Application of the Partitioning of Energy in the MNDO Method to the Study of the Basicity of Imidazole, Pyrazole, Oxazole, and Isoxazole

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The technique of energy partitioning of Fischer and Kollmar has been extended to the MNDO SCF-MO method and used in an effort to ascertain the main factors which determine the greater basicity of imidazole and oxazole relative to pyrazole and isoxazole, respectively. The importance of the different degree of destabilization of the five-membered ring π bonding in these azoles upon protonation is specially emphasized in relation to their relative basicity. Furthermore, it is found that the degree of destabilization of the π bonding can be ascribed to the amount of π electron charge density localized on the heteroatoms after protonation. An interpretation for this result is given in terms of the mutual electrostatic field effect due to the cores of the nearest-neighbor atoms.

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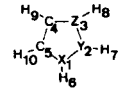
A clear understanding of the greater basicity of imidazole, $pK_a = 6.95$ (1), and oxazole, $pK_a = 0.8$ (1), relative to pyrazole, $pK_a = 2.47$ (2), and isoxazole, $pK_a = -2.03$ (1), respectively, has been a long-standing problem in heterocyclic chemistry. Moreover, the stronger basicity of imidazole relative to pyrazole is in striking contrast with the small difference between their second or acidic pK_a, equal to 14.52 (3) and 14.0 (2), respectively.

Seeking a plausible explanation for the above basicity differences into the original chemical literature as well as into the main books on heterocyclic chemistry, we have realized that only speculative arguments, not "self-

Table I

Optimized Geometries for 

bond	1	2	3	4	1·H⁺	2·H⁺	3·H⁺	4·H⁺	1⁻	2⁻
X_1-Y_2	1.396	1.333	1.364	1.301	1.369	1.350	1.336	1.320	1.371	1.299
Y_2-Z_3	1.340	1.354	1.336	1.351	1.369	1.384	1.364	1.377	1.371	1.380
Z_3-C_4	1.395	1.441	1.398	1.449	1.410	1.415	1.417	1.429	1.374	1.416
C_4-C_5	1.392	1.395	1.391	1.387	1.390	1.415	1.390	1.407	1.414	1.416
C_5-X_1	1.399	1.398	1.368	1.373	1.410	1.384	1.377	1.366	1.374	1.380
X_1-H_6	0.993	1.003	-	-	1.005	1.014	-	-	-	-
Y_2-H_7	1.085	-	1.086	-	1.090	1.014	1.095	1.022	1.085	-
Z_3-H_8	-	1.084	-	1.082	1.005	1.089	1.007	1.090	-	1.082
C_4-H_9	1.082	1.078	1.081	1.077	1.085	1.084	1.085	1.083	1.082	1.078
C_5-H_{10}	1.079	1.082	1.082	1.083	1.085	1.089	1.088	1.091	1.082	1.082
angle										
$Z_3Y_2X_1$	110.2	106.2	112.4	109.2	106.3	109.5	108.6	112.0	114.4	109.6
$C_4Z_3Y_2$	106.4	110.3	105.3	108.4	110.3	107.2	108.8	105.8	103.9	108.8
$C_5C_4Z_3$	110.4	105.1	108.2	103.4	106.6	106.6	104.8	105.1	108.9	103.3
$X_1C_5C_4$	105.1	105.6	107.8	108.5	106.6	107.2	108.7	109.4	108.9	108.8
$Y_2X_1C_5$	107.9	112.9	106.3	110.5	110.3	109.5	109.2	107.8	103.9	109.6
$Y_2X_1H_6$	126.4	120.3	-	-	124.9	121.5	-	-	-	-
$Z_3Y_2H_7$	126.5	-	128.2	-	126.8	129.0	129.4	131.0	122.8	-
$Y_2Z_3H_8$	-	121.7	-	122.6	124.9	121.4	125.9	122.5	-	122.0
$Z_3C_4H_9$	120.5	126.8	121.5	127.6	121.9	126.7	122.6	127.5	122.0	128.3
$C_4C_5H_{10}$	132.3	132.2	134.1	133.8	131.5	131.4	133.7	133.5	129.1	129.2

