J. Am. Chem. Soc. **1984**, *106*, 6552-6556

Relationship between Substituent-Induced Energy and Charge Effects in Proton-Transfer Equilibria Involving Heteroaromatic Nitrogen Systems. The "Lone Pair Charge" Approach

J. Catalán,[†] J. L. G. de Paz,[†] M. Yáñez,*[†] and J. Elguero[‡]

Contribution from the Departamento de Quîmica Fisica y Quîmica Cuântica, Centro Coordinado CSIC-UAM, Facultad de Ciencias, C-XIV, Universidad Autônoma de Madrid, Cantoblanco, Madrid, 34, Spain, and the Instituto de Quimica Mêdica, C.S.I.C., Juan de la Cierva, 3, Madrid, 6, Spain. *Received February 2, 1984*

Abstract: The relationship between substituent-induced changes in energy and charge is analyzed for proton-transfer equilibria involving 3- and 4-substituted pyridines, quinoline, isoquinoline, some mono- and bicyclic diazines, s-triazine, and 4- and 5-substituted pyrazoles and imidazoles, by using ab initio molecular orbital theory at the STO-3G level. We have found that the lone pair charge, whose evaluation is discussed here, correlates very well with the protonation energies of those compounds indicated above, although the correlations between gas-phase basicities and total charges are usually poor. We conclude that the lone pair charge is an adequate probe to investigate through-bond and/or through-space substituent effects on the intrinsic basicity of compounds that present the same kind of basic center. This confirms the old intuitive idea that the gas-phase basicity must bear a direct correlation to the charge of the basic center in the neutral molecule.

1. Introduction

Energy–charge relationships have been used very often in chemistry to interpret a great variety of processes and properties. The effects of para substituents on the barrier to inversion at the nitrogen atom in anilines[1] or on the torsional barrier in phenols[2] which have been readily correlated to the π-charge transfer between the aromatic system and the substituent, the correlation between atomic populations and ionization energies[3] or between atomic charges and ^{13}C (or ^{15}N) chemical shifts for carbon (or nitrogen) atoms which present similar hybridization and substitution,[4-8] and the relationship between the energy of a bond and the electron population of the bonded atoms[9] are good examples. These findings suggest that atomic charges are chemically meaningful when considering, on relative grounds, different compounds of a given series. Besides, in most of them, the assumption that energy variations are intimately related to displacements of charge within the system under consideration is implicit.

Energy–charge correlations have been specially useful regarding reactivity studies. In particular, a great deal of work was devoted to establish possible relationships between gas-phase proton affinities (or intrinsic basicities) and the amount of charge transferred to the proton along the corresponding protonation process. These correlations seem to reflect adequately the substituent effect on the relative basicity for a great variety of compounds: substituted phenols,[10,11] phenoxides,[11] and benzoic acids,[10] aliphatic aldehydes,[12] alkyl chlorides,[13] methylamines,[11] quinuclidines,[11] 3- and 4-substituted pyridines,[11] 4- and 5-substituted pyrazoles,[14] etc.

By contrast, it has been shown,[15] for a large set of 3- and 4-substituted pyridines, that the electronic population of the ring nitrogen, obtained using two different density-partitioning techniques in a SCF calculation, shows only a rough relationship to the energy variation of the corresponding proton-transfer equilibrium. Similar results were obtained by Hehre et al.[11] for a great variety of nitrogen, oxygen, and carbon bases. This reveals that the total charge of the basic center is not an adequate index to predict its intrinsic basicity, presumably because such a charge is affected, in a quite complex way,[11] by interactions with the orbitals centered on the other atoms of the molecule; interactions that change deeply with the substituent.

These results pose the question whether the substituent effect is passed over the chain of bonds which connect the substituent and the basic center or not. Regarding protonation energy changes, it seems clear that the effects of the substituent arise primarily from interactions in the charged form. Yoder and Yoder,[16] by means of an electrostatic field model, concluded that probably the predominant substituent effect is the charge–dipole interaction in the protonated form. Topsom, by means of the so-called isolated molecule approach,[17,18] has proved that in the protonation of alkylamines the through-bond inductive transmission is not significant. This term seems to have a relatively greater influence, mainly in the protonated forms, when considering the protonation of anilines, although field effects are still predominant.

Nevertheless, it is usually accepted that some characteristics of the neutral molecule must be somewhat related to its intrinsic basicity. Actually, it has been shown, for instance, that there exists a good linear correlation between the gas-phase proton affinity of substituted pyridines[15a] and azoles[16b] vs. the energy of the ring nitrogen lone pair. Analogous correlations between proton affinities and the electrostatic potential at the basic center created

---

[†] Universidad Autônoma de Madrid.

[‡] Instituto de Quimica Medica, C.S.I.C.

