REACTIVITIES AND STRUCTURES OF COMPOUNDS OF THE THIOPHENE AND FURAN SERIES BEARING ELECTRON-ACCEPTOR SUBSTITUENTS

Ya. L. Gol'dfarb, G. M. Zhidomirov,
N. D. Chuvylkin, and L. I. Belen'kii

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The experimental data on orientation in electrophilic substitution reactions of compounds of the furan and thiophene series that bear electron-acceptor substituents were examined. Within the framework of the CNDO/2 method, the electronic structures, dipole moments, and spin–spin coupling constants in the PMR spectra were calculated for model systems – 2-formylthiophene, furfural, and their oxygen-protonated forms. The results of the calculations are compared with the available experimental data on the dipole moments and spin–spin coupling constants, which made it possible to discuss the geometrical structures of the compounds. An analysis of data on the chemical behavior of these compounds demonstrated that, in contrast to the charges found using the π-electron approximation, the total charges on the atoms calculated by the CNDO/2 method are rather effective indexes of the reactivity.

One of the specific characteristics in the historical profile of the development of the chemistry of heterocyclic compounds is the fact that three heterocyclic systems – furan, thiophene, and pyrrole – are often considered jointly by comparing them with the benzene system. If, however, one proceeds from the fundamental formal-classification principles based on the number of atoms in the ring, this sort of comparison is invalid: from this point of view, a comparison of benzene with, for example, pyridine and other six-membered heterocycles would be more valid. However, a comparison of the above "triad" with benzene is, in fact, completely expedient if one proceeds from the totality of the chemical properties peculiar to these compounds, which can be termed aromatic compounds.* If this problem is approached from the positions of the electronic theory in its broad sense, it is known that the common character of their properties is associated with the presence of an electron sextet. In addition, it is quite apparent that the presence of an aromatic sextet all by itself cannot determine all of the peculiarities of the reactivity, and it is precisely in heterocyclic systems that nonequivalence of the positions is manifested; this nonequivalence is a consequence of the very structure of these compounds and is associated with the nonuniform distribution of the electron density in them. This is especially clearly seen in the case of compounds of the furan and thiophene series, which are the subject of this paper.

Orientation during Electrophilic Substitution in the Thiophene and Furan Series

In thiophene and furan, substitution reactions of any type (electrophilic, radical, protophilic, or nucleophilic) occur primarily at the α position of the ring. Data that make it possible to give a quantitative

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*In speaking of aromaticity, it should be borne in mind that this concept currently does not have a generally accepted definition. Nevertheless, the common character of such systems can be established at least with respect to some characteristics (see [1] for example).

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TABLE 1. Results of Calculation by the CNDO/2 Method of Unprotonated (I) and Protonated (II) Furfural and 2-Formylthiophene Molecules

Structure	ΔE_t, eV	$\vert\vec{\mu}\vert$, D	Spin – spin coupling constants, Hz							Total charges on the atom											
			J_{34}	J_{35}	J_{45}	$J_{CHO\text{-}3}$	$J_{CHO\text{-}4}$	$J_{CHO\text{-}5}$		Q_1^X	Q_2^C	Q_3^C	Q_4^C	Q_5^C	Q_{CHO}^C	Q_{CHO}^O	Q_{CHO}^H	Q_3^H	Q_4^H	Q_5^H	Q_+^H
					Furfural and its protonated forms					(X = O)											
IA	≡0	2,57	2,86	1,32	1,54	0,11	0,55	0,00		−0,14	+0,08	−0,01	−0,06	+0,12	+0,23	−0,24	−0,03	+0,02	+0,02	+0,01	
IB	0,08	3,59	2,86	1,32	1,48	0,00	0,00	0,50		−0,13	+0,09	−0,02	−0,05	+0,12	+0,22	−0,23	−0,02	0,00	+0,02	0,00	
IIA	≡0		2,64	1,16	1,32	0,00	0,06	0,44		−0,11	+0,06	+0,11	−0,05	+0,22	+0,36	−0,11	+0,06	+0,06	+0,07	+0,07	+0,26
IIB	0,08		2,64	1,16	1,32	0,00	0,00	0,33		−0,13	+0,04	+0,12	−0,05	+0,22	+0,33	−0,08	+0,09	+0,06	+0,08	+0,07	+0,25
IIC	1,86		3,38	1,10	0,93	0,08	0,08	0,34		0,00	+0,12	+0,04	+0,03	+0,12	+0,20	−0,16	+0,05	+0,09	+0,10	+0,09	+0,32
Experimental data for I		3,59[47]	3,55[48]	0,80[48]	1,70[48]	—	0,45[48]	0,45[48]													
					2-Formlythiophene and its protonated forms					(X = S)											
IA	≡0	2,49	3,14	1,32	5,22	0,11	0,50	0,00		−0,04	−0,04	+0,06	+0,02	−0,02	+0,25	−0,24	−0,04	+0,02	0,00	+0,03	
IB	0,06	2,87	3,14	1,38	5,22	0,16	0,00	0,72		−0,02	−0,05	+0,04	+0,02	−0,02	+0,23	−0,23	−0,04	+0,02	+0,02	+0,03	
IIA	≡0		2,97	1,32	4,73	0,28	0,00	0,55		+0,08	−0,10	+0,15	+0,02	+0,05	+0,41	−0,12	+0,04	+0,05	+0,06	+0,08	+0,28
IIB	0,09		2,97	1,32	4,62	0,16	0,00	0,38		+0,05	−0,12	+0,16	+0,02	+0,06	+0,38	−0,08	+0,08	+0,05	+0,07	+0,09	+0,24
Experimental data for I		3,48[49]	3,8[50]	—	5,0[50]	—	—	0,9[50]													