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consistent" in most cases, have been given. Thus, Schofield, *et al.* (4) state "...imidazole is in fact a surprisingly strong base, presumably because of the symmetry of its mesomeric cation". The same explanation is offered by two other excellent books (5,6), although Acheson (6) points out "...similar structures can be written for the cation derived from pyrazole, but in contrast this compound is a weaker base". In our opinion, there are however two books which, either true or not, give reasonable explanations (7,8). Palmer (7) suggests that the greater basicity of imidazole relative to pyrazole is due to the fact that the nitrogen atoms, which carry the bulk of the positive charge in the imidazolium cation, are further apart in imidazole, so the repulsion effects should be smaller than in pyrazole. On the other hand, Katritzky and Lagowski (8) afford a good discussion based on the relative importance of both mesomeric and inductive effects, the rather smaller basicity of the pyridine-like nitrogen of pyrazole being mainly attributed to the inductive effect of its pyrrole-like nitrogen (9).

In connection with the basicity of imidazole it is noteworthy that, as a side chain of the amino acid histidine, the imidazole ring plays an important role of many enzymes (10), where it acts, at the physiological p*H*, either as a proton donor or acceptor (11). It would therefore be of interest from the theoretical point of view as well as from its biological implications to find the origin of "the remarkable basicity of imidazole".

Although understanding of the origin of the differences in the basicities of the above heterocycles could be enhanced by theoretical studies, little effort has been expended on quantum mechanics calculations of this problem. Previous semiempirical (12-18) and *ab initio* (19-25) SCF-MO calculations on imidazole, pyrazole, oxazole, and isoxazole have been generally restricted to molecular properties such as dipole moment, quadrupole moment, diamagnetic susceptibility, diamagnetic shielding, electric field gradient, nuclear quadrupole coupling constant, electronic charge distribution, ionization potentials and binding energy. The only SCF-MO calculation on the trend observed in their basicities appears to be one reported by Berthier *et al.* (26) using the electrostatic molecular potential model, computed from minimum basis *ab initio* wavefunctions; these authors found a qualitative correlation between the relative depths of the electrostatic potential energy minima found near the pyridine-like nitrogen of these azoles and pK_a values. In addition to the correct forecast of the ordering of basicities, however, a theory should be able to interpret the results, or give reasons why such results were obtained. Toward this goal, we have applied the method of partitioning the total energy from MNDO SCF-MO calculations (27) into one- and two-center terms, proposed originally by Fisher and Kollmar (28) within the CNDO method, to the study of the basicity of the above five-membered heterocycles. Employing this method, we have been able to gain insight into the origin of the greater basicity of imidazole and oxazole with regard to pyrazole and isoxazole, respectively.

Theoretical Approach.

In the MNDO method (27) the total energy of a molecule (E_t) taking into account only the valence-electrons of atoms is expressed as a sum of the electronic valence energy (E_{el}) and the repulsions (E^C_{AB}) between the core charges at atoms A and B:

$$E_t = E_{el} + \sum\sum_{A<B} E^C_{AB} \qquad \text{(eq 1)}$$

Owing to the NDDO approximation (29), the basis of MNDO, the total energy also can be partitioned into one- and two-center terms as follows:

$$E_t = \sum_A E_A + \sum\sum_{A<B} E_{AB} \qquad \text{(eq 2)}$$

The monocentric terms (E_A) can be further partitioned into one-center core attraction terms (E^U_A), coulomb terms (E^J_A), and exchange terms (E^K_A):

$$E_A = E^U_A + E^J_A + E^K_A \qquad \text{(eq 3)}$$

Analogous partitioning of the bicentric terms (E_{AB}) into two-center core attraction terms (E^V_{AB}), coulomb terms (E^J_{AB}), exchange terms (E^K_{AB}), resonance terms (E^R_{AB}), and core repulsion terms leads to the following expression:

$$E_{AB} = E^V_{AB} + E^J_{AB} + E^K_{AB} + E^R_{AB} + E^C_{AB} \qquad \text{(eq 4)}$$

The detailed expressions of the above (eq 3) one-center energy components, in terms of standard monocentric integrals and elements of the bond order matrix, are identical to those derived for MINDO method (30); a brief outline of their physical meaning follows. E^U_A is the total one-electron energy of the electrons on atom A, E^J_A is the electronic repulsion of the electrons on atom A, and E^K_A is the corresponding electronic exchange interaction energy. It should be noted that for a stable molecule E_A is generally less negative than the energy of the valence electrons of free atom (E°_A). Thus, E_A-E°_A represents the change of energy of atom A in going from a free atom to an atom in a molecule. This energy change is attributable to a charge flow between A and its surroundings that gives rise to non-vanishing two-center terms E_{AB}, which are negative or positive depending on a bonding or antibonding situation, respectively.

