Substituent Effects on Imidazole Basicity and Photoelectron Spectroscopy Determined Ionization Energies

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The nitrogen lone pair orbital (n) and the two highest occupied π orbital vertical ionization energies (I^v) from the UV photoelectron spectra of 1-methyl-, 2-methyl-, 1,2-dimethyl-, 1-acetyl-, and 1-(trifluoroacetyl)imidazole and imidazole and the complete PE spectrum of benzimidazole are compared with the results of modified CNDO/2 calculations. Only in the PE spectra of 1-acetyl- and 1-(trifluoroacetyl)imidazole are the n and π_2 orbital I^v resolvable. A linear relationship between substituted imidazole pK_a values and CNDO lone pair orbital energies is found to be limited to substituents which leave the n orbital electron density at nitrogen unchanged. Perturbation molecular orbital arguments are developed which suggest that this result is the equivalent of a restriction on the observation of linear $I_n{}^v$–pK_a regressions that substituent interaction mechanisms be limited to inductive and field effects, with the exclusion of through bond resonance interactions between the substituent and nitrogen lone pair.

Experimentally determined substituent effects on molecular ionization energies often provide insight into other fundamental chemical properties of molecules. For example, several years ago we demonstrated[1] that in a series of substituted pyridines, the photoelectron (pe) determined nitrogen lone pair (n) vertical ionization energies ($I_n{}^v$) exhibited a linear correlation with solution phase pK_as, as well as with gas phase proton affinities (PA). Shortly thereafter, Heilbronner and Bieri[2] reported a similar linear relationship for a series of substituted quinuclidines between $I_n{}^v$ and pK_a while at the same time remarking that, "no conclusions can be drawn from such regressions concerning a close relationship between the electronic mechanisms responsible for the observed changes in pK or $I_n{}^v$".[2]

Although more recent reports of linear $I_n{}^v$–PA correlations have appeared in the literature,[3,4] still the original statement by Heilbronner and Bieri[2] remains unchallenged, and no rationale for the existence of, or substituent limitations on, these $I_n{}^v$–pK_a (PA) relationships has been offered.

In this paper the study of amine $I_n{}^v$–pK_a correlations is extended to substituted imidazoles, and it is suggested that conclusions based on perturbation molecular orbital (PMO) models concerning substituent interaction mechanisms can in fact be drawn from the presence of such regressions.

Results

Photoelectron spectra have been determined for imidazole (**1**), the substituted 1-methyl- (**2**), 2-methyl- (**3**), 1,2-dimethyl- (**4**), 1-acetyl- (**5**), and 1-(trifluoroacetyl)imidazoles (**6**), and benzimidazole (**7**).

The general features of the parent imidazole PE spectrum are already provided by a published spectrum of Craddock and co-workers.[5] In this work, the PE determined first I^v of imidazole was obtained as 8.96 eV, however, rather than the previously reported 8.78 eV, by first calibrating the PE spectrometer against methyl iodide ($I^v = 9.54$ eV) and argon (15.76 eV) followed by measuring the imidazole PE spectrum calibrated against internal argon. This procedure has been found to give results in satisfactory agreement with the use of a double internal standard such as argon–xenon. Modified CNDO/2 calculations using the parameterization procedures of Del Bene and Jaffe[6] were carried out on each molecule as an aid to the assignment of vertical ionization energies, I^v, observed in the PE spectra. For imidazole, these results may be compared with earlier CNDO/2 calculations by Del Bene and Jaffe[7] on the UV spectrum of imidazole, in which only π and nitrogen lone pair orbital energies were given, and with the minimal basis set "ab initio" calculations utilized by Craddock and co-workers[5] in a Koopmans' theorem[8] assignment of the imidazole PE spectrum.