(1) Hehre, W. J.; Radom, L.; Pople, J. A. *J. Chem. Soc., Chem. Commun.* **1972**, 669.

(2) Radom, L.; Hehre, W. J.; Pople, J. A., Carlson, G. L.; Fately, W. G. *J. Chem. Soc., Chem. Commun.* **1972**, *308*.

(3) Rao, C. N. R.; Baso, P. K.; Hedge, M. S. *Appl. Spectrosc. Rev.* **1979**, *95*, 1 and references therein.

(4) Hehre, W. J.; Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1972**, *12*, 1496.

(5) Olah, G. A.; Pittman, C. U., Jr. *Adv. Phys. Org. Chem.* **1966**, *4*, 305.

(6) Mô, O.; Yáñez, M. *Theor. Chim. Acta* **1979**, *53*, 337.

(7) Dorado M.; Mô, O.; Yáñez, M. *J. Am. Chem. Soc.* **1980**, *102*, 947.

(8) Escudero, F.; Mô, O.; Yáñez, M. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1735. Fliszar, S.; Cardinal, G.; Beraldin, M. T. *J. Am. Chem. Soc.* **1982**, *104*, 5287.

(9) Baronve, V.; Del Re, G.; Fliszar, S.; *J. Chem. Soc., Perkin Trans. 2* **1979**, 1309. Fliszar, S. *J. Am. Chem. Soc.* **1980**, *102*, 6942.

(10) Catalán, J.; Macias, A. *J. Chem. Soc. Perkin Trans 2* **1979**, 1632.

(11) Hehre, W. J.; Taagepera, M.; Taft, R. W.; Topsom, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 1344.

(12) Del Bene, J. E. *J. Am. Chem. Soc.* **1978**, *100*, 1673.

(13) Jorgenson, W. L. *J. Am. Chem. Soc.* **1978**, *100*, 1049, 1057.

(14) Gribov, L. A.; Savvin, S. B.; Reichstat, M. M.; Orlov, M. Yu. *J. Mol. Struct.* **1982**, **88**, 171.

(15) (a) Catalán, J.; Mô, O.; Perez, P.; Yáñez, M. *J. Am. Chem. Soc.* **1979**, *101*, 6520. (b) Catalán, J.; Pêrez, P.; Elguero, J. *Heterocycles* **1983**, *20*, 1717.

(16) Yoder, C. S.; Yoder, C. H. *J. Am. Chem. Soc.* **1980**, *102*, 1245.

(17) Topsom, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 39.

(18) Topsom, R. D. *Acc. Chem. Res.* **1983**, *16*, 292.

0002-7863/84/1506-6552$01.50/0

by the neutral molecule have also been found.[14,15,19] Moreover, Fossey et al.[20] have concluded that basicity and alkylation reactivity of aminopyridines reveal lone pair localization since, as they have shown, these processes take place through an attack which is under orbital overlap control, favoring reaction of the ring nitrogen. Powell et al.[21] have also found that the centroid of charge and the size of the electron lone pair, in acetylenic systems, are substituent dependent and show a rough relationship to the corresponding intrinsic acidity.

These results point toward the existence of some local character of the reactive center, which is substituent dependent and which should be measured by some index of the nonprotonated system. This reasoning has led us to analyze, in a preliminary work,[22] the possibility of defining this index as the "lone pair charge", i.e. as the charge located in the lone pair directly involved in the formation of the corresponding cation upon protonation. There, we have concluded that this "lone pair charge" correlates very well with the corresponding protonation energy, within a family of compounds. The correlation found is accurately followed even by compounds where the substituent has a polarity sufficiently low (as, for instance, the methyl group) to cause a noticeable alteration of the electronic distribution around the basic center, which, for the compounds considered there, is far away from the substituent.

In this paper we aim at showing that this local charge has a general character, in the sense that it would be a reliable index, not only within a family of compounds but also for species whose basic centers exhibit analogous characteristics. In other words, if this charge can be considered actually as a relative measure of the electronic charge available in the region of the neutral molecule where the proton attachment will take place, one should expect that the corresponding correlation, proton affinity vs. lone pair charge, must be unique for compounds as pyrazoles and imidazoles or pyridines and diazines.

We shall also show that these new correlations can help in the understanding of the relationship between substituent-induced energy and charge effects.

2. Calculations

We have included in this study a large set of azaaromatic ring systems: 3- and 4-substituted pyridines, quinoline, isoquinoline, pyrimidine, pyridazine, pyrazine, cinnoline, quinoxaline, s-triazine, 4- and 5-substituted pyrazoles, 5-substituted imidazoles, and the 2,4,5-trimethylimidazole.