estimate of the reactivities of five-membered heterocyclic compounds, including those that belong to the furan and thiophene series, have recently been obtained in a number of papers by means of direct kinetic measurement or by the method of competitive reactions. For example, bromination of thiophene in acetic acid at 25°C in the α position proceeds at a rate that is nine orders of magnitude greater than the bromination of benzene [2], while the bromination of furan proceeds at a rate that is 11 orders of magnitude greater than the bromination of benzene. We note in this case that the bromination of thiophene apparently proceeds via the same mechanism [4] as the bromination of benzene and represents the usual (for aromatic compounds) electrophilic substitution that proceeds through intermediate formation of a σ complex. The reactivities of the β positions are several orders of magnitude lower than the reactivities of the α positions. For example, deuterium atoms in the α position of thiophene are exchanged at a rate that is three orders of magnitude greater than in the β position [5] during protodedeuteration in acid, while bromination with molecular bromine in acetic acid proceeds at the α position at a rate that is 2.5 orders of magnitude greater than the rate in the β position [6]. It is important to note that the differences in the reactivities for the β positions of furan and thiophene are considerably less than for the α positions [7-9].

The high reactivities of the α positions of the thiophene and furan rings cause specific difficulties in the synthesis of β-substituted derivatives. Even when one of the α positions has electron-acceptor substituents, the orientation during electrophilic substitution reactions is determined to a considerable degree by the effect of the heteroatom, such that, under the usual conditions, the substituting group is directed mainly (and often almost exclusively) to the free α' position of the thiophene and, in particular, furan rings [10-12]. Investigations carried out in recent years in the Laboratory of Heterocyclic Compounds of the Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, have created broad possibilities for a change in the specificity of electrophilic substitution reactions of α-carbonyl compounds of the thiophene and furan series based on complexing with aluminum chloride [11, 13-16]* or protonation [17-21]. In the course of the investigations, it was ascertained that the products formed during the bromination [11, 14], acylation [13], and chloromethylation [15, 16] of complexes of 2-formylthiophene and 2-acetothienone with aluminum chloride contain no less than 93-99% of the 4-substituted derivatives. This effect is explained [11, 17] by reinforcement of the electron-acceptor capacity of the carbonyl group as a consequence of complexing or protonation. This leads to a substantial decrease in the electron density and, consequently, the re-

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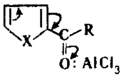
*See [11] for citations of earlier studies.

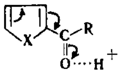
TABLE 2. Electron Populations of the π AO for Unprotonated (I) and Protonated (II) Furfural and 2-Formylthiophene Molecules

Computational method	Structure	$q_1{}^X$	$q_2{}^C$	$q_3{}^C$	$q_4{}^C$	$q_5{}^C$	$q_{CHO}{}^C$	$q_{CHO}{}^O$
				Furfural (X = O)				
Hückel MO	I	+0,13	−0,06	+0,12	−0,05	+0,16	+0,28	−0,58
	II	+0,13	−0,06	+0,20	−0,05	+0,23	+0,36	−0,81
C/PPP	I	+0,15	−0,04	+0,04	−0,06	+0,07	+0,18	−0,34
	II	+0,15	−0,06	+0,15	−0,06	+0,16	+0,37	−0,71
CNDO/2	I B	+0,26	−0,09	−0,01	−0,07	−0,03	+0,15	−0,21
	II A	+0,25	−0,19	+0,19	−0,08	+0,13	+0,36	−0,66
	II C	+0,14	−0,11	+0,06	+0,05	−0,11	+0,11	−0,14
				2-Formylthiophene (X = S)				
Hückel MO	I	+0,28	−0,07	+0,07	−0,08	+0,10	+0,28	−0,58
	II	+0,29	−0,07	+0,13	−0,07	+0,16	+0,37	−0,81
C/PPP	I	+0,27	−0,06	0,00	−0,08	+0,03	+0,18	−0,34
	II	+0,28	−0,07	+0,10	−0,08	+0,11	+0,38	−0,72
CNDO/2	I B	+0,03*	−0,04	+0,05	+0,01	0,00	+0,15	−0,20
	II A	+0,06*	−0,14	+0,21	−0,01	+0,12	+0,40	−0,64

*The total value of the electronic populations of the p_π and d_π AO. The electron population of the p_π AO is +0.21.

activity during electrophilic substitution in the 3 and 5 positions of the heterocycle, and a comparatively lesser reflection on the activity of the 4 positions, such that the latter proved to be more reactive than the free α' position.