In π orbital energies, agreement between the earlier calculations by Del Bene and Jaffe[7] and those reported here is close—differences are in no instance greater than 0.15 eV. A major difference between the two calculations is found, however, in the nitrogen lone pair orbital energy. The calculation reported here places the lone pair orbital 0.63 eV below π_2, whereas both the Del Bene and Jaffe, as well as the "ab initio" calculations,[5] place the nitrogen lone pair orbital only 0.1 eV below π_2. The difference between results in the two CNDO/2 procedures may lie in the use of an experimentally determined geometry for imidazole in the calculations reported here, as contrasted with a geometry used by Del Bene and Jaffe[7] based on calculated bond distances. This latter statement is based upon the observation of previous agreement[1] between the modified CNDO/2 program used and published results by Del Bene and Jaffe in other related molecules such as pyridine.[6,1]

A reasonable level of confidence may be placed in the results of the modified CNDO/2 calculations. A good linear correlation was found to exist between the reported[5] imidazole "ab initio" eigenvalues and the modified CNDO/2 eigenvalues and in the substituted imidazole series, **1** through **7**; the first $I_\pi{}^v$ is given by the linear regression of eq 1 with a 0.97 correlation coefficient.

$$I_\pi{}^v = -1.67\epsilon_{\mathrm{CNDO}} - 7.50 \text{ eV} \qquad (1)$$

Substituent effects on imidazole, I^v, and calculated SCF orbital energies, ϵ, are provided in Table I for the π_2 and π_3 functions.

Except for 1-acetyl- and 1-(trifluoroacetyl)imidazole, the PE spectra below 12 eV of the substituted imidazoles studied are in general features identical with the spectrum[5] of the parent imidazole, **1**. These PE spectra of **1** through **4** consist of a first band, π_3, containing prominent vibrational structure followed by a second band with twice the intensity of the first and associated with ionizations from π_2 and n_N orbitals but with no clear resolution into two separate PE bands or shoulders.

In the PE spectrum of **5**, the second band centered at 10.4 eV contains three I^v correlated with π_2, nitrogen lone pair, n_N, and carbonyl lone pair, n_o, orbitals. The CNDO/2 calculations suggest assignment of the shoulder of this 10.4 eV band at 10.9 eV to ionization from the n_N orbital although there is strong mixing evident between the n_n and n_o functions in the CNDO/2 calculations, a significant point in the discussion which follows.

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Among the imidazole PE spectra studied, only in the spectrum of **6** is the second band well resolved into its component I^v. The modified CNDO/2 calculations on **6** would assign observed I^v in this band at 10.85 eV (sh), 11.13 eV, and 11.60 eV (sh) to π_2 (imidazole), n_N, and n_o in the above order.

In an effort to find imidazoles in which the $I^v(n)$ might be resolved from $I^v(\pi)$, survey PE spectra of 1-(trimethylsilyl)- and 1-methyl-5-chloroimidazole, calibrated only against argon, were run without successful resolution of the $I^v(n)$ and $I^v(\pi_2)$ bands.

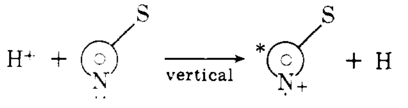
Discussion

The general lack of resolution between the PE bands associated with the nitrogen lone pair ionizations and overlapping π_2 ionizations render it impossible to examine any quantitative relationship between the substituted imidazole I_n^v and pK_a. It should however be possible to approach this problem through the back door and examine the related question of whether there is a linear relationship in the imidazole series between the n_N orbital CNDO/2 energy, ϵ_n, and the imidazole pK_a.

The presence (absence) of such a relationship between ϵ_n and pK_a would suggest the presence (absence) of an I_n^v–pK_a correlation, since without respect to the validity of Koopmans' theorem,[8] empirically reasonable linear correlations between $-\epsilon_{SCF}$ and I^v are usually found for a closely related molecular series and can be specifically found between I_n^v and $-\epsilon_{CNDO}$ for pyridines.[1] Before pursuing such a correlation, however, some understanding is needed, at least at the qualitative level of simple perturbation molecular orbital theory, of the relationship between substituent effects on I_n^v and PA or pK_a in amines.

