lost from the proton. Consequently, according to arguments of the preceding paragraph, there should exist a correlation between what we have called ΔA (the increase in aqueous basicity of non-N-methylated compounds with respect to that predicted if they would behave as N-methylated derivatives) and the charge of the hydrogen atom. These correlations have been represented in Figure 6 and within the precision of our calculations clearly confirm our discussion.

Conclusions

From the results discussed in this paper we can conclude that methyl-substituted imidazoles follow different protonation energy vs. N_{1s} orbital energy correlations. Moreover, within each family of compounds there are two different kinds of linear relationships: those with smaller slope give the relative variation of the gas-phase basicity

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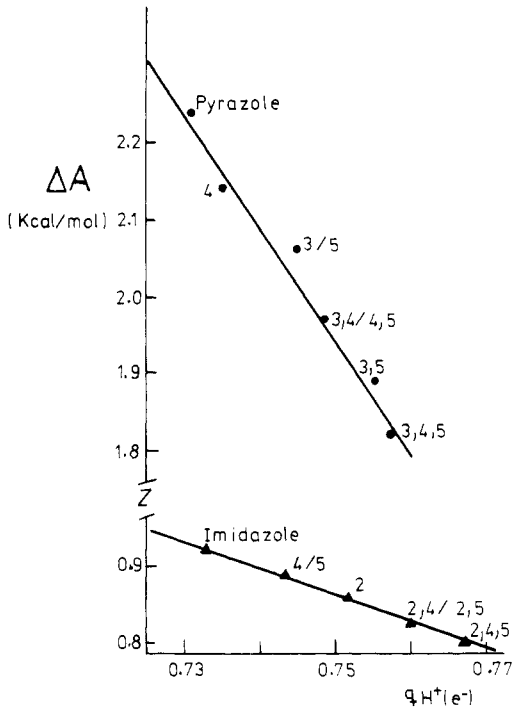

Figure 6. Quantitative attenuation effect on the aqueous solution basicity upon N-methylation (ΔA) vs. the net charge (YSP) on the basic hydrogen.

upon α-substitution, while those with a greater slope give that variation when substitution takes place on a β-position. These findings are not an artifact of our calculations since similar effects are found, though attenuated, when using experimental proton affinities and N_{1s} ionization energies for methyl-substituted pyridines. Accordingly, methylpyrazoles and methylimidazoles can be classified in three different groups with regard to the effect of the substituent on the intrinsic basicity and on the corresponding N_{1s} binding energy: (a) compounds which present α-substitution, exclusively; (b) compounds with, at least, one substituent in a β position; (c) compounds, at least, β,β'-substituted. Within each group, the correlation found for pyrazoles and imidazoles is different. These, so called, α- and β-effects are primarily due to hybridization and charge density changes induced by the substituent on the basic center.

The relative effects of the substituent on the N_{1s} orbital energies with respect to those on the protonation energies are opposite to those obtained for the HOMO energies. Hence, the correlations indicated in the previous paragraph become unique for pyrazoles and imidazoles if the variation of the HOMO energy is taken into account. This confirms that the *multivariant* linear correlations ΔEp vs. ΔE(1s) and ΔE(HOMO) are followed by families of compounds which cannot be considered as homologous when using *single* correlations between protonation energies and ionization energies.

The correlations involving the nitrogen lone pair energies are roughly unique for pyrazoles and imidazoles. Nevertheless, there are two different correlations; that involving α-substituted azoles and that including non-α-substituted ones. This fact reveals that the so-called hydrogen affinity depends, for this kind of compound, on the position which undergoes substitution through the hybridization changes produced on the basic center. Therefore, it is not always possible to establish a unique correlation between protonation energies and lone pair ionization energies, even within an homologous series of compounds.

A considerable attenuation of the basicity in aqueous solution with respect to that predicted for the gas phase is observed in both pyrazoles and imidazoles. This effect is about the same for both families, but considerably greater than that observed in other nitrogen-containing cyclic bases.

There is a clear contrast between the substituent effects on the gas phase and on the aqueous solution basicities. In fact, in the gas phase, methylation *always* causes an increment of the corresponding basicity, almost regardless of the position which undergoes substitution. In aqueous solution, however, this is not true for *N*-methyl-substituted compounds, whose solution basicity is always smaller than the corresponding non-N-methylated parent compound. This attenuation of the solution basicity upon N-methylation, which on the average is about 1.0 kcal/mol (0.7 pK_a units) for imidazoles and 2.0 kcal/mol (1.4 pK_a units) for pyrazoles, is not constant but varies inversely with the intrinsic basicity, reflecting a parallel weakening of the hydrogen bonds between the protonated molecule and the solvent.

Acknowledgment. All calculations have been performed at the UAM/IBM Center, Madrid. We thank Dr. M. Meot-Ner for sending us some results prior to publication.

Registry No. Pyrazole, 288-13-1; 1-methylpyrazole, 930-36-9; 3-methylpyrazole, 1453-58-3; 4-methylpyrazole, 7554-65-6; 5-methylpyrazole, 88054-14-2; 1,3-dimethylpyrazole, 694-48-4; 1,4-dimethylpyrazole, 1072-68-0; 1,5-dimethylpyrazole, 694-31-5; 3,4-dimethylpyrazole, 2820-37-3; 3,5-dimethylpyrazole, 67-51-6; 4,5-dimethylpyrazole, 88054-15-3; 1,3,4-trimethylpyrazole, 15802-99-0; 1,3,5-trimethylpyrazole, 1072-91-9; 1,4,5-trimethylpyrazole, 15802-97-8; 3,4,5-trimethylpyrazole, 5519-42-6; 1,3,4,5-trimethylpyrazole, 1073-20-7; imidazole, 288-32-4; 1-methylimidazole, 616-47-7; 2-methylimidazole, 693-98-1; 4-methylimidazole, 822-36-6; 5-methylimidazole, 822-36-6; 1,2-dimethylimidazole, 1739-84-0; 1,4-dimethylimidazole, 6338-45-0; 1,5-dimethylimidazole, 10447-93-5; 2,4-dimethylimidazole, 930-62-1; 4,5-dimethylimidazole, 2302-39-8; 1,2,4-trimethylimidazole, 1842-63-3; 1,2,5-trimethylimidazole, 1739-81-7; 1,4,5-trimethylimidazole, 20185-22-2; 2,4,5-trimethylimidazole, 822-90-2; 1,2,4,5-tetramethylimidazole, 1739-83-9; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 3-methylpyridine, 108-99-6; 4-methylpyridine, 108-89-4; 2,3-dimethylpyridine, 583-61-9; 2,4-dimethylpyridine, 108-47-4; 2,5-dimethylpyridine, 589-93-5; 2,6-dimethylpyridine, 108-48-5; 3,4-dimethylpyridine, 583-58-4; 3,5-dimethylpyridine, 591-22-0.