Basicity of Azoles. Part 2.† Theoretical Study of the Basicity of Methylpyrazoles and Methylimidazoles

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We present results obtained, using the INDO method, for the intrinsic basicities of 22 diazoles (pyrazoles and imidazoles carrying only methyl substituents). We found a linear relationship between the lone-pair orbital energies and the protonation energies. The presence of methyl groups α to the basic nitrogen atom lowers the aqueous basicity of diazoles by about 1.8 pK_a units. We predict an inversion of the tautomeric equilibria in going from the solution to the gas phase for 3(5)-methylpyrazoles and 4(5)-methylimidazoles.

In the last few years, the intrinsic basicity (gas-phase proton affinity; PA) of many organic molecules has been measured.[1] From the new data one can obtain both a better understanding of substituent effects [2-8] and an estimate of solvent contributions.[7,9-14] The comparison of ΔG° values in the vapour phase and in solution, coupled with calorimetric measurements, provides a way of studying the role of the solvent in phenomena taking place in solution. One conclusion of these studies [9-17] is that acid–base processes are dominated by interaction of the solvent (Sl) with the charged (protonated) species.

According to Kebarle and co-workers [18-21] these interactions are very specific. Through solvation studies in the gas phase, $BH^+(Sl)_{n-1} + Sl \rightleftharpoons BH^+(Sl)_n$ ($n \leqslant 4$), these workers have shown that the interaction takes place *via* hydrogen bonds and that only a few (solvent) molecules are required to produce the (attenuation) effect found in solutions of that solvent. Usually this attenuation effect, in homologous series of compounds, varies linearly with the substituent effect.

There is very little information about experimental PA values of azoles. We have, therefore, had to assume a relationship between PA values and those of several calculated properties, *e.g.*, ΔE of protonation, defined as the difference between the energy of the protonated azole and the corresponding azole. From two of these ΔE values one can obtain the energy variation of related isodesmic processes,[22] $AzH^+ + X{-}Az \rightleftharpoons Az + X{-}AzH^+$ (X–Az being a substituted azole). Another useful parameter is the electronic density of the proton bound to the basic nitrogen in the cation, q_H,[23,24] since it must be related [25] in both pyrazoles and imidazoles to the attenuation effect produced by specific interactions with the solvent (hydrogen bonds). We shall also use the lone-pair orbital energy corresponding to the N(2) in pyrazoles and to the N(3) in imidazoles, since the correlation between this property and PA is well established.[26,27] The relationship between basicity and the charge of the basic nitrogen [N(2) in pyrazoles and N(3) in imidazoles [28]] will also be analysed; however in pyridines the linear dependence [27] between these two parameters is not good.

In order to have a group of experimental basicities to compare with theoretical values and to avoid differential solvent effects, we have selected a set of 17 methyldiazoles whose pK_a values in water are known [the pK_a of the 18th diazole, 4,5-dimethylimidazole (13), has not been determined].

This group shares the following properties. (a) All compounds are monocyclic aromatic systems of the same dimensions with two nitrogen atoms in positions 1 and 2 (pyrazoles) or 1 and 3 (imidazoles). We have already discussed [29] the problems of comparing pK_a and PA values of a monocyclic system, imidazole, and a bicyclic system, benzimidazole. (b) The substituents, always methyl groups, do not present conformational problems (as, for example, methoxy [30] or acyl [31] groups do) and they are classified as ' chemically inert ' in hydroxylic solvents.[32] (c) The dipole moment is almost constant within each family (around 2.3 D for pyrazoles and 3.8 D for imidazoles).

In spite of its homogeneity the chosen group of diazoles covers a range of seven pK_a units, ranging from 1-methylpyrazole (17) (pK_a = 2.09) to 2,4,5-trimethylimidazole (16) (pK_a = 8.86).