The approach to the question at the level of first and second order molecular orbital perturbation theory is particularly appropriate since a linear PA–I_n^v or pK_a–I_n^v represents an *extrathermodynamic* linear enthalpy–enthalpy or linear free energy–enthalpy relationship, and therefore as extrathermodynamic relationships they cannot in any general case be expected to remain valid except in the limiting condition of small substituent perturbations.

The gas phase protonation of a substituted amine may be arbitrarily divided into two vertical reactions (reactions 2 and 3), in which the geometry of the amine remains fixed, followed by relaxation of the product protonated amine to its ground state geometry, eq 4. The negative value of the change in energy (enthalpy) associated with eq 3 has been termed[3] the vertical hydrogen atom affinity (HA^v).



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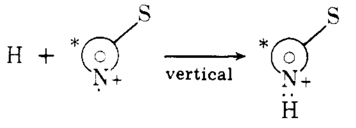

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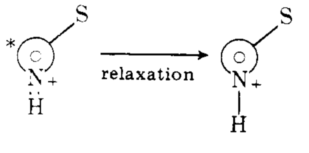

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The substituent effect (δ^s) on the enthalpy of reaction 2 is simply $\delta^s I_n^v$. It follows then that provided the substituent effect on step 4 is negligible, a reasonable assumption where the substituent is not directly attached to nitrogen, PA is a linear function of I_n^v only if δ^sHA^v is zero, or proportional to $\delta^s I^v$. These statements can be summarized by eq 5 and 6.

Table I. Substituted Imidazole π Vertical Ionization Energies, I^v, and Associated Modified CNDO/2 π Orbital Energies ϵ (eV)

imidazole substituent	π_3		π_2	
	I^v	$-\epsilon$	I^v	$-\epsilon$
H	8.96	9.86	10.30[a]	11.65
1-Me	8.66	9.75	9.85[a]	11.21
2-Me	8.50	9.56	10.08[a]	11.58
1,2-diMe	8.38	9.47	9.79[a]	11.15
1-MeCO	9.38	10.04	10.4[b]	11.72
1-CF$_3$CO	9.91	10.40	10.85[c]	12.18

[a] Maximum of PE band assigned to both π_2 and n_N. [b] Maximum of PE band assigned to both π_2 and carbonyl n_o. [c] Shoulder, maximum at 11.13 eV and shoulder at 11.60 eV assigned to n_n and n_o, respectively.

$$\delta^s\text{PA} = \delta^s I_n^v - \delta^s\text{HA}^v + \delta^s\text{relax} \qquad (5)$$

if HA^v = $aI^v + b$ and δ^srelax = 0, then

$$\delta^s\text{PA} = (1 - a)\delta^s I_n^v \qquad (6)$$

In this context, understanding the relationship between the electronic mechanisms responsible for observed changes in pK_a or PA and I_n^v then requires an understanding of what modes of substituent interaction mechanisms lead to a value of δ^sHA which is negligibly small or proportional to $\delta^s I_n^v$. As will be demonstrated in the discussion that follows, an understanding can be developed from a perturbation model in which the principal N–H SCF bonding orbital of the protonated amine is generated from a linear combination of the SCF n orbital and the hydrogen atom 1s atomic orbital.

The underlying assumption in the treatment that follows is that the substituent effect on the homolytic vertical bond energy of the protonated amine will be equal or proportional to the substituent effect on the absolute magnitude of the change, $\Delta\epsilon$, in either radical cation lone pair orbital or hydrogen atom 1s orbital energy on homolytic bond formation, times the number of electrons, two, in the bond orbital, i.e., δ^sHA^v equals $2\delta^2|\Delta\epsilon|$.