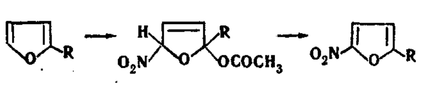




The dissimilar degree of reduction in the electron density in the various positions of the thiophene ring is graphically displayed on comparison of the chemical shifts of the protons in the PMR spectra of the free and $AlCl_3$-complexed 2-formylthiophene and 2-acetylthienone [16]. Although it does not lead to as pronounced a change in the orientation as during complexing with $AlCl_3$, protonation of the carbonyl group undoubtedly facilitates attack of the electrophilic reagent at the 4 position of the thiophene ring, which is demonstrated during the nitration [17-19], bromination [20], and chloromethylation [21] of 2-formylthiophene and 2-acetothienone in concentrated sulfuric acid.

Insofar as one can judge from the available and, as yet, scanty data, the complexes of carbonyl compounds of the furan series differ substantially in reactivity from the thiophene analogs. For example, the bromination of furfural and 2-acetylfuran gives 4,5-disubstituted derivatives as the major products, regardless of the amount of bromine used [11], and only insignificant amounts of 4- [22] and 5-monosubstituted [11] compounds can be isolated. In other reactions, which stop at the step involving the monosubstituted compounds, the 5-substituted 2-carbonyl compounds of the furan series are isolated as the major and, most often, the only reaction product. This sort of orientation may be considered to be a rule to which only one exception is known: 4-isopropylfurfural [23] is formed, although in low yield, in the isopropylation of furfural in the presence of excess aluminum chloride. The exclusiveness of this result is emphasized by the fact that, according to the results in [24], 5-tert-butylfurfural is formed during the tert-butylation of furfural under similar conditions.

The predominant substitution in the 5 position of furan rings that bear electron-acceptor substituents can be considered to be a consequence of the above-noted higher activity of the α positions in furan as compared with thiophene. However, this sort of explanation cannot be considered to be complete, since the mechanisms of the reactions of furan compounds and their thiophene analogs may differ from one another. In fact, the furan system has a number of peculiarities as compared with the thiophene system. Included among these peculiarities are its acidophobic character, clearly expressed conjugated diene properties, and a capacity for ring opening, which are also retained for compounds that bear electron-acceptor substituents. For example, the nitration of furan compounds, including furfural, 2-acetylfuran, and esters of furan-2-carboxylic acid, by acetyl nitrate proceeds through addition to the 2,5 positions to form a rather stable adduct, which is converted to 5-nitro-substituted furans under the influence of bases [25]:



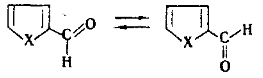
The furan ring may open under the influence of acidic agents in protic solvents, and this is often accompanied by oxidation; compounds that are stabilized by negative substituents can participate in such reactions [26-28]. Thus a study of the specificity of the electrophilic substitution in the furan series is often substantially complicated by side processes and the specific peculiarities of the mechanism.

Results of Calculations by the CNDO/2 Method and Discussion

For a qualitative and semiqualitative discussion of the information stated above, we felt it would be useful to perform quantum-chemical calculations of several model systems, which would make it possible, on the basis of the reactivity indexes found, to compare and interpret the chemical behavior of furan and thiophene compounds that bear electron-acceptor substituents. We selected the simplest model compounds – 2-formylthiophene and 2-formylfuran (I) and their carbonyl-oxygen-protonated forms (II).

The energies (ΔE), dipole moments (μ), total charges on the atom (Q), and the spin–spin coupling constants (J) calculated for these systems are presented in Table 1. The indicated values were obtained within the framework of the MO LCAO method with "complete neglect of differential overlap" (CNDO/2) using the parametrization proposed in [29].* This method recommends itself well in practical calculations of many properties of molecules (see [35], for example), including those that are associated with the reactivities of a number of organic compounds [36-42]. In particular, the total electronic charges of the reaction centers, found by the CNDO/2 method, were taken in [42] as a measure of the reactivities, and the reactivities of benzene derivatives were interpreted on the basis of a comparison of them. The CNDO/2 method with several different parameter values was used in calculations of the furan [43] and thiophene [44] molecules.