The deviation of the expressions for the two-center energy components in eq 4, not previously performed within NDDO approximation, is straightforward and will

be reported elsewhere. The physical meaning of these terms may be interpreted as follows: E^V_{AB} is the potential energy of electrons on atom A in the field of nucleus B plus that of the electrons on atom B in the field of nucleus A; E^J_{AB} is the electronic repulsion of the electrons on the atoms A and B; E^K_{AB} is the electronic exchange interaction of the electron on the atoms A and B; E^R_{AB} is the contribution of the one-electron core resonance integrals to the energy of the A-B bond, representing the main feature of the covalent bond; and the E^C_{AB} is the above mentioned energy repulsion between the core charges of atoms A and B.

As Dewar and Lo have already noted (30), the partitioning of the total energy into one- and two-center terms leads to the traditional picture of molecules as composed of atoms linked by chemical bonds. E_{AB} provides a good measure of bond strength, both from its sign and from its magnitude. A large negative value for E_{AB} implies a strong bonding while a positive value implies an antibonding interaction (30).

In order to gain insight into the nature of the energy contribution to E_{AB} that determines the bonding or antibonding character of the overall interactions between a pair of atoms in a molecule, it is convenient to group the net coulomb interaction and the electronic exchange interaction into a single term (E^E_{AB}) written in the form:

$$E^E_{AB} = E^V_{AB} + E^J_{AB} + E^C_{AB} + E^K_{AB} \qquad \text{(eq 5)}$$

E^E_{AB} represents the *net electrostatic interaction*, including the exchange "correction", between atoms A and B. The total two-center energy term associated with atoms A and B is written then as

$$E_{AB} = E^E_{AB} + E^R_{AB} \qquad \text{(eq 6)}$$

Early studies on the total energy partitioning by Fischer and Kollmar (28) and others (30-32) have indicated that E^E_{AB} is generally relatively small as compared with the value of the contributing terms (eq 5); thus the exchange contribution, electron-core attractions, and electron-electron and core-core repulsions quite precisely cancel each other as contributions to the two-center terms E_{AB}. Therefore, the energy contribution to E_{AB} that determines the effective bond energy of the A-B bond is attributed to the one-electron core resonance integrals term E^R_{AB}.

Finally, it may be useful to note that the terms of E^R_{AB} are directly related to the overlap components of the population analysis of the wave function developed by Mulliken (33). Fischer and Kollmar (28) have described the analysis of the terms E^R_{AB} as an overlap population analysis in which the individual terms are weighted with an energy factor. Since a Mulliken overlap population analysis is not suited for wave functions computed from MO methods in which the diatomic overlap is neglected (*i.e.*, CNDO, INDO, MINDO, MNDO), the terms E^R_{AB} can be employed as an alternative approach to the measure of the bond electron densities between any two atoms.

Calculations.

All numerical values in the following sections were obtained using a modified version of the MNDO program, reprogramed for an UNIVAC 1108 computer by one of us (S.O.). The modifications allow for the calculation of the various energy terms in the partitioning method. In all cases the geometries were calculated by minimizing the total energy with respect to *all* geometrical parameters, using the standard DFP (Davidon-Fletcher-Powell) procedure.

Results and Discussion.

Equilibrium Geometries, Heats of Formation, and Dipole Moments.

The optimized equilibrium geometries for imidazole (**1**), pyrazole (**2**), oxazole (**3**), and isoxazole (**4**), as well as for their azolium ions (**1**·H^+, **2**·H^+, **3**·H^+, and **4**·H^+), formed by protonation of the pyridine-like nitrogen, are given in Table I. For the sake of comparison, the calculated geometries for the anions derived from pyrrole-like nitrogen deprotonation of **1** (**1**$^-$) and **2** (**2**$^-$) are also given in Table I. As expected, all these molecules are found to be planar.