All calculations have been carried out using the GAUSSIAN 70 series of programs, at the STO-3G level. Due to the size of the compounds under study, a complete geometry optimization, even at the minimal basis set level, is beyond our computational capacity. Therefore, we have employed fully optimized INDO geometries, where the CH and NH bond lengths were conveniently scaled as described elsewhere.[23]

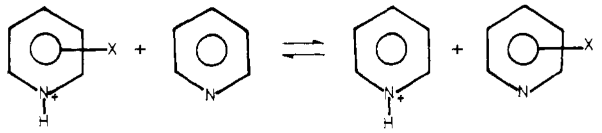
The corresponding molecular electrostatic potentials were evaluated using the equations of Srebrenick et al.[24] implemented by us in the frame of the GAUSSIAN 70 series of programs.

Finally, we have carried out a localization of the canonical molecular orbitals by the Foster–Boys method,[25] in order to obtain the position of the centroid of charge of the corresponding lone pair orbital.

3. Definition of the Lone Pair Charge

As indicated in the Introduction, one of our main goals is to evaluate the relative charge centered at the nitrogen σ-lone pair directly involved in the protonation process of heteroatomatic nitrogen systems. This charge is what we call "lone pair charge".

Scheme I



As discussed in our preliminary work,[22] a quantitative determination of this charge would imply performing numerical integrations of the corresponding electronic distribution function. These numerical integrations are so cumbersome that they have been only carried out for very simple cases.[26,27] We proposed a less quantitative but more straightforward and economical procedure which, in some manner, can be considered equivalent to project the electronic distribution in a new component (a lone pair function), which, due to its location in the area physically occupied by the nitrogen lone pair, should yield information on the electronic density to be found in that region. This "lone pair function" (LPF) is formed by one s-type and three p-type (x, y, z) GTO's with identical exponents and centered at the same point in space. This basis (to be added to the STO-3G minimal basis set) is initially located on the line that joins the basic center (in this case a ring nitrogen) to the centroid of charge of the corresponding localized lone pair orbital. Its relative position along this line and its exponent are then simultaneously optimized.

The values obtained for several pyridines, pyrazoles and imidazoles show that neither the exponent nor the position is very sensitive to the kind of heterocycle and/or substituent. In consequence, the previously reported values (exponent = 0.1 and position = 0.85 Å away from the nitrogen atom)[22] obtained for substituted pyrazoles were assumed to be fixed for all compounds included in this work. In our preliminary study[22] we have proved that the basis set so defined (STO-3G+LPF) does not present any pathological behavior regarding either the energy, the convergency of the SCF procedure, or the corresponding charge distribution.

Therefore, in general, in addition to the STO-3G SCF calculations necessary to determine the corresponding protonation energies, another one, using the STO-3G+LPF basis set, has to be carried out, for the neutral molecule, in order to obtain the value of the lone pair charge. Of course, if in the analysis of the energy–lone pair charge relationships the protonation energies employed are experimental ones, only the latter SCF calculation has to be performed.

It should be also pointed out that the lone pair charge obtained following the procedure outlined above cannot be taken as a quantitative measure of the total charge located at the nitrogen lone pair, mainly due to the lack of flexibility of a minimal basis set (even with the inclusion of the LPF) to adequately describe the charge density in a region quite apart from the nucleus. However, we have shown previously,[22] using the isolated molecule approach,[17] that this local charge reflects both through-space and through-bond substituents effects, either when they act simultaneously or when one of them is clearly predominant.

4. Pyridine-Type Compounds

We have selected the set of compounds listed in Table I because their experimental gas-phase basicities are accurately known. Hence, any possible relationship to the lone pair charge would be significant.

Table I presents our calculated lone pair charges (q_{LPF}) together with (a) the values of the corresponding experimental gas-phase basicities (considered as the $\delta\Delta G$ values of the proton transfer equilibrium, relative to pyridine (Scheme I) and (b) the calculated STO-3G protonation energies of the corresponding isodesmic process (Scheme I) ($\delta\ \Delta E_{\mathrm{p}}$). Values in (a) and (b), unless oth-

---

[19] Scrocco, E.; Tomasi, J. *Top. Curr. Chem.* **1973**, *42*, 95.

[20] Fossey, J.; Loupy, A.; Strzelecka, H. *Tetrahedron* **1981**, *37*, 1935.

[21] Powell, M. F.; Peterson, M. R. Csizmadia, I. G. *J. Mol. Struct.* **1983**, *92*, 323.

[22] Catalán, J.; de Paz, J. L. G.; Yáñez, M.; Elguero, J. *J. Mol. Struct.* **1984**, *108*, 161.

[23] Catalán, J.; Pérez, P.; Yáñez, M. *Tetrahedron* **1982**, *38*, 3693.

[24] Srebrenick, S.; Weinstein, H.; Pauncz, R. *Chem. Phys. Lett.* **1973**, *20*, 419.

[25] Foster, J. M.; Boys, S. F. *Rev. Mod. Phys.* **1960**, *32*, 300.