The electronic energies of the radical cation and protonated amine of eq 3 can be expressed as sums over SCF orbital energies plus molecular orbital electron repulsion integrals. In turn the substituent effect on the vertical hydrogen atom affinity, δ^sHA, is given by sums over changes in corresponding molecular orbital energies, $2\delta^s\Sigma\epsilon_i$, plus sums over changes in MO electron repulsion integrals. Assuming substituent effects on changes in molecular orbital repulsion integrals to be negligibly small, substituent effects on HA^v may be divided into α and π orbital energy contributions. Since the σ framework accommodates a positive charge in both the amine radical cation and the protonated amine, substituent effects on changes in π orbital energies between protonated amine and radical cation should be small with respect to changes in σ orbital energies. With these assumption δ^sHA equals $-2\delta^s\Sigma\Delta\epsilon_\sigma$. If this last summation is determined by or is proportional to the change in n orbital energy, $\Delta\epsilon_n$, we are left with the expression δ^sHA equals $2\delta^s|\Delta\epsilon|$.

The magnitude of the change in orbital energies $|\Delta\epsilon|$ is given by the usual second-order perturbation expression (eq 7) where $C_{N\cdot}$ is the nitrogen lone pair atomic orbital coefficient in the amine radical cation, $n_{N\cdot}$, orbital. (Strictly, $C_{N\cdot}$ is the square root of the sum of the squares of contributing nitrogen 2p and 2s atomic orbitals in the SCF function.) The H· atom coefficient is unity and β represents the effective N–H atomic orbital resonance integral between nitrogen and hydrogen orbitals. The $\epsilon_{N\cdot}$ and $\epsilon_{H\cdot}$ are the one-electron SCF orbital

Table II. Benzimidazole Vertical Ionization Energies and Modified CNDO/2 Eigenvalues below 21 eV I^v

I^v, eV	$-\epsilon$, eV	assign[a]	I^v, eV	$-\epsilon$, eV	assign
8.44	9.47	π_5	14.0	15.32	$C^2H; C^6C^7$
8.79[b]	9.91	π_4	14.55	16.34	$N^1C^{7a}C^{3a}; C^5C^6$
10.04	11.78	n_N	15.6	16.72	$C^7H; C^4H$
10.75	12.42	π_3		17.83	π_1
11.4	13.58	$C^{3a}C^4$ $C^5H; n_N$		19.16	$C^5H; C^2N^3$
12.18	13.99	C^4C^5 $C^6H; n_N$		19.43	$C^2N^1; C^6H$
12.9	14.06	π_2		22.23	N^1H

[a] σ functions are described according to their principal bond contributions beginning with σ_{17} at 15.32 eV; for example, $C^2H; C^6C^7$ is mainly carbon (2) to hydrogen and carbon (6) to carbon (7) bonding. [b] Shoulder.

Table III. A Comparison of Lone Pair Nitrogen Modified CNDO/2 Orbital Energies (ϵ_N), Electron Density at Nitrogen in the Lone Pair Orbital (q_N), and Solution pK_a (pK_{BH^+}) in Water

imidazole	$-\epsilon_N$	q_N	pK_{BH^+}[a]
benz-	11.78	0.80	5.53[b]
1,2-diMe	12.07	1.38	7.85[d]
1-Me	12.21	1.38	7.33[b]
2-Me	12.23	1.36	7.56[b]
H-	12.38	1.40	6.65[b]
1-Me, 5-Cl	12.43	1.16	6.23[c]
1-CH_3CO	12.80	0.82	3.6[d]

[a] pK_a are symmetry corrected by −log 2 for imidazole and 2-methylimidazole. [b] Reference 14a. [c] Reference 14b. [d] Reference 13.

energies of the amine radical cation and the H· atom, respectively.

$$|\Delta\epsilon| = \frac{C_{N\cdot}^2 \cdot 1^2 \cdot \beta^2}{|\epsilon_H - \epsilon_{N\cdot}|} \qquad (7)$$

At the level of Koopmans' theorem approximation $C_{N\cdot}^2$ of the radical cation may be replaced with C_N^2 of the amine. For reasons that will shortly become evident, we wish to examine the behavior of expression 7 when $C_{N\cdot}^2$ is constant. With the restriction of $C_{N\cdot}^2$ to a constant, eq 7 may be approximated by a binomial expansion which is truncated after the second term, eq 8.