The calculated structure for imidazole is very close to that recently reported by Del Bene and Cohen (34), obtained from an *ab initio* STO-3G basis set calculation, although the C_4-C_5 bond distance is in our case somewhat longer. For **2**, the optimized geometry is in good agreement with the geometrical structure obtained from microwave spectroscopy (35), all bond lengths (except N_1-C_5) and

Table II

Dipole Moments and Heats of Formation

	μ_D, D		ΔH°_f, kcal/mole	
	calcd	exptl	calcd	exptl
1	3.48	3.8 ± 0.4 (a)	33.2	30.6 ± 1.8 (e)
2	2.11	2.2 (b)	45.4	43.3 ± 2.1 (e)
3	1.54	1.5 (c)	−8.3	−3.7 ± 0.1 (f)
4	2.73	2.8 (d)	19.2	18.8 ± 0.1 (f)

(a) J. H. Griffiths, A. Wardley, V. E. Williams, N. L. Owen, and J. Sheridan, *Nature*, **216**, 1301 (1967); see also P. Mauret, J. P. Fayet, and M. Fabre, *Bull. Soc. Chim. France*, 1675 (1975); (b) W. R. Kirchoff, *J. Am. Chem. Soc.*, **89**, 1312 (1967); (c) See R. Lakhan and B. Ternai, in "Advances in Heterocyclic Chemistry", vol. XVII, A. R. Katritzky and A. J. Boulton, eds., Academic Press, New York, 1974, p. 158; (d) J. Kraft and S. Walker, in "Physical Methods in Heterocyclic Chemistry", vol. IV, A. R. Katrtizky, ed., Academic Press, New York, 1971, p. 246; (e) A. F. Bedford, P. B. Edmonson, and C. T. Mortimer, *J. Chem. Soc.*, 2927 (1962); (f) D. G. McCormick and W. S. Hamilton, *J. Chem. Thermodyn.*, **10**, 275 (1978).

angles being ±0.02 A and ±2°, respectively, within the experimental values.

In Table II the calculated dipole moments (μ_D) and heats of formation (ΔH_f°) for compounds **1** to **4** are compared with available experimental data. These results, which give evidence of the accuracy and reliability of the MNDO method when applied to the calculation of molecular properties of the above heterocyclic ring systems, prompted us to attempt the understanding of the factors that determine the basicity of azoles **1** to **4** by means of such a theoretical procedure.

Table III

Calculated Proton Affinities (PA) and Deprotonation Energies (DE) (a)

	PA	DE
1	173.1	300.5
2	154.0	294.9
3	160.2	-
4	143.9	-

(a) All values in kcal/mole.

Proton Affinities and Deprotonation Energies.

The calculated gas phase proton affinities (PA's) for heterocycles **1** to **4** and the deprotonation energies (DE's) of **1** and **2** are given in Table III. The gas phase PA's were computed as the difference between the total energies of the above azoles and the corresponding azolium ions **1**·H$^+$ to **4**·H$^+$. Likewise, the gas phase DE's were calculated as the difference between the total energies of anions **1**$^-$ and **2**$^-$ and the corresponding azoles **1** and **2**. No precise experimental data have been given for the gas phase PA of these compounds.

In order to compare the free energies of protonation in solution obtained from pK_a values with the PA values in gas phase it is necessary to assume that the entropy variations and the changes in solvation energy following protonation are very similar along the series studied. In our case, such assumptions do not seem to be unrealistic, at least within each pair of isomers considered (36). The qualitative accordance between the calculated PA and the pK_a values is gratifying, MNDO correctly predicting azoles **1** and **3** to be more basic than azoles **2** and **4**, respectively. On the other hand, the small difference between the calculated DE of **1** and **2** is consistent with the greatly reduced difference in their second pK_a values.

Using the calculated PA's (Table III) and heats of formation (Table II) it will be seen that the energy difference between **1** and **2** (12.2 kcal/mole) increases by 19.1 kcal/mol upon protonation of both azoles. Similarly, the extra stability of **3** with respect to **4** (27.5 kcal/mol) increases by 16.3 kcal/mol following protonation.

Partitioning of Total Energy.

The total energy (E_t), total sums of one-center and two-center terms (ΣE_A and ΣE_{AB}, respectively), and a breakdown of the latter terms into their net electrostatic interactions and core resonance integrals components (ΣE_{AB}^E and ΣE_{AB}^R, respectively) for azoles **1** to **4** and azolium ions **1**·H$^+$ to **4**·H$^+$ are given in Table IV. The last column of Table IV also shows the π bond components of the total sum terms ΣE_{AB}^R, denoted by $\Sigma(E_{AB}^R)_\pi$.