[26] Politzer, P.; Harris, R. R. *J. Am. Chem. Soc.* **1970**, *92*, 6451.

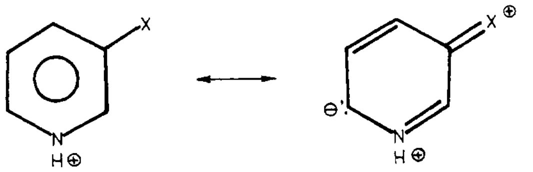
[27] Politzer, P. *Theor. Chim. Acta* **1971**, *23*, 203. Politzer, P.; Reggio, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 8308.

Table I. Experimental ($\delta\Delta G$) and Calculated ($\delta\Delta E_p$) Gas-Phase Basicities and Calculated Lone Pair Charges (q_{LPF}) for 3- and 4-Substituted Pyridines and Related Compounds

compd	$\delta\Delta G$, kcal/mol[a]	$\delta\Delta E_p$, kcal/mol[a]	q_{LPF}, e⁻
4-(dimethylamino)pyridine	15.6	19.3[d]	0.2216
3-(dimethylamino)pyridine	9.5	7.0[d]	0.1957
4-aminopyridine	9.4,[b] −11.4[h]	15.6	0.2180
3-aminopyridine	0.6[b]	3.5	0.1940
4-methoxypyridine	−7.2	9.3	0.2064
3-methoxypyridine	3.0	−0.3	0.1924
4-methylpyridine	4.3	5.0	0.2033
3-methylpyridine	2.9	2.5	0.1976
pyridine	0.0	0.0	0.1953
4-fluoropyridine	−4.1	−0.2	0.1946
3-fluoropyridine	−7.0	−6.3	0.1841
4-(trifluoromethyl)pyridine	−8.3	−6.8	0.1792
3-(trifluoromethyl)pyridine	−8.6	−6.8	0.1787
4-cyanopyridine	−11.2	−11.4	0.1774
3-cyanopyridine	−12.0	−12.4	0.1753
4-nitropyridine	−12.7	−16.7	0.1684
3-nitropyridine	−13.6	−17.4	0.1683
3,5-dimethylpyridine	5.1[b]	5.5[d]	0.1991
quinoline	5.6[c]		0.2007
isoquinoline	5.5[c]		0.2052
pyridazine	−4.1[e]		0.1857
pyrimidine	−8.1[e]		0.1790
pyrazine	−11.8[e]		0.1746
cinnoline	1.9[f]		0.1921[g]
quinoxaline	−4.9[f]		0.1844
s-triazine	−18.6[f]		0.1616

[a] Values taken from ref 28, unless otherwise stated. [b] Values taken from ref 30. [c] Values taken from ref 29. [d] This work. [e] Average values obtained from those reported in ref 29 and 31, adequately corrected by a factor $RT \ln 2$. [f] Values taken from ref 29, adequately corrected by a factor equal to $RT \ln 2$ for cinnoline and quinoxaline and equal to $RT \ln 3$ for s-triazine. [g] Average value obtained from those calculated for the two nonequivalent ring nitrogens ($q_{LPF}(N1) = 0.1917$, $q_{LPF}(N2) = 0.1925$). [h] Gal, F. G.; Taft, R. W., private communication.

Scheme II



erwise stated, were taken from ref 28 (Table VI).

In Figure 1a we have plotted $\delta\Delta G$ vs. the ring nitrogen lone pair charge (q_{LPF}). Clearly, there is a quite good linear correlation between both magnitudes, in contrast with the lack of correlation, pointed out previously,[16] when using the total charge centered on the pyridine-type nitrogen.

Several facts should be singled out for comment: (a) This correlation includes 3- and 4-substituted pyridines with both resonance-donating and resonance-accepting substituents. This point is quite important since it has been found[11] that relationships between experimental (or calculated) protonation energies and the charge on the acidic proton are usually bilinear for a great variety of bases.

Nevertheless, one can observe that for π-electron donor substitutents, as $-CH_3$, $-NH_2$, $-N(CH_3)_2$, or $-OCH_3$, when in the 3-position in pyridines, the calculated lone pair charge is smaller than it should be expected from their gas-phase basicities. Hence, these points deviate more from the linear correlation than those corresponding to 4-substituted compounds. This probably points to a certain limitation of the lone pair charge approach. This magnitude is evaluated for the nonprotonated system and therefore is not able to reproduce completely π-donor effects[28] (see Scheme II) induced by the field of the positively charged pyridinium ion.