The basicity of pyrazoles has been discussed theoretically by Burton and Finar [33] and the large basicity gap between both parent diazoles (1) and (9) (ΔpK_a = 4.4) has been examined by Berthier *et al.* (using *ab initio* wavefunctions) [34] and more recently by Olivella and Vilarrasa (using semi-empirical MNDO calculations).[35]

Calculations

All the heavy atoms and the hydrogen atoms directly bonded to the ring lie on a plane. For the methyl groups, a conformation with a hydrogen atom in the same plane has been chosen. When two methyl groups are in neighbouring positions, they were placed in a ' geared ' conformation.[36]

Molecular geometries were fully optimized using the INDO method [37] and the Rinaldi and Rivail [38] technique. Convergence was assumed to be attained when changes in bond lengths, angles, and total energy values were within ±0.0007 Å, ±0.02°, and $\pm 10^{-7}$ a.u., respectively. The geometries so optimized are in good agreement with recent microwave data for imidazole [39] and pyrazole.[40]

It must be noted that two diazole tautomers, for instance, 3-methyl- (2) and 5-methylpyrazole (3), led to a common cation, ($2H^+$).

All the values, calculated and experimental, necessary to the discussion are presented in Table 1. The calculated values are: the charge of the acidic proton in the cation, q_H; the protonation energy, ΔE(kcal mol^{-1}), which is negative; the total charge of the ' pyridinic ' nitrogen, q_N; the energy of the lone pair, ε_N (eV); the charge of the NH proton (if any) in the neutral molecule; the calculated dipole moment (D); and finally, the calculated ionisation potentials from the literature [sp^2 transition centred on the ' pyridinic ' nitrogen, N(2) in pyrazoles and N(3) in imidazoles]. It must be noted that we found a linear relationship between (INDO) ΔE and proton affinities for several homologous series of organic compounds. The

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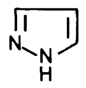
† Part 1 is ref. 29.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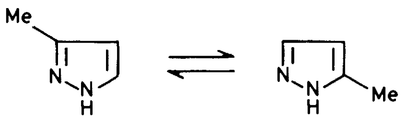
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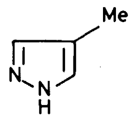
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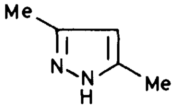
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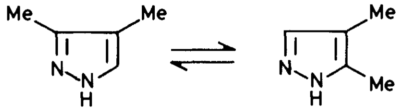
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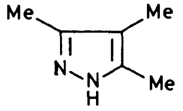
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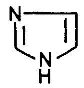
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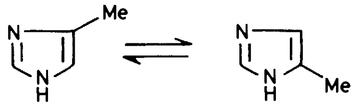
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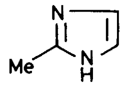
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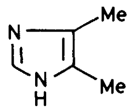
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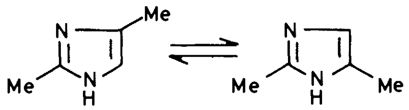
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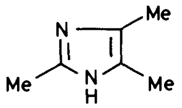
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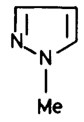
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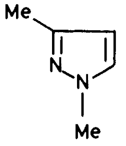
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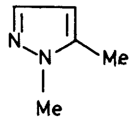
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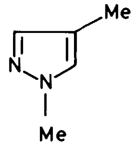
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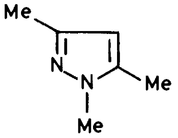
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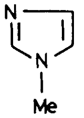
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experimental values include the pK_a values from the literature for the diazoles as bases (17 values) and as acids [only two values, those of the parent molecules (1) and (9)], and some experimental dipole moments (which are in excellent agreement with the calculated ones).

Results and Discussion

Relationships between the Different Theoretical Magnitudes.—The relationships between the four theoretical parameters, ΔE, ε_N, q_N, and q_H, have been analyzed for each family (pyrazoles and imidazoles), separately, and for the 22 diazoles together (Tables 2 and 3). Different units are used for the charges (electrons), the protonation energies (kcal mol^{-1}), and the orbital energies (eV). However, the most interesting results are the squared correlation coefficients (Table 3).

For the pyrazoles (13 compounds), three parameters are well correlated: ΔE, ε_N, and q_H; however, q_N is poorly correlated with these three parameters. For imidazoles (nine compounds) the four variables are strongly correlated. The different behaviour of q_N in imidazoles and pyrazoles is probably related to the fact that the nitrogen atoms are directly bonded in pyrazoles. As a consequence, part of the charge variation on N(2) could arise from modifications of the N(1) charge induced by the substituents.