$$|\Delta\epsilon| = \left|\frac{C_{N\cdot}^2\beta^2}{\epsilon_H} + \frac{\epsilon_{N\cdot}}{\epsilon_H^2}\right| \qquad (8)$$

This leads to (9) since all of the first term in (8) is constant with respect to δ^s.

$$\delta^s|\Delta\epsilon| = \frac{\delta^s|\epsilon_{N\cdot}|}{\epsilon_H^2} \qquad (9)$$

At this point it is evident that although $\epsilon_{N\cdot}$ and ϵ_H must be of similar magnitude (10–20 eV), $\delta^s|\epsilon_{N\cdot}|$ is unlikely to exceed a few electron volts. δ^sHV is therefore likely to be of the magnitude of 0.01 eV or within the experimental error with which I_n^v and PA may normally be determined, and a linear I^v–PA relationship may be observed.

If the value of expression 9 is not negligible, a further approximation may be made that substituent effects on amine and radical cation n orbital energies will be equal, as they differ only in a single term expressing the electron repulsion between two electrons in the same molecular orbital. This n molecular orbital electron repulsion term should be sensibly constant for substituents which produce only small perturbations in the amine.

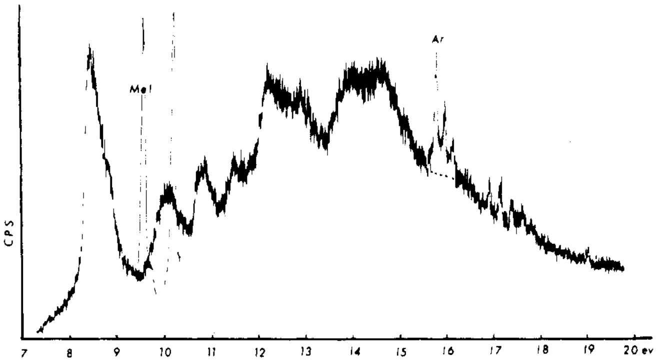


Figure 1. The photoelectron spectrum of benzimidazole calibrated against internal argon.

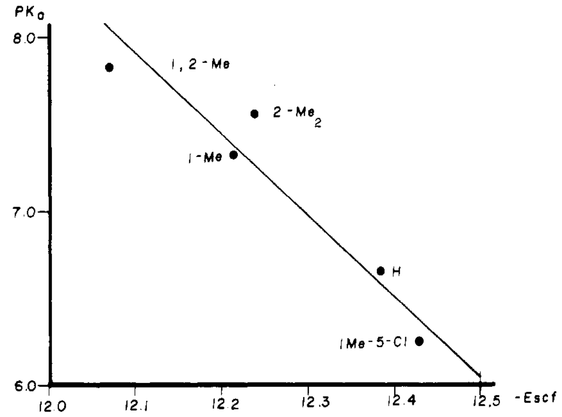


Figure 2. pK_a values of 1,2-dimethyl-, 2-methyl-, 1-methyl-, and 1-methyl-5-chloroimidazole and imidazole in water as a function of nitrogen lone pair orbital energies from modified CNDO/2 calculations.

Combining this last assumption that $\delta^s\epsilon_{N\cdot}$ equals $\delta^s\epsilon_N$ with Koopmans' theorem in the form $\delta^s\epsilon_N$ equals $-\delta^s I^v$ leads to expression 10 which is of the same form as eq 6.[9]

$$\delta^s PA = \delta^s(1 - 2\epsilon_H^{-2})I_n^v \qquad (10)$$

The conclusion from this result is that provided substituents are chosen such that within a series of substituted amines the value of C_N^2, and therefore the electron density on nitrogen in the SCF lone pair orbital, remains constant, a linear relationship between I_n^v and PA is to be expected.[9]

If the restriction of constant C_N^2 is lifted and the second term of eq 8 is considered to be negligible, $\Delta\epsilon$ and therefore HA might easily vary by as much as 1 eV, based for example on differences in ($2\cdot C_N^2$) calculated for various substituted imidazoles, Table III, and β_{NH} values of the magnitude 10 eV taken from modified CNDO/2 calculations on imidazoles and pyridines.[1]

The above conclusions, which are not out of keeping with chemical intuition that amine basicity should in some way depend on lone pair electron density, q_N, at nitrogen, may now be applied to the imidazoles.

