ELECTRON-DENSITY DISTRIBUTION AND REACTIVITIES OF ETHYNYL-IMIDAZOLES AND -PYRAZOLES

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The electron shells of imidazole, pyrazole, and their ethynyl derivatives were calculated by the CNDO/2 method (complete neglect of differential overlap). The dipole moments, ionization potentials, and energies of heterolytic cleavage of the CH bonds of the ethynyl groups were calculated. The results are compared with the experimental data on the reactivities and acidities. The ethynyl substituent is a weak electron acceptor. The donor capacity of the ring correlates with the charges on the corresponding carbon atoms. The 4 and 5 positions of imidazole constitute an exception to this. The energy of heterolytic cleavage of the CH bond decreases as the electronic charge on the ethynyl group increases.

The aim of the present research consisted in an investigation of the electron-density distribution in molecules of the recently synthesized ethynyl-substituted imidazoles and pyrazoles [1-3] and in a discussion, on this basis, of their chemical properties, specifically, the acidities of the ethynyl protons and the reactivities of the various carbon centers. The total (q_i) and π-electron (q_i^π) charges on the atoms are considered as reactivity indexes.

The electronic structures were calculated by the CNDO/2 method (complete neglect of differential overlap) [4] with the standard selection of the parameters. The geometrical characteristics obtained for all of the atoms by the neutron-diffraction method [5] were used for the pyrazoles. The x-ray diffraction data from [6] were used for the imidazole ring, and the protons were situated on extensions of the bisectors of the corresponding ring angles at distances l_{CH} = 1.08 Å and l_{NH} = 1.04 Å. The deviations of the lines of the bonds and the ring angles of imidazole and pyrazole from the average values (l = 1.375 Å for imidazole, l = 1.356 Å for pyrazole, 1.08°) are relatively small and do not exceed 0.03 Å and 4°, respectively. The geometrical parameters of the rings were not changed for the ethynyl-substituted molecules. The distances l_{CC} = 1.4 Å, $l_{C\equiv C}$ = 1.205 Å, and l_{CH} = 1.06 Å were assumed for the linear ethynyl substituent, and it was assumed that its direction coincides with the direction of the CH bond undergoing substitution. The molecules were considered to be planar. The calculations were made from the CNDO/SP program [7] in the computer center of the Siberian Branch of the Academy of Sciences of the USSR. The calculated q_i and q_i^π charges of the carbon and nitrogen atoms are presented in Tables 1 and 2.

The specific character of the charge distribution in imidazole and pyrazole is determined by the donor properties of the "pyrrole" $N_{(1)}$ nitrogen atoms in the π system of bonds and the acceptor properties in the σ system of bonds. The role of σ-charge redistribution is extremely substantial. As a result, the $N_{(1)}$ atoms have low negative charges, whereas the carbon atoms, except for the 4 atom of pyrazole, are positively charged. The "pyridine" nitrogen atoms bear the maximum negative charge, and the charge in the imidazole ring is greater than the charge in the pyrazole ring. Imidazole should therefore have the greater

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affinity for a proton. This is confirmed experimentally (pK_a 6.95 for imidazole, and pK_a 2.53 for pyrazole [8]) and also by CNDO calculations of the protonation energies [9].

Of the imidazole carbon atoms, the $C_{(2)}$ atom has the greatest positive charge. The charges of the 4 and 5 atoms are relatively low. It is seen from Table 1 that the q_i and q_i^{π} charges lead to identical sequences: the $C_{(5)}$ atom should be the most reactive atom in electrophilic reactions, followed by $C_{(4)}$ and the considerably less active $C_{(2)}$ atom ($5 > 4 \gg 2$). Calculation of imidazole by the molecular orbital method with allowance for the σ bonds [10] also gives this sequence. At the same time, calculations within the π approximation by the Pariser—Parr—Pople (PPP) method leads to a somewhat different sequence ($4 > 5 > 2$) [11] and even to a clearly inaccurate sequence ($5 > 2 > 4$) [8].

The pyrazole $C_{(4)}$ atom bears a negative charge, whereas the 3 and 5 atoms are positively charged. The sequence $4 \gg 3 > 5$ is predicted from the total charges and the results of calculations in [10, 12]. However, the PPP method [8] and the CNDO method with allowance for only the π contribution give the sequence $4 \gg 5 > 3$. A comparison with the results in [12] for pyrazole shows that allowance in the calculations for a regular geometry of the ring, which we made in our calculations, has a relatively slight effect on the charge distribution. The most appreciable difference is the somewhat greater nonuniformity of the distribution, which is manifested, in particular, as an increase in the negative charge on $C_{(4)}$ and of the positive charge on $C_{(3)}$ and $C_{(5)}$ (the corresponding q_i values are —0.072, 0.055, and 0.063, according to the data in [12]).