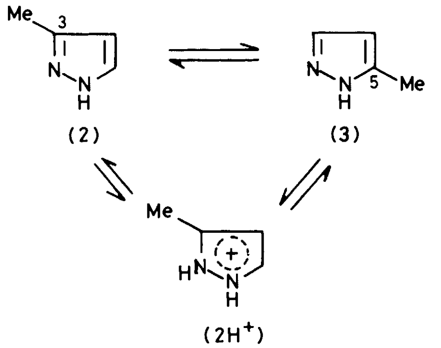
If pyrazoles and imidazoles are studied as a single series, ΔE and ε_N (Figure 1) continue to be strongly correlated, q_N is correlated to a lesser extent (owing to the inclusion of pyrazoles), but q_H is no longer correlated with ΔE and ε_N. We conclude that any correlations with the charge of the acidic proton should be carried out within a heterocyclic family of compounds. Figure 2 shows the relationship between q_H and q_N for both pyrazoles and imidazoles.

In view of these results we decided to examine the pK_a variations (Table 1) *versus* the q_H charges, for both imidazoles and pyrazoles, and, also pK_a *versus* the ε_N energies, for all compounds studied. It is preferable to use ε_N rather than ΔE (which gave very similar results) since the former requires only a calculation on the neutral molecule.

Table 1. Comparison of properties of imidazoles and pyrazoles with experimental data

Compound	q_{H}- (cation)	ΔE (prot.)	q_{N}- (base)	ε_N/eV	pK_a (as base)	q_{H}- (neutral)	pK_a (as acid)	$\mu_{calc.}$	$\mu_{exp.}$	IP$_{calc.}$/eV
(1), Pyrazole	0.8100	355.7	5.1736	−13.03	2.52 [a]	0.9212	14.21 [e]	2.31	2.30 [f]	−13.84 [g]
(2), 3-Methylpyrazole	0.8245	363.7	5.1876	−12.72	3.32 [a]	0.9211		2.29		
(3), 5-Methylpyrazole	0.8170	362.4	5.1710	−12.87		0.9280		2.41		
(4), 4-Methylpyrazole	0.8121	356.9	5.1696	−12.98	3.09 [a]	0.9188		2.25		
(5), 3,5-Dimethylpyrazole	0.8304	369.7	5.1872	−12.57	4.12 [a]	0.9267		2.39		
(6), 3,4-Dimethylpyrazole	0.8253	364.1	5.1847	−12.67	3.91 [a]	0.9184		2.21		
(7), 4,5-Dimethylpyrazole	0.8181	363.4	5.1690	−12.83		0.9237		2.40		
(8), 3,4,5-Trimethylpyrazole	0.8304	369.3	5.1834	−12.51	4.63 [a]	0.9240		2.31		
(17), 1-Methylpyrazole	0.8185	360.1	5.1835	−12.88	2.09 [a]			2.14	2.23 [f]	
(18), 1,3-Dimethylpyrazole	0.8320	367.4	5.1978	−12.59	2.82 [a]			2.10		
(19), 1,5-Dimethylpyrazole	0.8244	366.0	5.1853	−12.75	2.89 [a]			2.25		
(20), 1,4-Dimethylpyrazole	0.8204	361.1	5.1810	−12.85	2.48 [a]			2.06		
(21), 1,3,5-Trimethylpyrazole	0.8370	372.7	5.1980	−12.44	3.80 [a]			2.23		
(9), Imidazole	0.8114	368.5	5.2397	−12.45	6.95 [b]	0.9013	14.27 [e]	3.96	3.90 [f]	−12.83 [g]
(10), 4-Methylimidazole	0.8226	373.7	5.2539	−12.18	7.52 [b]	0.9000		3.94		
(11), 5-Methylimidazole	0.8149	371.3	5.2385	−12.43		0.9061		3.86		
(12), 2-Methylimidazole	0.8269	378.0	5.2576	−12.09	7.86 [b]	0.9104		3.90		
(13), 4,5-Dimethylimidazole	0.8245	375.8	5.2532	−12.18		0.9049		3.84		
(14), 2,4-Dimethylimidazole	0.8376	382.7	5.2714	−11.86	8.36 [b]	0.9089		3.90		
(15), 2,5-Dimethylimidazole	0.8297	380.2	5.2561	−12.09		0.9150		3.79		
(16), 2,4,5-Trimethylimidazole	0.8388	384.3	5.2706	−11.86	8.86 [c]	0.9135		3.77		
(22), 1-Methylimidazole	0.8148	370.6	5.2373	−12.53	7.20 [d]			3.49	3.75 [f]	

