MNDO Studies on Five-Membered 1,3-Heterocyclic Systems. Part I. The Acidity of the Azolium Cations

Fernando Geijo, Francisco López-Calahorra and Santiago Olivella

Departamento de Química Orgánica, Facultad de Química, Universidad de Barcelona,
Av. Diagonal, 647, Barcelona-28, Spain

Received April 16, 1984

The technique of energy partitioning in the MNDO SCF-MO method has been used to understand the main electronic factors which determine the acidity order of the azolium cations. It is found that the greater acidity of thiazolium cation relative to the imidazolium one can be ascribed to a substantial stabilization of the one-center energy term associated to the sulphur atom in the conjugate base, suggesting a higher effective electronegativity of this atom.

J. Heterocyclic Chem., **21**, 1781 (1984).

Introduction.

Since 1935, when Williams *et al.* [1] established the presence of a thiazole ring in the thiamine, which pyrophosphate plays a coenzyme role in several enzymatic processes of the primary metabolism [2], the azolium cations have been the subject of many research lines. The first step of the action mechanism postulated by Breslow [3] is the deprotonation at the C_2 position of the thiazolium moiety of the thiamine. In this connection, the acidity of the azolium ions has been the subject of many studies from both theoretical and experimental standpoints [4]. From the reported data in the literature it is concluded that the decreasing acidity order of such cations is: oxazolium, thiazolium and imidazolium. The fact that thiazolium cations are more acidic than the imidazolium ones has been justified in terms of unsound hypothesis, despite that according to the electronegativity values of the heteroatoms involved, the expected order would be the opposite.

In the present paper we use the technique of the total energy partitioning in the MNDO SCF-MO method [5] to ascertain the main electronic factors which determine the greater acidity of thiazolium cations relative to the imidazolium ones. This technique has already proved to be useful in a recent study on the origin of the differences in the basicities of imidazole, pyrazole, oxazole and isoxazole [6].

Computational Procedure.

All numerical values in the following section were obtained using a locally modified version of the MNDO program [7], reprogrammed for an IBM 4341/2 computer, with standard parameters [5], [8]. All equilibrium geometries were determined by minimizing the total energy with respect to all geometrical variables using the standard DFP algorithm [9].

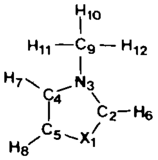
The deprotonation energies (DE) of the cations have been calculated as the difference between the total energy of each conjugate base and the corresponding azolium cation.

Results and Discussion.

a) Equilibrium Geometries.

The MNDO optimized equilibrium geometries for 3-methyloxazolium, ($\mathbf{1}^+$), 1,3-dimethylimidazolium ($\mathbf{2}^+$) and 3-methylthiazolium ($\mathbf{3}^+$) cations and their conjugate bases ($\mathbf{1}^\pm$, $\mathbf{2}^\pm$ and $\mathbf{3}^\pm$ respectively) are shown in Table I. All these species are planar and the geometries of $\mathbf{2}^+$ and $\mathbf{3}^+$ are in good agreement with the ones obtained by X-ray diffraction for thiamine and histamine hydrochloride [10].

Table I



Bond	1^+	2^+	3^+	$1^\pm$	$2^\pm$	$3^\pm$
X_1—C_1	1.335	1.375	1.663	1.335	1.381	1.696
C_2—N_3	1.369	1.375	1.357	1.402	1.381	1.362
N_3—C_4	1.425	1.414	1.426	1.424	1.429	1.436
C_4—C_5	1.387	1.386	1.371	1.373	1.377	1.359
C_5—X_1	1.375	1.414	1.687	1.383	1.429	1.694
C_2—H_6	1.095	1.090	1.091	—	—	—
C_4—H_7	1.084	1.085	1.088	1.080	1.081	1.084
C_5—H_8	1.089	1.085	1.084	1.082	1.081	1.079
N_3—C_9	1.491	1.486	1.495	1.459	1.457	1.469
C_9—H_{10}	1.110	1.110	1.110	1.112	1.113	1.112
C_9—H_{11}	1.112	1.112	1.111	1.114	1.114	1.113
C_9—H_{12}	1.111	1.112	1.112	1.114	1.114	1.113
Angle						
$X_1C_2N_3$	109.0	108.2	114.3	106.1	108.7	108.7
$C_2N_3C_4$	108.0	108.6	111.5	109.2	108.0	114.8
$N_3C_4C_5$	105.1	107.3	111.2	105.0	107.7	110.8
$C_4C_5X_1$	108.8	107.3	111.8	108.7	107.6	111.2
$C_5X_1C_2$	109.2	108.6	92.4	111.0	108.0	94.5
$H_6C_2X_1$	121.6	125.9	122.2	—	—	—
$H_7C_4C_5$	132.0	130.5	129.0	131.7	130.1	129.1
$H_8C_5X_1$	117.4	122.2	119.5	117.7	122.3	119.6
$C_9N_3C_4$	126.1	126.1	124.4	126.2	126.9	123.5
$H_{10}C_9N_3$	109.3	109.3	109.6	110.9	110.8	110.9
$H_{11}C_9N_3$	109.0	109.4	109.1	110.3	110.4	110.1
$H_{12}C_9N_3$	109.0	109.3	108.9	110.3	110.4	110.1