Imidazole modified CNDO/2 n orbital energies (ϵ_N), calculated nitrogen lone pair electron densities at nitrogen (q_N), and symmetry corrected values for pK_{BH^+} in water are collected in Table III. In the previously studied substituted pyridines, q_N were remarkably constant between 0.8 and 1.0 electrons. In the imidazole series, however, q_N varies from 0.8 to 1.4 electrons.

As may be seen from Figure 2, a reasonable linear correlation does in fact exist between $-\epsilon_n$ and solution pK_a for those imidazoles 1 through 4 where q_N ranges between 1.2 and 1.4. The regression line of Figure 2 is given by eq 11.

$$\mathrm{p}K_a = 4.48\epsilon_{\mathrm{SCF}} + 62.01 \qquad (11)$$

1-Acetylimidazole and benzimidazole, for which q_n is 0.8, in contrast differ from this regression by 1.1 and 4.3 pK units, respectively.

If a linear I_n^v–pK_a correlation is assumed on the basis of the finding of a limited correlation of $-\epsilon_n$ with pK_a, it follows, as was previously pointed out in the pyridine series, that substituent effects on the changes in solvation energy between amine and protonated amine must be negligible or constant. Further, since the I^v–pK_a correlation is a linear ΔH^0 (gas phase) $- \Delta G^0_{\mathrm{soln}}$ expression, the results are supportive of the idea[10] that $\delta^s\Delta G^0_{(\mathrm{soln})}$ is a measure of $\delta^s\Delta H^0$ internal for amine protonation in solution.

Although the previous discussion indicates that constant lone pair orbital electron density at nitrogen is a requirement for linear I^v(n)–PA (or pK_a) correlations, the subject of what kinds of substituent interaction mechanisms will satisfy this requirement remains to be considered.

If we identify substituent inductive and field effects as those associated with changes in MO orbital energies due *only* to changes in diagonal elements, f_{ii}, of the final SCF Hartree–Fock matrix in the modified CNDO/2 calculation, the substituent effect on the n orbital energy is given by the familiar first order perturbation expression:

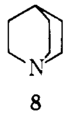
$$\delta^s\epsilon_n = \sum_i^{\mathrm{AO}} C_{in}^2 \delta f_{ii} \qquad (12)$$

The coefficients C_{in} in expression 12 are those of the *unsubstituted* amine, and the summation is over all contributing atomic orbitals on all atoms.

To a first order approximation of the change in energy, inductive and field effects will change ϵ_n without altering the value of $C_{\ddot{N}}$.[11] Further, since expression 12 is summed over all contributing atomic orbitals on all atoms, a change in ϵ_n can be brought about without any significant change in C_n or even f_{ii} (nitrogen). At this point it is also important to emphasize that substituent p–π resonance effects which alter the p_π electron density at nitrogen in planar aromatic molecules such as pyridine and imidazole are felt by the n orbital in the σ plane as an *inductive effect only* and will also therefore leave C_N unchanged in the first-order approximation to the change in energy. The point which is stressed here is that substituent inductive-field effects are expected to alter I_n^v and $-\epsilon_n$ without significant change in q_n (C_n), and under these conditions linear I^v–PA or pK_a correlations may be obtained, provided substituent perturbations are small enough to be treated as first-order perturbations. It remains only to identify substituent σ plane resonance effects as a substituent interaction mechanism which will produce a failure of a correlation of I^v (or $-\epsilon_n$) with PA.