An ethynyl substituent has a slight effect on the charge distribution in the heterocyclic rings. In this case, the ratio of the charges on the unsubstituted carbon atoms does not change qualitatively, i.e., the substituent does not change the order of reactivities obtained for the starting molecules. In all cases, the ethynyl group as a whole acts as an electron acceptor both through its π system and mainly through the accumulation of charge in the σ system. This distinguishes it from a methyl substituent, which is a π-electron donor and a σ-electron acceptor, as a result of which, the charge on the methyl group changes very slightly ($\Delta q \sim \pm 0.01$) [12]. The charge is accepted primarily from the carbon to which the substituent is attached and is borrowed by the other atoms to a very small degree. In the ethynyl group the negative charge is localized primarily on the terminal $C_{(7)}$ atom both in the π orbitals and in the σ orbitals. With the exception of 4-ethynylpyrazole, the $C_{(6)}$ atom bears a small negative charge. The acetylenic hydrogen atoms are positively charged. The magnitude of the charge on the substituent and its distribution depend on the site of addition. The least asymmetry in the charge distribution between the $C_{(6)}$ and $C_{(7)}$ atoms is observed for 2-ethynylimidazole. On the other hand, in the case of 4-ethynylpyrazole it reaches a maximum value. Within the limits of substituents of a single series one observes a definite correlation between the initial charge of the carbon atoms and the charge of the ethynyl substituents attached to it (Tables 1-3): the lower the positive charge of the carbon atom, the higher the amount of negative charge transmitted to the substituent. In other words, depending on the site of substitution, the heteroring manifests its electronegative donor properties in different ways. A similar effect is observed for methyl-substituted pyrazoles [12]. The 4 and 5 positions of imidazole constitute exceptions to this. The 4 position of the ring is less electronegative (a stronger donor) than the 5 position. This is probably associated with the effect of the adjacent $N_{(3)}$ atom, which has a large negative charge. Despite the small effect of the methyl group on the distribution of the electron density in the pyrazole ring, a distinct correlation between the charge of the $N_{(2)}$ atom and the experimental pK_a values for the conjugate acids of methylpyrazoles was observed in [12]. The same sequence of charge magnitudes, according to which the following ratios between the pK_a values are predicted, is observed for ethynyl-substituted pyrazoles: $3 > 5 > 0 > 4$ (0 denotes the unsubstututed compound). The predicted sequence for imidazoles has the form $4 > 0 \approx 5 > 2$.

The calculated dipole moments of the molecules are presented along with the charges of the substituents in Table 3. Their directions coincide approximately with the $N_{(1)} \rightarrow N_{(3)}$ direction for imidazole and the $N_{(1)} \rightarrow N_{(2)}$ direction for pyrazole and their ethynyl derivatives. A more detailed examination shows that the additive rule is approximately satisfied: the dipole moment is the vector sum of the dipole moments of the ring and the ethynyl group, the absolute values of which change relatively little. The dipole moment of the ring plays a decisive role. The experimental dipole moments of imidazole (3.99 D [13]) and pyrazole (2.21 D [14]) are in good agreement with the calculated values. The

TABLE 1. Charges on the Atoms of Imidazole and Its Ethynyl Derivatives*

R		Atom						
		1	2	3	4	5	6	7
H	q_i	−0,064	0,144	−0,207	0,022	0,012	—	—
		(0,103)	(−0,006)	—	(−0,007)	(0,003)	—	—
	$q_i\pi$	0,404	−0,029	−0,183	−0,073	−0,119	—	—
2-C≡CH	q_i	−0,092	0,188	−0,194	0,030	0.007	−0,028	−0,086
		(0.108)	—	—	(−0,004)	(0,004)	—	(0,067)
	$q_i\pi$	0,389	−0,020	−0,183	−0,063	−0,116	−0.002	−0,006
4-C≡CH	q_i	−0.062	0,148	−0,212	0,073	0,007	−0.009	−0,119
		(0,106)	(−0.003)	—	—	(0.010)	—	(0.061)
	$q_i\pi$	0,410	−0.016	−0,195	−0,055	−0,126	0.006	−0.024
5-C≡CH	q_i	−0,076	0,145	−0,205	0,018	0.073	−0.001	−0,123
		(0,108)	(−0,004)	—	(0,000)	—	—	(0.064)
	$q_i\pi$	0,394	−0,021	−0.178	−0,077	−0.096	0.012	−0.036

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*The charges on the adjacent hydrogen atoms are indicated in parentheses. Atoms 6 and 7 are the α and β atoms of the ethynyl grouping.