[a] Values from ref. 41. [b] Values from ref. 42. [c] Value from ref. 43. [d] According to Dedichen [44] 1-methylimidazole (22) is 0.25 pK_a unit more basic than imidazole (9) (7.33 and 7.08, respectively), other workers [45] have found for (22) a value of 7.20 which is also 0.25 unit higher than the pK_a of (9) (6.95). [e] Values from ref. 46; two other values have been published for imidazole, 14.44 [47] and 14.52,[48] that agree better with the calculations (the smaller the q_H value for the neutral molecule, the more acidic is the compound); however, correlations with q_H must also be made separately for each group. [f] Values from ref. 49. [g] Values from ref. 50, *ab initio* calculations, the experimental values are 10.7 and 10.3 eV for (1) and (9), respectively (IP$_{exp.}$ = 0.799 IP$_{calc.}$).[50]



Relationship between the Basicity in Water and the Charge of the Acidic Proton in the Conjugated Acid.—Figure 3 represents pK_a *versus* the charge, q_H. In solution, the tautomeric equilibrium constant, K_T, for *C*-methyl-substituted pyrazoles and imidazoles is almost equal to 1.[28] Thus, the pK_as have been compared with the mean charge of the two protons in the cations corresponding to the tautomeric pairs (2)–(3), (6)–(7), (10)–(11), and (14)–(15). For instance, for the (2H$^+$) cation the mean value of 0.8207 has been used, (I), in Figure 3. This implies that we have assumed that the departure of both protons is equally probable in solution.

When *N*-H and *N*-methyl derivatives are discussed as a whole, it is necessary to take the statistical effect into account.[28,41] A simple protonated pyrazole, such as (1H$^+$), can lose either acidic protons, whereas a cation such as (17H$^+$), can only lose its one proton. The same applies to imidazoles.

This characteristic of *N*-substituted diazoles brings in a corrective term, $\log_{10}2 = 0.30$, when the two series are compared. This correction lowers by 0.3 pK_a unit the value of the *N*-methyl derivatives: (17) 1.79, (18) 2.52, (19) 2.59, (20) 2.18, (21) 3.50, and (22) 6.90 in the study of *N*-H and *N*-methyldiazoles. In Figure 3, the black triangles correspond to corrected pK_a values of *N*-methyldiazoles.

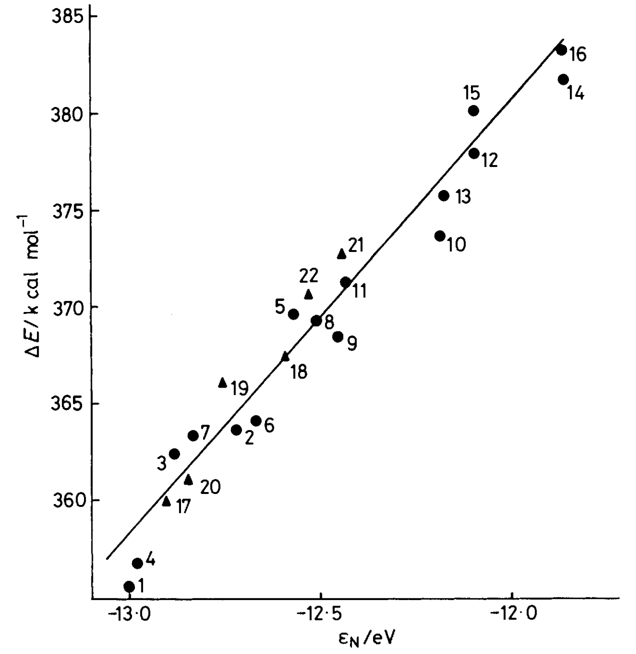


Figure 1. Relationship between ΔE (kcal mol^{-1}) and ε_N (eV) for pyrazoles and imidazoles, $\Delta E = 649 + 22.4\ \varepsilon_N$. ● *N*-Unsubstituted diazoles. ▲ *N*-Methyldiazoles

The results for imidazoles are almost linear, including the *N*-methyl derivative (22) (pK_a = −50.4 + 70.6 q_H, r^2 =