b) Deprotonation Energies.

The most reliable data in the literature on the acidity of the azolium cations are the rate constants (k_D) of the OD^- catalyzed deuterium interchange at the C_2 position [11]. In Table II are shown the calculated values of the DE for **1**$^+$, **2**$^+$ and **3**$^+$ and the k_D for the 3,4-dimethyloxazolium, 1,3,4-trimethylimidazolium and 3,4-dimethylthiazolium cations. Figure 1 shows the high degree of coincidence between the experimental and the calculated values (it is reasonable to assume that the presence of an additional methyl group in the same position in all the series should not be important).

Table II

X	$k_D/M^{-1}s^{-1}$	DE/eV
O	3.8×10^8	8.241
NCH_3	1.3×10^2	9.063
S	3.7×10^5	8.738

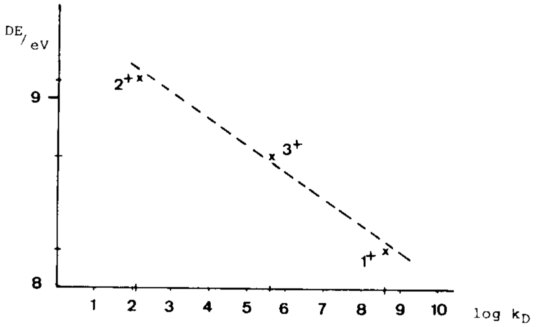


Figure 1

c) Energy Partitioning and C_2 Acidity.

The energy partitioning technique [6] decomposes the total energy (E_T) in a sum of one-center (E_A) and two-center (E_{AB}) terms according to the expression:

$$E_T = \Sigma E_A + \Sigma_{A<B} E_{AB}$$

Such technique also allows to group the energy terms corresponding to a certain molecular fragment and, therefore, one can calculate the energy associated to the atoms directly involved in the deprotonation processes (C_2 and H_6) as a differentiated part of the total energy. The total energy E_T is written as:

$$E_T = E_2 + E_6 + E_{26} + \Sigma_{A \neq 2,6} E_A + \Sigma_{A<B, AB \neq 26} E_{AB}$$

The calculated values are given in Table III.

Now it is worthwhile to express the DE values as:

$$DE = \Delta E_2 - E_6 - E_{26} + \Sigma_{A \neq 2,6}(\Delta E_A) + \Sigma_{A<B, AB \neq 26}(\Delta E_{AB})$$

where ΔE represents the change in a particular energy term after deprotonation of the azolium cation (Table IV).

The analysis of the results in Tables III and IV reveals the following trends:

-The values of the two-center terms E_{26} associated to the C_2-H_6 bonds (Table III) follow the electronegativity order of the heteroatoms in position 1; that's to say, the more electronegative the heteroatom the weaker the bond.

-Following deprotonation of the azolium cations, the variation on the change of the one-center terms (ΔE_2-E_6) associated with the C_2-H_6 fragment (Table IV) works in the same direction. Therefore, the global energy destabiliza-

Table III

Energies Expressed in eV

	E_T	E_2	E_6	E_{26}	$\Sigma_{A \neq 2,6} E_A$	$\Sigma_{A<B AB \neq 26}(E_{AB})$
1^+	−1117.883	−101.164	−7.313	−12.463	−835.063	−161.880
$1^\pm$	−1109.643	−108.905	—	—	−838.392	−162.346
2^+	−1174.155	−101.161	−7.581	−12.745	−840.801	−211.867
$2^\pm$	−1165.094	−108.516	—	—	−843.791	−212.785
3^+	−1033.768	−102.593	−7.613	−12.808	−755.445	−155.309
$3^\pm$	−1025.029	−109.235	—	—	−760.567	−155.227