Resonance effects appear in the final SCF Hartree–Fock matrix as non-zero off-diagonal elements between substituent orbitals and amine framework orbitals. Changes in lone pair orbital energy due to resonance effects have been separated into through space and through bond interactions by Hoffmann[12] and it is the latter which are of greatest importance here. Changes in orbital energy due to mixing between substituent orbitals and unsubstituted amine orbitals must be treated by a second order perturbation correction to the n orbital energy and an accompanying *first order* correction in the wave function. This first order change in the amine wave function will contain a change in C_N and of course q_n. Therefore we expect substituent resonance effects in the σ plane of a planar molecule or the through bond through space interactions as described by Hoffman to produce failures in any linear I_n^v–PA(pK_a) correlation. This is the case in 1-acetylimidazole where substantial mixing between n_o and n_N orbitals was found in the CNDO/2 calculations. Application of eq 11 to the pK_a of **5** provides a reasonable calculated value of $-\epsilon_n$ of 13.04 eV for **5** to be expected in the absence of through bond mixing between oxygen and nitrogen lone pair orbitals.

It needs to be emphasized that although "through bond interactions" may have a profound effect on orbital energies, *they* do *not* appreciably affect the overall pK_a or PA of an acid or base. This may most readily and simply be appreciated by realizing that since both amine and protonated amine represent closed shell molecules, the difference in energy between the two may presumably be calculated to the same accuracy utilizing *either* SCF delocalized orbitals *or* an equivalent set of bond localized functions. The truth of this statement is evident in comparing the PA's of quinuclidine and 1,4-diazabicyclooctane, **8** and **9** below, with their I_n^v.[3] The basicity of **9** is less than that of **8** because of N atom mutual inductive and field effects even though I_n^v of **9** is less than **8** because of the through bond interactions of the identical localized nitrogen lone pair orbitals of **9** which in fact produces two split SCF n orbitals.



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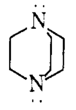
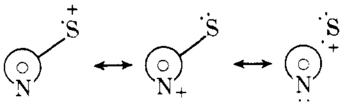
I^v = 185.6 kcal; PA = 235.7 kcal



9

I^v = 173.4 kcal; PA = 233 kcal

This paper is concluded with the observation that its results are in agreement with traditional models of physical organic chemistry which focus on the effect of substituent on the energies of the radical cation and the protonated amine and which regard the I_n^v–PA correlation as a linear enthalpy relationship. To the extent that resonance structures such as **10** through **12** are necessary to describe the energy of the radical cation but are unimportant in determining the energy of the protonated amine, there must be a failure of any linear substituent enthalpy–enthalpy relation between the two reactions, ionization and protonation of the ring. If substituent effects on the enthalpdies of both reactions are controlled only by inductive-field effects, there is then a single common interaction mechanism in both reactions, and a linear energy relationship is to be expected. There is at this level a complete correspondence between the requirements for a substituent linear energy correlation between I^v and PA (or pK_a) as developed by perturbation MO methods and the traditional extrathermodynamic requirements of physical organic chemistry.



10 **11** **12**

Experimental Section

Compounds were provided by F. A. Walker of San Francisco State University and their properties are described in ref 13. The pK_a values of **1** through **7** were obtained from ref 13 and 14.

Photoelectron spectra calibrated against argon were determined at the Institute for Inorganic Chemistry, University of Frankfurt, on a Perkin-Elmer PE spectrometer with heated inlet after first calibrating the spectrometer against argon (15.76 eV) and methyl iodide (9.54 eV).

Modified CNDO/2 calculations were carried out using a modified CNDO/2 program supplied by H. Bock and described in ref 15. The geometry of imidazole was taken from ref 16.

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Registry No.—**1**, 288-32-4; **2**, 616-47-7; **3**, 693-98-1; **4**, 1739-84-0; **5**, 2466-76-4; **6**, 1546-79-8; **7**, 51-17-2; 5-chloro-1-methylimidazole, 872-49-1.