Table 2. Intercept of ordinate (A) and slope (B) of regression lines

Regression line	Pyrazoles, n = 13		Imidazoles, n = 9		Together, n = 22	
q_H *versus* ΔE	A	0.262	A	0.168	A	0.548
	B	0.001 54	B	0.001 75	B	0.000 75
q_H *versus* q_N	A	−2.973	A	−3.110	A	0.402
	B	0.732	B	0.749	B	0.081
q_H *versus* ε_N	A	1.375	A	1.300	A	1.023
	B	0.043	B	0.039	B	0.016
ΔE *versus* q_N	A	−1 595.6	A	−1 791.7	A	−619.7
	B	378.1	B	412.7	B	189.7
ΔE *versus* ε_N	A	701.5	A	642.3	A	649.3
	B	26.47	B	21.84	B	22.40
q_N *versus* ε_N	A	5.71	A	5.89	A	6.45
	B	0.042	B	0.052	B	0.099

Table 3. Squared correlation coefficients of Table 2 equations

	Pyrazoles, n = 13				Imidazoles, n = 9				Diazoles, n = 22			
	ΔE	ε_N	q_N	q_H	ΔE	ε_N	q_N	q_H	ΔE	ε_N	q_N	q_H
ΔE	1	0.939	0.525	0.919	1	0.920	0.901	0.982	1	0.965	0.789	0.476
ε_N		1	0.629	0.967		1	0.989	0.957		1	0.861	0.414
q_N			1	0.762			1	0.957			1	0.122
q_H				1				1				1

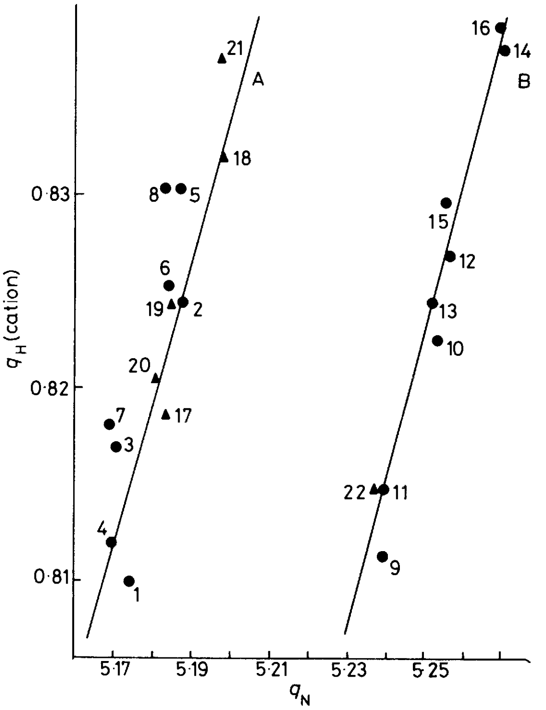


Figure 2. Relationship between the charges q_H(cation) and q_N. A, Pyrazoles, $q_H = -2.97 + 0.73\,q_N$; B, imidazoles, $q_H = -3.11 + 0.75\,q_N$