TABLE 2. Charges on the Atoms of Pyrazole and Its Ethynyl Derivatives*

R		Atom						
		1	2	3	4	5	6	7
H	q_i	−0,013	−0.147	0,067	−0.087	0,075	—	—
		(0,103)	—	(−0,006)	(0,011)	(−0.002)	—	—
	$q_i\pi$	0.419	−0.255	−0,008	−0.129	−0.028	—	—
3-C≡CH	q_i	−0.013	−0,154	0,116	−0,095	0.079	−0.012	−0.104
		(0.105)	—	—	(0,016)	(0.000)	—	(0.061)
	$q_i\pi$	0,425	−0,272	0,007	−0.138	−0.017	−0,003	−0.002
4-C≡CH	q_i	−0.013	−0,143	0.060	−0.021	0.066	0.012	−0.136
		(0,107)	—	(0,001)	—	(0.006)	—	(0,060)
	$q_i\pi$	0.425	−0,240	−0.018	−0.104	−0.040	0.010	−0.033
5-C≡CH	q_i	−0,026	−0.150	0,067	−0,094	0.132	−0,009	−0.102
		(0.107)	—	(−0,006)	(0.015)	—	—	(0,065)
	$q_i\pi$	0.402	−0.246	−0.004	−0,135	−0,011	−0.001	−0.006

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*See the note to Table 1.

TABLE 3. Charges of the Ethynyl Substituents (q_{et}), Dipole Moments of the Molecule (μ), and Ionization Potentials (I) Calculated by the CNDO Method.

R = imidazole	q_{et}	μ, D	I, eV	R = pyrazole	q_{et}	μ, D	I, eV
H	—	4,10	8,06	H	—	2.39	8,30
2-C≡CH	−0,047	3,93	7,28	3-C≡CH	−0,055	2,71	7,88
4-C≡CH	−0,067	4,55	7,41	4-C≡CH	−0,064	2,36	7,57
5-C≡CH	−0.060	3,75	7,17	5-C≡CH	−0,045	2.26	7,44

calculated ionization potentials (I) with a shift in the reference level of −4 eV are also presented in Table 3 [12]. We see that the ethynyl substituents decrease the ionization potentials, and the sequence of the values is the same for the ethynyl-pyrazoles as for the methyl-substituted derivatives [12], despite the difference in the acceptor properties.

An important chemical characteristic of the ethynyl derivatives is the acidity of the ethynyl proton. On comparing the acidities of the protons of the various ethynyl derivatives of the same series or of structurally similar compounds one might expect that the solvation contributions and the entropy effects would be approximately identical. The major factor that determines the difference in the acidities of the protons is therefore apparently the energy of heterolytic cleavage of the CH bond in the gas phase — $\Delta pK_a \sim \Delta E$. This approach is similar to the above-noted analysis of the basicities of the heterocycles

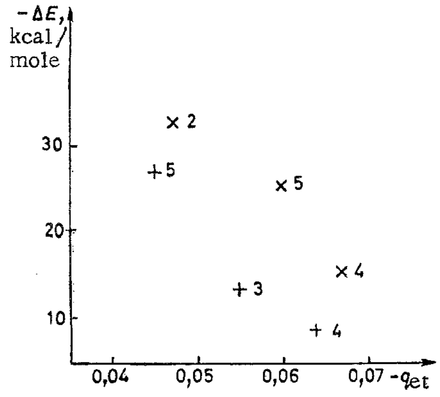

Fig. 1. Correlation between the energies of heterocyclic cleavage of the CH bonds (ΔE) and the charge on the ethynyl group (q_{et}): "+") ethynylpyrazoles; "×") ethynylimidazoles.