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(9) If $\delta^s HA^v$ is assumed to be only proportional to $\delta^s \Delta\epsilon$ by a constant κ, eq 10 becomes $\delta^s PA = \delta^s(1 - \kappa\epsilon_H^{-2})I_n^v$ without any changes in the conclusions of this paper.
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Substituent Effects on Pyridine Nitrogen Reactivity

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The observations of Johnson, Roberts, and Taylor which were interpreted to indicate that electron acceptor substituents exert only a localized (field and/or inductive) effect can be accounted for by a constant delocalized (resonance) effect. Contrary to the claim of Johnson et al. and in accord with the observations of Ehrenson, Brownless, and Taft, the LD (extended Hammett) equation is much more effective in describing substituent effects on pyridine nitrogen reactivity than is the simple Hammett equation. This conclusion is based on correlations obtained with both equations for 13 sets of 4-substituted pyridine acidity data and 5 sets of rate constants for their reaction with alkyl halides.

In a recent publication, Johnson, Roberts, and Taylor[1] have made an important claim. They state that substituents which are electron acceptors by both the localized (field and/or inductive) and delocalized (resonance) electrical effects (LaDa groups) exert only a localized effect upon the reactivity at the nitrogen atom of substituted pyridines. On the basis of the evidence they cite in support of this claim, they have come to two important conclusions. They are:

1. The validity of multiparameter correlation equations such as the LD (extended Hammett) equation and the Yukawa–Tsuno equation is in doubt. The former equation in the form

$$(Q_X/Q_H) = L\sigma_{IX} + D\sigma^*_{RX} \tag{1}$$

was reported by Ehrenson, Brownlee, and Taft[2] to be the best choice for the correlation of reactivity of substituted pyridines.

2. The best equation for correlating data for substituted pyridine reactivities is the Hammett equation

$$Q_X = \rho\sigma_X + h \tag{2}$$

When eq 2 is applied, σ_I constants are used for LaDa groups and σ_m or σ_P constants for all other groups.

The first of these conclusions is of the utmost importance. An enormous number of correlations of chemical reactivities, physical properties, and biological reactivities have been carried out with multiparameter equations. It is therefore of great importance to determine whether the conclusions of Johnson et al. are warranted. The arguments cited in favor of the conclusions are: The equation

$$\frac{\log (k_X/k_H)_P}{\log (k_X/k_H)_Q} = c \tag{3}$$

where P refers to the ionization of pyridinium ions, Q refers to the ionization of quinuclidinium ions, X may be any LaDa substituent, H is the hydrogen point, the k's are ionization constants, and c is a constant, is obeyed. The equation

$$pK_{a(X,P)} = a_1[pK_{a(X,Q)}] + a_0 \tag{4}$$

is obeyed when only LaDa groups are considered. The only LaDa groups available for study were NO_2, CN, CO_2Me, and Ac. The quantity defined by the equation

$$\frac{\log (k_{4(Ac)}/k_H)}{\log (k_{3(Ac)}/k_H)} = \frac{\sigma_{4(Ac)}}{\sigma_{3(Ac)}} = \alpha \tag{5}$$

has a value of 0.95 ± 0.11. This value was obtained by examination of a number of reactions. A correlation of pK_a data for 4-substituted pyridinium ions with eq 2 using σ_I for LaDa groups and σ_P constants for all other groups gave excellent results with $r = 0.998$ and $s\gamma = 0.12$.

Examination of the σ^+_R values[3] for all the LaDa groups we have studied shows that they have a mean value of 0.104 with a standard error of 0.0262. The groups considered by Johnson et al., CN, NO_2, Ac, and CO_2Me, have a σ^+_R value of 0.0875 with a standard error of 0.0222. It follows then, that for the groups studied σ^+_{RX} is constant, and therefore eq 1 may be rewritten as

$$\log (k_X/k_H)_P = L_p\sigma_{IX} + C^* \tag{6}$$

where