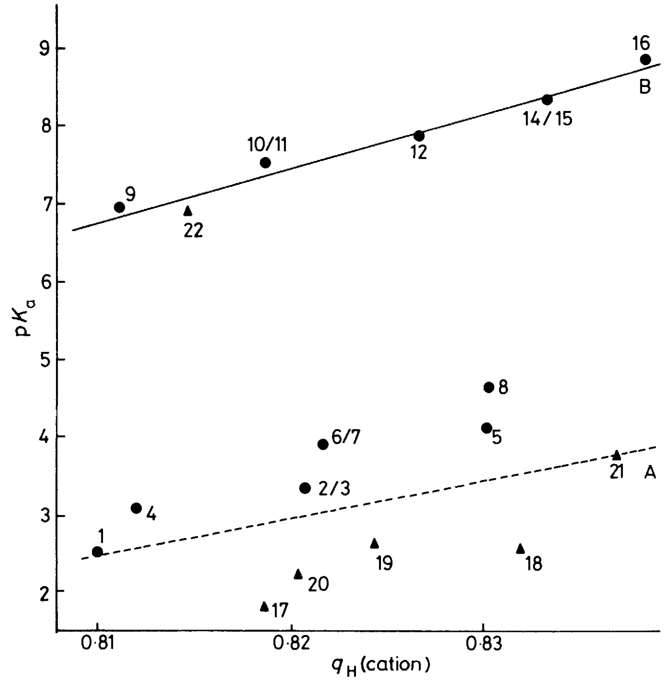


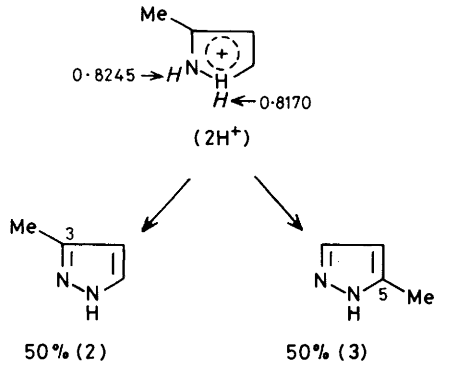
Figure 3. pK_a *versus* the charge of the acidic proton. A, Pyrazoles; B, imidazoles

0.972); this allows an estimation of the pK_a value of 4,5-dimethylimidazole (13) of 7.81 corresponding to $q_H = 0.8245$ (Table 1). The results for pyrazoles appear to be dispersed around a line p$K_a = -35.1 + 46.4\,q_H$, with most *N*-H and *N*-methyl derivatives situated at opposite sides.

For a long time[41] it has been recognized that *N*-methylation only slightly affects the basicity of imidazoles [compare (9) 6.95, with (22) 6.90, corrected value] but markedly diminishes the basicity of pyrazoles [compare (1) 2.52, with (17) 1.79, corrected value]. This difference between both diazoles was assigned[41] to a steric hindrance to solvation in cation ($17H^+$) owing to the adjacent *N*-methyl group.

Relationship between the Basicity in Water Solution and the Energy of the Lone Pair.—If the 17 pK_a values (after correction of the statistical effect) are compared with the ε_N energies (Table 1) (mean value for the tautomeric pairs) equation (1) is obtained.

$$\text{p}K_a = 83.9 + 6.3\,\varepsilon_N,\ r^2 = 0.785 \qquad (1)$$



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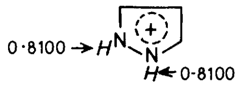
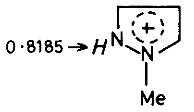


(1H$^+$)



(17H$^+$)

The fact that a single equation is valid for both pyrazoles and imidazoles (including a large set of compounds, and not just the two parent derivatives) [34,35] is very interesting, since it gives a simple and clear explanation of the large difference in basicity between both families. Results from the literature, quoted in the introduction,[26] show the existence of a linear relationship between PA and ε_N. Owing to the homogeneity of the set of diazoles and to the inertness of the methyl group, there are some similarities between pK_a and PA.

The correlation found is far from perfect but a representation of the pK_a values *versus* the ε_N energies (in eV) shows the existence of three families of compounds (Figure 4).* The relevant characteristic in this new classification is whether the compound has two, one, or zero methyl groups in position α to a basic centre [N(2) in pyrazoles and N(3) in imidazoles] *i.e.*, methyl groups in positions 1 or 3 in pyrazoles and in positions 2 or 4 in imidazoles. Three excellent correlations were obtained, equations (2)—(4).

No α-methyl groups (1), (3), (4), (7), (9), (11), (22):

$$n = 7,\ \mathrm{p}K_a = 110.8 + 8.32\ \varepsilon_N,\ r^2 = 0.982 \quad (2)$$

One α-methyl group (2), (5), (6), (8), (10), (12), (15), (17), (19), (20):

$$n = 10,\ \mathrm{p}K_a = 104.1 + 7.93\ \varepsilon_N,\ r^2 = 0.991 \quad (3)$$

Two α-methyl groups (14), (16), (18), (21):

$$n = 4,\ \mathrm{p}K_a = 109.4 + 8.50\ \varepsilon_N,\ r^2 = 0.995 \quad (4)$$

The second equation yields a calculated pK_a value of 7.41 (compared with the value of 7.81 previously obtained) for 4,5-dimethylimidazole (13) (one α-methyl group, $\varepsilon_N = -12.18$).