A detailed examination of the changes in the above partitioned energy terms in passing from the neutral molecules to the corresponding cations reveals several interesting trends:

(i) The protonation of azoles **1** to **4** involves a moderate change in the total sum of the one-center terms and a substantial change in the total sum of the two-center terms. This result of course agrees with current intuition which attributes the lowering of the total energy of azoles **1** to **4** upon protonation of the pyridine-like nitrogen to the formation of a new N-H bond, besides the apparition of extra two-center interaction terms.

(ii) Regarding the electrostatic and core resonance components of the total sum of the two-center terms, it will be seen that following protonation there is a large change in the value of the former, but that this is largely out-

Table IV

Total Energy and Total Sums of One-Center and Two-Center Energies (a)

	E_t	ΣE_A	ΣE_{AB}	ΣE_{AB}^E	ΣE_{AB}^R	$\Sigma(E_{AB}^R)_\pi$
1	−853.917	−710.583	−143.334	2.204	−145.539	−11.081
1·H$^+$	−861.422	−708.982	−152.440	6.228	−158.668	−10.713
2	−853.389	−710.775	−142.614	2.310	−144.924	−10.706
2·H$^+$	−860.067	−709.320	−150.747	6.231	−156.978	−9.793
3	−954.522	−824.894	−129.628	4.241	−133.869	−11.140
3·H$^+$	−961.467	−823.133	−138.334	8.802	−147.136	−10.823
4	−953.329	−825.371	−127.958	4.333	−132.289	−10.503
4·H^3	−959.570	−824.080	−135.490	8.442	−143.932	−9.500

(a) All values in eV.

weighted by an even larger opposing change in the value of the latter component. Undoubtedly the increase in the value of the net electrostatic interactions is primarily attributable to the increase in the total core repulsion energy due to the presence of an extra core charge in the molecule of the azolium ions. On the other hand, the substantial increase in absolute value of the total sum of the core resonance terms can be mainly ascribed to the additional energy term E^R_{AB} associated to the new N-H bond. Accordingly, the σ bond component of ΣE^R_{AB} exhibits nearly the same increase in absolute magnitude as the whole ΣE_{AB} term itself. Therefore, the lowering found in the total sum of the two-center energy terms is primarily due to an energy stabilization of the σ bonding in the azoles upon protonation.

(iii) The π bond component of the total sum of the core resonance integrals energy terms undergoes a significant decrease in absolute value. Thus, the protonation of azoles **1** to **4** involves a destabilization of the π bonding of their five-membered rings. As it will be shown below, this interesting result plays an important role in connection with the origin of the greater basicity of imidazole and oxazole as compared with pyrazole and isoxazole.

Protonation of Imidazole *versus* Pyrazole.

Now it is worthwhile to examine the relative changes in the partitioned energy terms in Table IV on passing from imidazole to imidazolium ion as compared with the corresponding changes on passing from pyrazole to pyrazolium ion. This may allow us to ascertain which energy terms are responsible for the extra stabilization (0.827 eV) of imidazole relative to pyrazole upon protonation.

It will be seen that the change in the ΣE_A value is nearly the same for both azoles. Accordingly, the most significant difference between the protonation of **1** and **2** is reflected by the change in the total sum of the two-center terms; in fact, the change in the ΣE_{AB} value is calculated to be 0.973 eV larger for **1** as compared with that of **2**. Since the ΣE^E_{AB} component of ΣE_{AB} increases about the same amount for both azoles, it becomes clear that the difference in the change of ΣE_{AB} can be related directly to the difference (1.075 eV) in the change of the ΣE^R_{AB} component. This can in turn be related mainly to the difference in the change of the π bond component of the latter term. This follows from the fact that the calculated destabilization of the π bond component of ΣE^R_{AB} is 0.545 eV larger for the protonation of **2** as compared with that of **1**. One may argue that this energy change difference only amounts about the 51% of the total difference found for the change of the ΣE^R_{AB} value. However, the point to be emphasized here is that the π bond contribution to these terms is only about the 8% in both azoles. Thus, although the π bond contribution to the ΣE^R_{AB} value is rather small as compared with that of the σ bond component, it has a large effect on the greater stabilization of **1** relative to **2** upon protonation. It therefore seems very likely that *the greater basicity of imidazole with regard to pyrazole can be primarily ascribed to the extra destabilization of the π bonding in the latter compound after protonation.*

In order to clarify the essential features of the π bonding reorganization caused by the protonation of both azoles, it may be worthwhile to briefly discuss the changes undergone by the π bond components of the terms E^R_{AB} for the five-membered rings upon protonation. To simplify the discussion we only consider the π bond components of E^R_{AB} for pairs of atoms which are bonded to each other. These are given in Table V for azoles **1** to **4** and azolium ions **1**·H$^+$ to **4**·H$^+$.