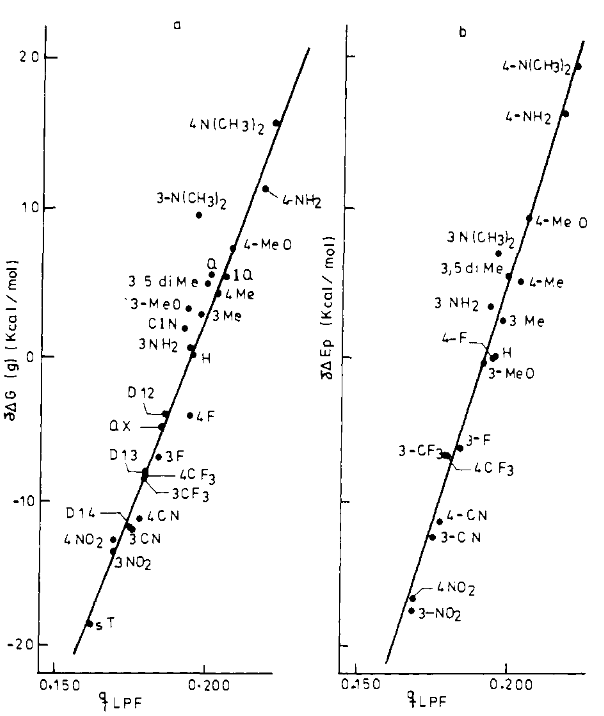


Figure 1. (a) Correlation of experimental $\delta\Delta G$(g) and the nitrogen lone pair charge for 3- and 4-substituted pyridines and quinoline (Q), isoquinoline (IQ), cinnoline (CIN), quinoxaline (QX), pyridazine (D12), pyrimidine (D13), pyrazine (D14), and s-triazine (sT). (b) Correlation of calculated protonation energies $\delta\Delta E_p$ and the nitrogen lone pair charge for 3- and 4-substituted pyridines.

(b) This relationship is accurately followed by monocyclic diazines (pyridazine (D12), pyrimidine (D13), and pyrazine (D14)) and s-triazine (sT), where, in principle, strong nitrogen-nitrogen interactions should be expected, at least in some particular cases as pyridazine, for instance.

(c) It is also important to note that this correlation is followed by molecules such as quinoline (Q), isoquinoline (IQ), cinnoline (CIN) and quinoxaline (QX), which present an increment of their intrinsic basicity, relative to that of monocyclic compounds, due to a typical annelation effect. This effect has been explained by Meot-ner[29] as a result of charge-induced dipole interactions in the protonated form.

(d) Finally, it is important to realize that the basicity of the compounds under investigation cover a wide range (of about 40 kcal/mol) in the scale of experimental gas-phase basicities.

For the particular case of 4-NH_2-pyridine, the value measured by Taft et al. fits better our correlation than other values reported in the literature (see Table I).

In order to check whether the lone pair charge approach works properly, when interactions between the basic center and the substituent are presumably very important, we have carried out similar calculations for some 2-substituted pyridines: -CN, -F, $-CF_3$, $-OCH_3$, $-CH_3$, $-NH_2$, and $-N(CH_3)_2$. Our results showed that, while cyano, methyl, and amino-derivatives fit quite well the linear correlation of Figure 1, the remaining substituted compounds present very important deviations.

Several factors can be responsible for this behavior: (a) very likely, strong interactions between the LPF and the orbitals centered on the substituent lead to a "contamination" of the lone pair charge; in other words, the charge associated to the LPF reflects, in those cases, not only the one located on the nitrogen lone pair but partially that on orbitals of the substituent. (b) Also due to these orbital interactions, the LPF's used (which have been optimized for distant substituents) may be not adequate when the

---

(28) Taagepera, M.; Summerhays, K. D.; Hehre, W. J.; Topsom, R. D.; Press, A.; Radom, L.; Taft, R. W. *J. Org. Chem.* **1981**, *46*, 891.

(29) Meot-Ner (Mautner), M. *J. Am. Chem. Soc.* **1979**, *101*, 2396.

(30) Aue, D. H.; Bowers, M. T. "Gas-phase Ion-chemistry"; Bowers, R. T., Ed.; Academic Press: New York, 1979.

(31) Taft, R. W. *Prog. Phys. Org. Chem.* **1983**, *14*, 247.