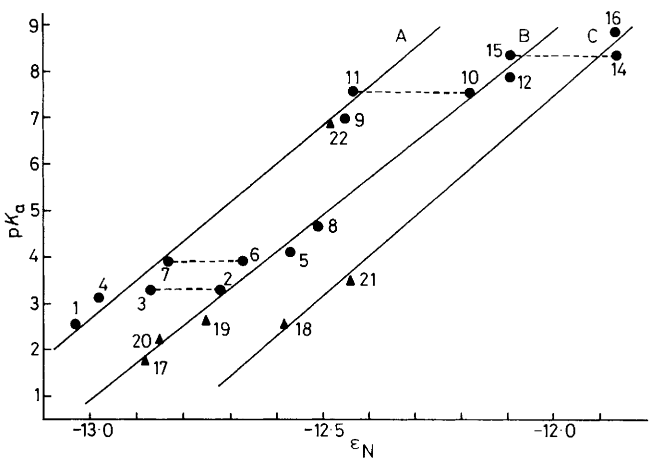


Figure 4. pK_a *versus* ε_N (pyrazoles and imidazoles). A, pK_a = 110.8 + 8.3 ε_N; B, pK_a = 104.1 + 7.9 ε_N; C, pK_a = 109.4 + 8.5 ε_N

Both steric hindrance to solvation of the cation and charge dispersion [4,29] through hydrogen bonding with the solvent could explain why the α-methyl derivatives have basicities in aqueous solutions lower than those calculated (about 1.8 pK_a units, the vertical separation of the lines in Figure 4). If the solvent effect could be removed, the points in Figure 4 belonging to compounds with α-methyl groups would be shifted vertically towards the upper line. For instance, 1,3,5-trimethylpyrazole (21) (pK_a = 3.50, corrected value) would be as basic as imidazole (9) (pK_a = 6.95), since both have comparable ε_N energies, −12.44 and −12.45 eV, respectively.

For tautomeric pairs we have assumed that both tautomers have the same pK_a. This is consistent with the fact that in aqueous solutions $K_T \simeq 1$ (pK_T = pK_{a_1} − pK_{a_2}).[28] A more detailed analysis [28] discloses that the equilibrium constant for pyrazoles is 1.17 [54% of the 3-methyl tautomers (2) and (6)] and 0.60 for imidazoles [40% of 4-methyl tautomers (10) and (14)]. Considering that $\log_{10} K_T$ is the pK_a difference between the tautomers, the following calculated pK_a values are obtained: (2) 3.29, (3) 3.35; (6) 3.88, (7) 3.94; (10) 7.63, (11) 7.41; (14) 8.47, (15) 8.25. All points, except for (10), have shifted towards the corresponding regression lines [equations (1) and (2)].

Proton Affinity and Tautomerism in the Gas Phase.—Since ε_N is linearly related to PA, the results obtained for the tautomeric pairs of pyrazoles and imidazoles (Table 3 and Figure 4), indicate that there will be differences in the intrinsic basicity between the tautomers. The higher intrinsic basicities will correspond to 3-methylpyrazoles (2) and (6) and the 4-methylimidazoles (10) and (14). Since the most basic tautomer would be the least abundant at equilibrium,[28] we can make the following prediction: in the gas phase the equilibrium would not be shifted either towards the 3-methylpyrazoles (2) and (6) or the 5-methylimidazoles (11) and (15) as it is in solution.

The same conclusion is reached when considering the relative acidities of the NH-protons in a common cation. In the gas phase, the most acidic one (that with the lowest q_H value) is more easily removed than the other. For instance, from the (2H$^+$) cation, either the 5-methyl tautomer (3) or the 3-methyl tautomer (2) could be formed. However, the corresponding values of q_H (0.8170 and 0.8245, respectively) indicated that the 5-methyl tautomer (3) is more likely to be formed.

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* *Note added in proof.* Considering pyrazoles only (● and ▲ in the lower left-hand corner of Figure 4) two new relationships can be obtained, one for *N*-unsubstituted (●) pyrazoles [(1)—(8)] and another for *N*-methyl (▲) pyrazoles [(17)—(21)]. The corresponding regression lines (r^2 = 0.93 and r^2 = 0.83, respectively) are separated by about 1.4 pK_a units. A similar effect is also observed in Figure 3.

Conclusions

This theoretical study provides a better understanding of the basicity of pyrazoles and imidazoles. The calculated value of the lone-pair orbital energy is the key parameter required to estimate the intrinsic basicities and tautomeric equilibria in the gas phase. The important role played by α-methyl groups on $\mathrm{p}K_a$ values in aqueous solution has been demonstrated.

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