It will be seen from Table V, as regards the π bond components of the terms E^R_{AB}, that the protonation of nitrogen N_3 of imidazole involves a substantial destabilization (0.725 eV) of the C_2-N_3 bond, a corresponding stabilization (0.628 eV) of the N_1-C_2 bond, a moderate destabilization (0.354 eV) of the N_3-C_4 bond, and a small stabilization (0.117 eV) of the C_4-C_5 bond, whereas the N_1-C_5 bond remains nearly constant. The net effect is a rather small

Table V

π Bond Component of Two-Center Terms E^R_{AB} for Nearest-Neighbor Pair Interactions (a)

	X_1-Y_2	Y_2-Z_3	Z_3-C_4	C_4-C_5	C_5-X_1
1	−1.964	−3.317	−2.076	−2.446	−1.766
1·H$^+$	−2.592	−2.592	−1.722	−2.563	−1.722
2	−2.028	−3.280	−1.534	−2.389	−2.001
2·H$^+$	−1.379	−2.411	−2.009	−2.009	−2.411
3	−1.912	−3.503	−1.914	−2.559	−1.701
3·H$^+$	−2.553	−2.822	−1.588	−2.639	−1.673
4	−1.683	−3.516	−1.333	−2.587	−1.834
4·H$^+$	−1.086	−2.681	−1.748	−2.260	−2.080

(a) All values in eV.

destabilization (0.368 eV) of the π bonding for the five-membered imidazole ring.

If we can regard the energy terms E^R_{AB} as a measure of the bond electron density between the pair of atoms A and B, the essential features of the above results may be interpreted qualitatively in terms of the π bond electron densities as follows: the C_2-N_3 bond shows a substantial loss of π bond electron density upon protonation of nitrogen N_3 while the N_1-C_2 bond reflects an accompanying increase. It is plausible that the π bond electron density lost from C_2-N_3 bond should contribute to increase the π electron charge density at nitrogen N_3 in order to palliate the σ electron charge density lost from this atom upon protonation, while the increase of the π bond electron density in the N_1-C_2 bond should reflect on accompanying decrease of the π electron charge density at nigrogen N_1. The calculated total and π electron charge distributions for **1** and **1**·H^+, shown in Table VI, fully support this interpretation. Specifically, the nitrogen N_3 shows a loss (0.377) of σ electron charge density upon protonation at the same time as the corresponding π electron charge density increases (0.323), while the nitrogen N_1 loses π electron density (0.095). In other words, *the π lone pair on nitrogen N_1 contributes significantly to the delocalization of the positive charge which arises on nitrogen N_3* upon protonation.

In keeping with the above reorganization of the π system, the N_1-C_2 bond length should decrease and the C_2-N_3 bond length should increase after protonation of imidazole. This is, indeed, just what we observe from Table I. Thus, all the above results indicate, not unexpectedly, that the imidazolium cation can be adequately represented by the structure **5**.

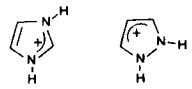
Next we turn to the π bonding reorganization accompanying protonation of pyrazole. It will be seen from Table V, as regards the π components of the terms E^R_{AB}, that the protonation of nitrogen N_2 of pyrazole involves a substantial destabilization of the N_2-C_3 and N_1-N_2 bonds (0.869 eV and 0.649 eV, respectively), a moderate destabilization (0.380 eV) of the C_4-C_5 bond, and a moderate stabilization of C_3-C_4 and N_1-C_5 bonds (0.475 eV and 0.410 eV, respectively). The net effect is a considerable destabilization (0.913 eV) of the π bonding for the pyrazole ring.