Table II. Calculated Values for Protonation Energies (ΔE_P), Total Charge of the Basic Center (q_{N2} or q_{N3}), Lone Pair Charge (q_{LPF} (N2 or N3)), Minimum of the Electrostatic Molecular Potential (PE_{min}), and Relative Position of the Nitrogen Lone Pair Centroid of Charge (r_{cc}) for Substituted Pyrazoles and Imidazoles

compd	ΔE_P, kcal/mol	$q_{N2/N3}$, e⁻	q_{LPF}, e⁻	PE_{min}, kcal/mol	r_{cc}[a]
pyrazole	−264.8	7.1587	0.2185	−84.7	0.6668
5-aminopyrazole	−277.4	7.1732	0.2352	−89.5	0.6623
4-aminopyrazole	−265.0	7.1528	0.2159	−84.9	0.6666
5-methylpyrazole	−270.8	7.1608	0.2226	−85.8	0.6669
4-methylpyrazole	−268.5	7.1613	0.2217	−85.8	0.6652
5-fluoropyrazole	−262.9	7.1620	0.2175	−83.2	0.6647
4-fluoropyrazole	−258.2	7.1458	0.2040	−79.8	0.6688
5-cyanopyrazole	−251.1	7.1304	0.1900	−69.8	0.6662
4-cyanopyrazole	−251.0	7.1458	0.1961	−72.1	0.6625
5-nitropyrazole	−245.7	7.1224	0.1794	−66.3	0.6688
4-nitropyrazole	−245.8	7.1403	0.1867	−68.5	0.6648
imidazole	−283.3	7.2670	0.2507	−98.1	0.6490
5-aminoimidazole	−286.5	7.2607	0.2490	−100.5	0.6472
5-methylimidazole	−287.3	7.2690	0.2543	−99.8	0.6476
5-fluoroimidazole	−277.2	7.2574	0.2408	−95.2	0.6480
5-cyanoimidazole	−270.2	7.2577	0.2274	−85.0	0.6460
5-nitroimidazole	−265.0	7.2533	0.2182	−81.1	0.6476
2,4,5-trimethylimidazole	−298.0	7.2878	0.2700	−106.0	0.6572

[a] Distance, in Å, from the lone pair centroid of charge to the nitrogen atom.

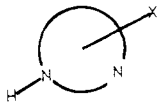
substituent is at ortho, relative to the basic center, and they should be reoptimized. (c) Since the substituent is very close to the basic center, the experimental free-energy variations ($\delta\Delta G$) can be strongly influenced by effects induced by the positive charge in the protonated form, which cannot be reproduced by the lone pair charge. All these points are under investigation.

Figure 1b presents an analogous correlation, exclusively for 3- and 4-substituted pyridines, but using calculated protonation energies instead of experimental ones. The new correlation is equally good and considerably corrects the deviation observed for 3-(dimethylamino)pyridine with respect to the regression line $\delta\Delta G$ vs. q_{LPF} (Figure 1a).

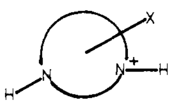
5. Pyrazoles and Imidazoles

We present in Table II the different magnitudes calculated for those pyrazoles and imidazoles included in this study.

We have first examined the possible correlation between the calculated protonation energy (ΔE_p)[32] obtained as the energy difference between the protonated (II) and the nonprotonated (I) forms vs. the total net charge (q_{N2} of q_{N3}) on the corresponding nitrogen atom. It is evident (see Figure 2) that in the present case, as in other types of bases,[11,15] only a rough proportionality between the protonation energy and the total charge on the basic center is observed. Besides, the relationships for both families of compounds are clearly distinct.



I



II

In Figure 3, the calculated protonation energy (ΔE_P) has been plotted vs. the nitrogen lone pair charge (q_{LPF}). Once more, the linear correlation obtained, which obeys the equation

$$\Delta E_P = -590.06 q_{LPF} - 137.20 \text{ kcal/mol} \quad r = 0.993 \quad (1)$$

presents a very small dispersion, reflected in a quite high correlation coefficient.

Similar facts as those discussed in the case of pyridines are observed here, in the sense that both types of substituents (resonance donating and resonance accepting) are present. However, the most important fact is that the two different relationships obtained for both families of compounds when using the total

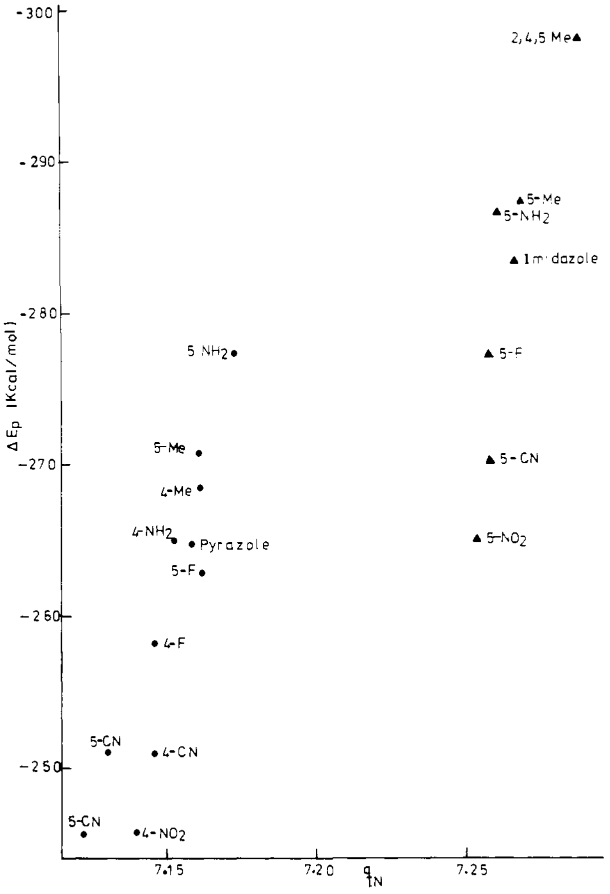


Figure 2. Plot of calculated protonation energies (ΔE_P) vs. the total charge of the basic center for pyrazoles (●) and imidazoles (▲).