Table IV

Energies Expressed in eV

Pair	DE	ΔE_2-E_6	ΔE_2-E_6-E_{26}	$\Sigma_{A<B\ AB \neq 26}(\Delta E_{AB})$	$\Sigma_{A \neq 2,6}(\Delta E_A)$
1	8.240	−0.115	12.035	−0.466	−3.329
2	9.063	+0.226	12.971	−0.918	−2.990
3	8.739	+0.971	13.779	+0.082	+5.112

Table V

Pair	X_1	N_3	C_4	C_5	H_7	H_8	C_9	H_{10}	H_{11}	H_{12}
1	−1.086	−1.025	+0.018	−0.154	−0.488	−0.615	+0.591	−0.365	−0.262	−0.262
2	−0.769	−0.769	−0.154	−0.154	−0.355	−0.355	+0.592	−0.341	−0.233	−0.233
3	−3.321	−0.851	+0.085	−0.067	−0.354	−0.356	+0.551	−0.340	−0.265	−0.265

tion (ΔE_2-E_6-E_{26}) of this fragment increases along with the decrease of the electronegativity of the heteroatom in position 1.

-Along with the above destabilization of the C_2-H_6 fragment there is a stabilization effect on the rest of the molecule that causes that the calculated DE actually are smaller than these destabilizations.

-The above stabilization is not provided by the change on the remaining two-center terms, $E_{A<B,AB\neq 26}(\Delta E_{AB})$, (Table IV) since their contribution to the DE is relatively small and, furthermore, works in the direction of increasing the acidity of imidazolium cation with respect to that of thiazolium and oxazolium cations.

-Finally, the last component of the DE, namely, the change undergone by the remaining one-center terms, $\Sigma_{A\neq 2,6}$ (ΔE_A), (Table IV), contributes toward a stabilization of the conjugated bases that is much higher in thiazolium than in oxazolium and somewhat higher in the latter than in imidazolium.

These features suggest that the acidity of the azolium cations is the result of a delicate balance between two opposite factors: a) the increase in the electronegativity of the differentiating heteroatom, that works diminishing the DE by means of a decrease on the destabilization energy of the C_2-H_6 fragment along the deprotonation, and b) the stabilization of the conjugate base through an increase of the stabilization of the one-center energy terms associated with the remaining atoms ($\Sigma_{A\neq 2,6}(\Delta E_A)$), that causes a decrease of the DE. In the particular case of the imidazolium and thiazolium cations, the first factor operates in the direction favouring the acidity of the former with respect to the latter but the second factor, which is the dominant, works in the opposite direction and the result is an inversion of the expected relative acidities based on the electronegativity factor. Now it is worthwhile to examine the stabilization undergone by each one-center term (ΔE_A, $A \neq 2,6$) after deprotonation of the azolium cations $\mathbf{1}^+$, $\mathbf{2}^+$ and $\mathbf{3}^+$. These are given in Table V. It will be seen that the most striking difference between the three azolium cations is the remarkable stabilization of the one-center term associated with the sulphur atom of thiazolium as compared with the corresonding stabilization of the one-center term associated with the nitrogen N_1 of the imidazolium, or with the oxygen O_1 of oxazolium cations. Therefore, *thiazolium cation is more acidic than the imidazolium because upon deprotonation the stabilization undergone by the heteroatom in position 1 is much larger for sulphur than for nitrogen.*

To gain insight into the physical meaning of the above result it is worth noting that the deprotonation of the azolium cations involves an increase of the electron density on the heterocyclic ring that is redistributed among its atoms and bonds. The change undergone by the one-center and two-center energy terms of the ring is directly related to the electron density gained by the atoms and bonds associated with these terms. In the case of azolium cations $\mathbf{1}^+$ and $\mathbf{2}^+$, it turns out that some stabilization appears in the two-center terms, $\Sigma_{AB\neq 2,6}E_{AB}$, (Table IV). In contrast, deprotonation of the two-center energy terms, that is accompanied by the stretching of the corresponding bonds, and a significant stabilization of the one-center terms. Specifically, the C_2-S_1 bond undergoes the largest stretching and the one-center energy term associated with the sulphur atom experiences the greatest stabilization. In other words, *the conjugate base of the thiazolium cation is more efficiently stabilized by enhancing the electron density on the sulphur atom rather than on the C_2-S_1 bond.*