Recalling once again the assumed correlation between the energy terms E^R_{AB} and the bond electron densities, the reorganization of the π bonding for the pyrazole ring may be qualitatively interpreted in terms of the bond electron densities as follows: the N_2-C_3 and N_1-N_2 bonds show a substantial loss of π bond electron density upon protonation of nitrogen N_2 at the same time as the C_4-C_5 bond shows moderate decrease of π bond electron density and the C_3-C_4 and N_1-C_5 bonds reflect a corresponding increase. Furthermore, the calculated total and π electron density distributions for **2** and **2**·H^+, as seen in Table VI, indicates that following protonation of pyrazole the nitrogen N_2 shows a loss (0.367) of σ electron charge density at the same time as the corresponding π electron charge density increases (0.376), while the π electron charge density at nitrogen N_1 shows a slight increase (0.005). The most significant feature here is this extremely small increase of the π electron charge density at nitrogen N_1. This result is in sharp contrast with that found for the protonation of imidazole, where the nitrogen N_1 showed a decrease (0.095) of π electron charge density. This means that the π lone pair on nitrogen N_1 of pyrazole does not appreciably contribute to the delocalization of the positive charge which arises on nitrogen N_2 upon protonation. Instead, there is a substantial shift of π bond electron density from the N_1-N_2 and N_2-C_3 bonds to the nitrogen N_2 $2p_\pi$ atomic orbital, that palliates the σ electron charge density lost from this atom, at the same time as the π bond electron density in the C_4-C_3 bond is being increased at the expense of that of C_4-C_5 bond. In keeping with these π bond electron density changes, in passing from **2** to **2**·H^+, the N_1-N_2 and N_2-C_3 bond lengths should increase at the same time as the C_3-C_4 and C_4-C_5 bond lengths should decrease and increase, respectively. This is, indeed, just what we observe from Table I. Thus, the pyrazolium ion can be satisfactorily represented by the structure **6**.

Table VI

Calculated Total and π Electron Charge Densities on the Atoms

	X_1		Y_2		Z_3		C_4		C_5						
	total	π	total	π	total	π	total	π	total	π	H_6	H_7	H_8	H_9	H_{10}
1	5.248	1.630	3.945	1.002	5.230	1.212	4.063	1.112	4.062	1.044	0.791	0.873	-	0.896	0.893
1·H^+	5.176	1.535	3.788	0.886	5.176	1.535	3.969	1.022	3.969	1.022	0.726	0.805	0.726	0.832	0.832
2	5.176	1.599	5.126	1.228	4.056	1.003	4.173	1.125	4.002	1.044	0.772	-	0.894	0.906	0.896
2·H^+	5.135	1.604	5.135	1.604	3.824	0.851	4.155	1.092	3.824	0.851	0.709	0.709	0.833	0.844	0.833
3	6.137	1.720	3.931	0.965	5.226	1.198	4.066	1.031	4.049	1.087	-	0.843	-	0.881	0.868
3·H^+	6.052	1.653	3.733	0.814	5.185	1.514	3.982	1.026	3.943	0.994	-	0.772	0.713	0.818	0.804
4	6.056	1.724	5.094	1.213	4.045	0.960	4.175	1.110	3.986	0.994	-	-	0.880	0.893	0.870
4·H^+	5.985	1.749	5.129	1.585	3.772	0.768	4.165	1.090	3.815	0.808	-	0.681	0.819	0.829	0.804



5 6

Figure

An understanding of the relative destabilizations of the π bonding of imidazole and pyrazole upon protonation, and hence of their relative basicity, is now possible. *The destabilization of the π bonding for pyrazole is larger than for imidazole because the π lone pair on the pyrrole-like nitrogen of the former compound does not appreciably contribute to the delocalization of the positive charge that appears after protonation of the pyridine-like nitrogen.*

The question naturally arises: Why the π lone pair on the nitrogen N_1 of pyrazole does not contribute to the positive charge delocalization? The explanation lies on the fact that the close proximity of the two atoms with the largest core charges in $\mathbf{2}\cdot H^+$ prevents the shift of the π electron density from these atoms toward the nearest-neighbor carbon atoms. This is mainly due to the strong electrostatic attraction between the π charge density on a nitrogen atom and the core charge of the other nitrogen atom. It is therefore a purely electrostatic effect due to direct electrostatic interaction across space rather than to polarization of the intervening bond, *i.e.*, due to the *mutual field effect* of the cores of both heteroatoms rather than to the classical *inductive effect.*