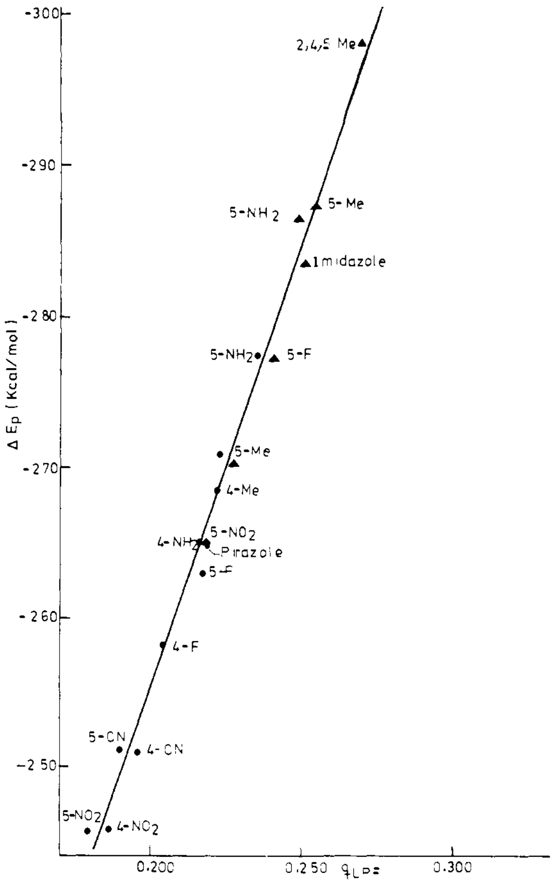


Figure 3. Plot of calculated protonation energies (ΔE_P) vs. the nitrogen lone pair charge (q_{LPF}) for pyrazoles (●) and imidazoles (▲).

---

[32] The values for 4- and 5-substituted pyrazoles were taken from ref 22.

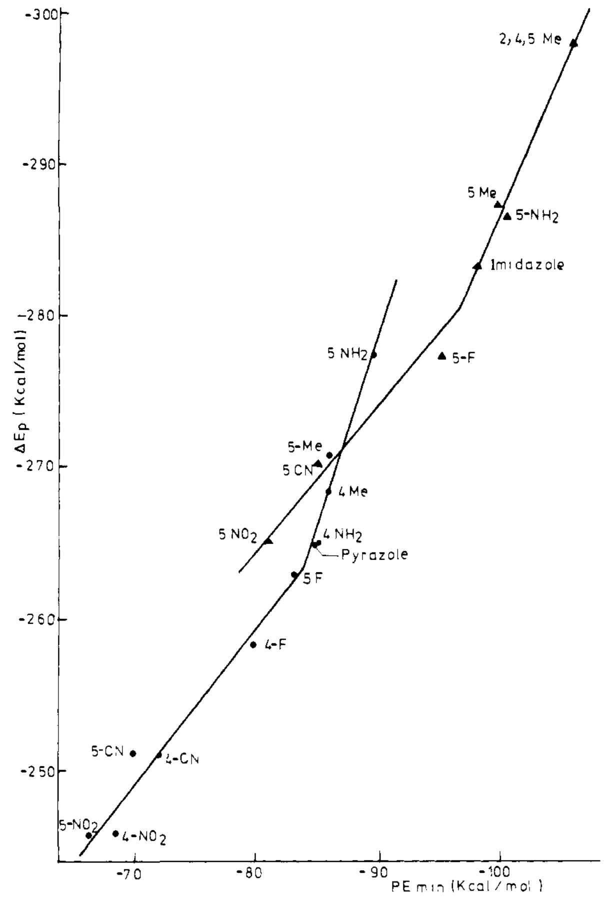


Figure 4. Correlation between calculated protonation energies (ΔE_P) and the minimum of the electrostatic molecular potential close to the basic center (PE_{min}) for pyrazoles (●) and imidazoles (▲).

charge on the nitrogen atom (Figure 2) become now a unique linear correlation. Moreover, this unique relationship shows a drastically reduced scatter if compared with those of Figure 2.