This theoretical result can be understood by considering the components of the one-center and two-centers energy terms [6]. To simplify our analysis, first we recall [6] that the two-center energy terms E_{AB} quite precisely coincide with the one-electron core resonance integral component E^R_{AB}, which can be written as:

$$E^R_{AB} = \Sigma_\mu \Sigma_\nu P_{\nu\nu} (\beta^A_\mu + \beta^B_\nu) S_{\mu\nu}$$

where the indexes μ and ν refer to atomic orbitals (AO's) ϕ_μ and ϕ_ν centered at atoms A and B, respectively, $P_{\mu\nu}$ is the corresponding bond order matrix element, β^A_μ and β^B_ν are the two-center one-electron core resonance parameters characteristic of each AO, and $S_{\nu\nu}$ is the overlap integral between these AO's. Regarding the one-center energy terms, E_A, we note that its most negative component is the one-center core attraction term E^U_A, which is given by:

$$E^U_A = \Sigma_\mu P_{\mu\mu} U_{\mu\mu}$$

where the index μ refers to the AO's centered at atom A, $P_{\mu\mu}$ is the electron density on this AO and $U_{\mu\mu}$ is the one-center one-electron energy characteristic of this AO. Since the absolute values of β parameter for sulphur (−11.1422 eV [8]) is substantially smaller than that of nitrogen (−20.4958 eV [5]) or oxygen (−32.6880 eV [5]) and the overlap integrals associated to the C-S bond are rather small, it becomes clear that an increase of the electron density on this bond, measured by the bond order matix elements $P_{\mu\nu}$, does not contribute significatively to the stabilization of the conjugate base **3**$^{\pm}$. On the other hand, although the $U_{\mu\mu}$'s parameters for sulphur ($U_{ss} = -75.2391$ and $U_{pp} = -57.8320$ eV [8]) are less negative than those for oxygen ($U_{ss} = -99.6431$ and $U_{pp} = -77.7975$ eV [5]), they are more negative than those for nitrogen ($U_{ss} = -71.9321$ and $U_{pp} = -57.1723$ eV [5]) and therefore it seems very likely that an increase of the electron density on the sulphur atom leads to a more efficient lowering of the total energy of **3**$^{\pm}$.

In summary, although the electronegativity of sulphur atom is smaller than that of the nitrogen atom, the sulphur atom in the thiazolium cation shows an enhanced *effective electronegativity,* ascribed to the inefficient stabilization of the C_2-S_1 bond through the increase of its bond order, that causes a more effective stabilization of the conjugate base by increasing the electron charge density on this atom, leading to a greater acidity of the thiazolium cation as compared with that of the imidazolium.

Acknowledgements.

The computer time provided by the "Centro de Cálculo de la Universidad de Barcelona" is gratefully acknowledged.

REFERENCES AND NOTES

[1] R. Williams and A. E. Ruehle, *J. Am. Chem. Soc.*, **57**, 1856 (1935).

[2] See for example: T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms", Vol II, W. A. Benjamin Inc, New York, NY, 1966, p 181.

[3] R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).

[4a] J. Ullrich and A. Maanschreck, *Biochem. Biophys. Acta,* **115**, 46 (1966); [b] P. Haake, L. P. Bausher and W. B. Miller, *J. Am. Chem. Soc.*, **91**, 1113 (1969); [c] R. F. W. Hopmannn and G. P. Brugnoni, *Nature New Biol.*, **246**, 157 (1973); [d] H. C. Sorensen and L. L. Ingraham, *J. Heterocyclic Chem.*, **8**, 551 (1971); [e] H. Aldrich, W. L. Alworth and L. Clement, *J. Am. Chem. Soc.*, **100**, 2362 (1978).

[5] M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977).

[6] S. Olivella and J. Vilarrasa, *J. Heterocyclic Chem.*, **18**, 1189 (1981).

[7] W. Thiel, *QCPE.*, **10**, 353 (1978).

[8] M. J. S. Dewar, M. L. McKee and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 3607 (1978).

[9a] R. Fletcher and M. J. D. Powell, *Compt. J.*, **6**, 163 (1963); [b] W. C. Davidon, *Compt. J.*, **10**, 406 (1968).

[10a] J. Kraut and H. J. Reed, *Acta Crystallogr.*, **15**, 747 (1962); [b] C. Rérat, *Bull. Soc. Fr. Mineral. Cristallogr.*, **85**, 153 (1962).

[11] A. A. Gallo, J. J. Mieyal and H. Z. Sable, *Bioorg. Chem.*, 147 (1978).