The physical situation depicted here may be quantitatively emphasized by considering the numerical value of the potential energy of the π electrons on nitrogen N_1 due to the electrostatic field of the core charge of the atoms adjacent to that nitrogen in pyrazolium and imidazolium ions. To this end, we have calculated the two-center one-electron attraction energy between an electron in the $2p_\pi$ atomic orbital on nitrogen N_1 and the core charge of nitrogen N_2 in $\mathbf{2}\cdot H^+$, and the core charge of carbon C_5 in $\mathbf{1}\cdot H^+$, using the MNDO expression for these terms ($V_{\mu\mu,B}$) (29). The numerical values are -40.618 eV and -31.082 eV, respectively. These results provide strong support to the above interpretation of the origin of the lack of an appreciable contribution of the π electron charge density on the nitrogen atoms to the delocalization of the positive charge in the pyrazolium ion as compared with the imidazolium ion.

Protonation of Oxazole *versus* Isoxazole.

An examination of the relative changes in the partitioned energy terms in Tables IV and V on passing from oxazole to oxazolium ion as compared with the corresponding changes on passing from isoxazole to isoxazolium ion clearly shows that the protonation of oxazole and isoxazole parallel completely those of imidazole and pyrazole, respectively. In particular, the larger stabilization (0.704 eV) of oxazole relative to isoxazole upon protonation can be directly correlated with the rather small destabilization (0.317 eV) of the π bonding in the former compound as compared with the corresponding much larger destabilization (1.003 eV) in the latter. On the basis of the results in Table V, these remarkable differences in the destabilization of the π bonding can in turn be ascribed primarily to the corresponding differences in the contribution of the π electron charge density on the oxygen atom to the delocalization of the positive charge which arises at the nitrogen atom upon protonation. In fact, as is seen in Table VI, the π electron charge density on the oxygen atom in **3** decreases (0.067) while in **4** it increases (0.025).

As in the pyrazolium ion, the lack of an appreciable contribution of the π electron charge density on the heteroatom X_1 to the delocalization of the positive charge in the isoxazolium ion is attributed mainly to the mutual electrostatic field effect between the cores and electrons of the heteroatoms with the largest core charges, namely X_1 and Y_2, due to their close proximity.

A final point worth noticing is that the larger one-center one-electron energies of the π electrons (U_{pp}) on an oxygen atom ($U_{pp} = -77.797$ eV) (27) as compared with that for an nitrogen atom ($U_{pp} = -57.172$eV) (27) helps to explain the smaller decrease of the π electron charge density on heteroatom X_1 in **3** upon protonation as compared with **1**, as well as the corresponding larger increase of that in **4** as compared with **2**.

Summary and Conclusions.

It has been shown in this work that following protonation the total energy of imidazole, pyrazole, oxazole, and isoxazole decreases substantially due primarily to the energy stabilization of the corresponding σ bonding, reflected in the total sum of the σ bond component of the two-center one-electron core resonance integrals energies. In sharp contrast, the π bonding of the five-membered ring of those azoles undergoes a significant destabilization, also reflected in the total sum of the π bond components of the above two-center energy terms. This destabilization is traced back to the redistribution of the π electron density caused by the shift of σ electron charge density on the pyridine-like nitrogen to the attacking proton.

The difference in the numerical value of the above π bonding destabilization energy calculated for the protonation of imidazole and oxazole relative to that of pyrazole and isoxazole, respectively, is found to be the major cause for the larger decrease in the total energy of the former compounds as compared with the latter upon protonation. We conclude therefore that the greater basicity of im-

idazole and oxazole relative to pyrazole and isoxazole, respectively, is primarily due to the rather small destabilization of the π bonding in the former azoles as compared with that in the latter.

Moreover, the above difference in the π bonding destabilization reflects the ability of the π lone pair on the heteroatom X_1 to absorb the positive charge in the corresponding azolium ion, through the mesomer effect; that is to say, the π electron charge density on the nitrogen N_1 (oxygen O_1) in imidazole (oxazole) contributes significantly to the delocalization of the positive charge that appears at the pyridine-like nitrogen after protonation, while that in pyrazole (isoxazole) it does not contribute appreciably. In other words, imidazole behaves as should be expected for a pyridine-like base, whereas pyrazole is an abnormal base in that sense.

Finally, we conclude that the lack of participation of the π electron charge density on the heteroatom X_1 in pyrazole and isoxazole to the delocalization of the positive charge at the vicinal heteroatom Y_2 is mainly due to the mutual electrostatic field effect between both heteroatoms.

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