on the basis of calculations of the proton affinities, an approach that has had experimental confirmation [9, 12]. We calculated this energy by the CNDO method. The correlation diagram, which displays an approximately linear relationship between the energies of heterolytic cleavage and the charge on the ethynyl group (q_{et}), is presented in Fig. 1. The energies ($-\Delta E$), which are the differences between the energies of detachment of a proton in acetylene and in the molecules under consideration, are plotted along the axis of ordinates. We see that $\Delta E < 0$ for all of the ethynyl-substituted compounds, i.e., the proton is detached more easily than in acetylene. A correlation also exists between the ΔE values and the charge of the acetylene hydrogen or the charge on $C_{(7)}$. The higher the positive charge on the hydrogen and the lower the negative charge on the $C_{(7)}$ atom, the more readily a proton is detached. Exceptions are again offered by the 4 and 5 positions of imidazole, for which the correlation with the charges on $C_{(7)}$ and with the starting charges of the ring carbons is disrupted. Thus the relationships of the predicted pK_a values of the ethynyl protons for imidazoles (4 > 5 > 2) and for pyrazoles (4 > 3 > 5) coincide, excluding the above-noted anomaly, with the order of reactivities of the corresponding ring carbon atoms in unsubstituted azoles predicted on the basis of the calculated total charges. The acetylenic group has the greatest acidity in the positions that are least reactive in electrophilic reactions. For pyrazoles, the indicated order of pK_a values is indirectly confirmed by data on aminoalkylation of their N-methyl-substituted acetylenic derivatives [2].

In conclusion, let us examine some experimental data on the reaction of N-methylpyrazoles and N-methylimidazoles with butyllithium. In the case of N-methylpyrazoles this reaction proceeds only in the 5 position [15], whereas in the case of N-methylimidazoles the only unreactive position is the 4 position [16]. Inasmuch as the orders of reactivity are reversed for electrophilic and nucleophilic reactions, one might assume that the sequence 3 > 5 holds for pyrazole in electrophilic reactions as compared with the sequence 4 > 5 for imidazole. The first of these sequences is in agreement with the results of the calculations, whereas the second is not (Tables 1 and 2). The reason for the disagreement might have been sought in the manifestation of the orienting effect of the N-methyl group. However, a definitive experimental argument against this assumption is the result obtained in [2]. In [2] it is shown that the reactivities of the 3 and 5 positions are practically the same in the iodination of 1-methylpyrazole in acidic media. This means that the effects of H and CH_3 are almost identical. The calculations presented above also lead to a similar conclusion regarding the weak effect of substituents. The observed anomaly in the reactivity of imidazole can be linked with the anomaly in the donor capacity of its 4 position. The greater polarizability and donor capacity of the 4 position as compared with the 5 position apparently also lead to an increase in its reactivity. This is also promoted by a negative charge on $N_{(3)}$ and the direction of the $N_{(1)} \rightarrow N_{(3)}$ dipole moment, which facilitate the approach of the electrophilic reagent to the 4 position. In the case of pyrazole, these factors additionally activate the 3 atom, which itself bears a higher negative charge than the competing 5 atom.

LITERATURE CITED

1. S. F. Vasilevskii, M. S. Shvartsberg, and I. L. Kotlyarevskii, Izv. Akad. Nauk SSSR, Ser. Khim., 1764 (1971).
2. S. F. Vasilevskii, P. A. Slabuka, E. G. Izyumov, M. S. Shvartsberg, and I. L. Kotlyarevskii, Izv. Akad. Nauk SSSR, Ser. Khim., 2524 (1972).
3. M. S. Shvartsberg, L. N. Bizhan, E. E. Zaev, and I. L. Kotlyarevskii, Izv. Akad. Nauk SSSR. Ser. Khim., 472 (1972).
4. J. A. Pople and G. A. Segal, J. Chem. Phys., 44, 3289 (1966).
5. F. K. Larsen, M. S. Lehmann, I. Sotoffe, and S. E. Rasmussen, Acta Chem. Scand., 24, 3248 (1970).

6. S. Martinez-Carrera, Acta Cryst., 20, 783 (1966).
7. N. D. Chuvylkin, Master's Dissertation, Institute of Organic Chemistry, Moscow (1972).
8. M. Kamiya, Bull. Chem. Soc. Japan, 43, 3344 (1970).
9. J. D. Vaugham and M. O'Donnell, Tetrahedron Lett., 3727 (1968).
10. M. Roche and L. Pujol, Bull. Soc. Chim. France, 273 (1970).
11. I. Fischer-Hjalmars and J. Nag Chandhuri, Acta Chem. Scand., 23, 2963 (1969).
12. R. E. Burton and I. L. Finar, J. Chem. Soc., B, 1692 (1970).
13. V. I. Minkin, O. A. Osipov, A. D. Garnovskii, and A. M. Sinonov, Zh. Fiz. Khim., 36, 469 (1962).
14. W. H. Kirchoff, J. Amer. Chem. Soc., 89, 1312 (1967).
15. P. W. Alley and D. A. Shirley, J. Amer. Chem. Soc., 80, 6271 (1958).
16. V. V. Burykin, Master's Dissertation, Rostov-on-Don (1971).