These results and those discussed in the previous section clearly indicate that this local charge reflects well the influence of the substituent on the reactive center of the neutral molecule, even if they are of a quite different nature and/or in a different position.

One might wonder whether a similar correlation could be obtained by using, instead of the nitrogen lone pair charge, another magnitude which must be, in principle, closely related to it as the minimum of the electrostatic molecular potential evaluated at the vicinity of the basic center. Such a correlation has been plotted in Figure 4.

Some aspects must be noticed. The linear relationships obtained show less scatter than those of Figure 2 (where the total charge on the nitrogen atom was employed) but more than that shown by Figure 3 (where the lone pair charge was used). Besides, the relationships are, once more, distinct for pyrazoles and imidazoles, and, similarly to what is usual for correlations between protonation energies and the charge on the acidic hydrogen, they are bilinear.

We can conclude, therefore, that the "lone pair charge" is a much more general index than the value of the corresponding electrostatic molecular potential to probe intrinsic basicities. The fact that those correlations presented in Figure 4 are bilinear illustrates that the electrostatic molecular potential is influenced not only by the electronic distribution close to the reactive center but also by that of the remaining parts of the molecular system, even if they are remote to it. Since the charge redistribution undergone by the molecule upon substitution depends strongly on the nature of the substituent, it is not surprising finding the ΔE_P vs. PE_{min} relationships to be bilinear, with different slopes for resonance-donating than for resonance-accepting substituents.

According to our model, keeping in mind the limitation outlined in point a of section 4, it is also reasonable to expect a good correlation between protonation energies and the charge of the acidic hydrogen, since this charge must depend essentially on the amount of charge that is available in the region where the proton attachment will occur (i.e., what we have called "lone pair charge"). However, the amount of charge transferred from the base to the bare proton depends also on other factors, mainly charge–dipole and charge-induced dipole interactions, which are commonly substituent dependent. As a consequence such correlations are frequently bilinear and only valid for a given family of compounds.

There is still another index related to the lone pair involved in the proton-transfer equilibrium, which could bear, in principle, some relationship to the corresponding protonation energy. This index is the position of the centroid of charge of that lone pair. Actually Powell et al.[21] have found, for a number of acetylenic anions, that the position of the centroid of charge of the electron lone pair of the reactive center roughly parallels the corresponding intrinsic acidity. In fact, they showed that the centroid gets closer to the reactive center (leading to a tighter lone pair) the more acidic the compound in question is. One should expect, therefore, the reverse behavior when the intrinsic basicity is being considered.

We have evaluated the position of the centroid of charge (r_{cc}) of the nitrogen lone pair (see Table II) for all compounds included in this section. It is evident that the position of the centroid is practically unsensitive to the nature of the substituent, and it is different for pyrazoles and imidazoles. Moreover, our results would predict a much tighter lone pair precisely for those compounds (imidazoles) that are stronger bases. Hence, at least for this kind of compounds and at this level of accuracy, this index is not at all meaningful.

6. Concluding Remarks

Although the correlation between gas-phase basicities and the total charge of the basic center is usually poor, we have shown that such a correlation is accurately followed when employing what we have defined as the "lone pair charge". This local charge is then an adequate probe to investigate substituent effects on the intrinsic basicity of compounds that present the same kind of basic center. Moreover, this arises again and confirms the old intuitive idea that the reactivity of a given compound, and in particular its gas-phase basicity, must bear a direct relationship to the charge of the basic center in the neutral molecule.

Acknowledgment. All calculations were performed at the UAM/IBM Centre (Madrid). We thank a referee for pointing us a possible limitation of the lone pair charge approach, now incorporated in our discussion. We also thank Prof. R. W. Taft for valuable suggestions and for making available to us unpublished results.

Registry No. 4-(Dimethylamino)pyridine, 1122-58-3; 3-(dimethylamino)pyridine, 18437-57-5; 4-aminopyridine, 504-24-5; 3-aminopyridine, 462-08-8; 4-methoxypyridine, 620-08-6; 3-methoxypyridine, 7295-76-3; 4-methylpyridine, 108-89-4; 3-methylpyridine, 108-99-6; 4-fluoropyridine, 694-52-0; 3-fluoropyridine, 3796-23-4; 4-(trifluoromethyl)pyridine, 3796-24-5; 3-(trifluoromethyl)pyridine, 3796-23-4; 4-cyanopyridine, 100-48-1; 3-cyanopyridine, 100-54-9; 4-nitropyridine, 1122-61-8; 3-nitropyridine, 2530-26-9; 3,5-dimethylpyridine, 591-22-0; quinoline, 91-22-5; isoquinoline, 119-65-3; pyridazine, 289-80-5; pyrimidine, 289-95-2; pyrazine, 290-37-9; cinnoline, 253-66-7; quinoxaline, 91-19-0; *s*-triazine, 290-87-9.