Geometrical Structure. The geometrical structures of the furan and thiophene ring in calculations of systems I and II were taken in conformity with the experimental data [45, 46], and the standard angles and bond lengths [31] were assumed for the CHO substituent. Two planar conformations (IA and IB) were considered:



IA IB

Calculation predicts only a slight difference in the total energies of these forms ($\Delta E_t = E_{IB} - E_{IA} > 0$), which is in qualitative agreement with the estimate [51] made on the basis of experimental data on J con-

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*The calculations were made with a BÉSM-6 computer with the program presented in [30]. The dipole moments were calculated in accordance with the method in [31]. The 3d-AO was taken into account for the sulfur atom [32, 33]. The indirect spin–spin coupling constants of the protons were estimated from the expression

$$J_{HH'} = \lambda_J \cdot J^0_{HH'} = \lambda_J \cdot \frac{32\pi}{9} \cdot \hbar \cdot \gamma_H^2 \cdot \beta_e^2 \cdot |S_H(0)|^4 \cdot \pi_{HH'}, \tag{1}$$

where

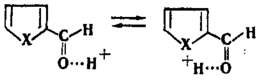
$$\pi_{HH'} = 4 \sum_{i}^{\text{occ}} \sum_{j}^{\text{free}} \frac{c_{iH} \cdot c_{iH'} \cdot c_{jH} \cdot c_{jH'}}{E_i - E_j} \tag{2}$$

The $\pi_{HH'}$ values are the mutual atomic-atomic polarizabilities of the 1s-AO of the H and H' atoms. The summation in (2) is carried out with respect to the occupied (Ψ_i) and free (Ψ_j) molecular orbitals with energies (in atomic units, one atomic unit = 27.2 eV) E_i and E_j, respectively (c_{iH} and c_{jH} are the coefficients of expansion of the MO in terms of the AO). The same symbols as in [34] are taken in expression (1), but the semiempirical parameter $\lambda = 5.5$ is additionally introduced. This parameter is invoked first to take into account the fact of the difference in the effective charge (ξ_H) of the nucleus of the H atom from unity, since s_H (0) values were calculated for $\xi_H = 1$ (for greater detail see [35], for example), and second, to "compensate" for the approximation consisting in the use in (2) of the difference in orbital energies ($E_j - E_i$) instead of the average energy of the singlet–triplet excitation $\Delta^3 E_{i \rightarrow j} = E_j - E_i - J_{ij}$ (J_{ij} is the coulombic integral between the Ψ_i and Ψ_j MO).

stants, although calculation and experimental data in [52] indicate that these very J_{CHO-5H} and J_{CHO-4H} constants were erroneously assigned for structures IA to IB, and vice versa, in [51]. In addition, calculation indicates that the dipole moment in both cases (X = O and X = S) should be larger for conformation IB than for conformation IA. It can therefore be expected that 2-formyl-substituted furan and thiophene will exist primarily in form IB in polar solvents, which is due to the influence of solvation effects, which are capable of quite markedly shifting the equilibrium to favor the conformation with the larger dipole moment. On the basis of the data in the literature [52-56], it can be concluded that the IB conformation (X = O, S) is actually apparently the primary one for aldehydes and ketones of the furan and thiophene series.

The formation of protonated forms of aldehydes, ketones, and carboxylic acids in strongly acidic media was studied by NMR spectroscopy, and it was demonstrated that the protonated forms can exist as two geometrical isomers relative to the C = O bond, or in other words, the COH^+ angle (θ) differs from 180° [57-61]. A similar structure was established also for a number of adducts formed by oxygen-containing donors and Lewis acids [62-64]. The results of the CNDO/2 calculation of protonated formaldehyde and acetaldehyde, in which it was found that $\theta = 120°$, which is in qualitative agreement with sp^2 hybridization of the oxygen atom [65] (see also [66]), are in agreement with this conclusion.

To follow how the electron density in the protonated form is redistributed as compared with the unprotonated form, we examined two structures (IIA and IIB) with $\theta = 120°$ and $r_{OH} = 0.96$ Å. Calculations within the framework of the CNDO/2 method led to only a slight difference between the total energy of these structures ($\Delta E_{AB} \simeq 2$ kcal/mole) and a similar redistribution of charges for both forms as compared with their distribution in unprotonated form IB.



IIA IIB

<u>Electronic Populations of the π AO.</u> The electronic populations of the π AO, which are often used as reactivity indexes [67], were calculated along with the total charges on the atoms presented in Table 1. These calculations were performed by the CNDO/2 method, i.e., with allowance for all of the valence electrons, and in two variants of the Hückel method: 1) C/PPP – in the zero approximation of the Pariser–Parr–Pople scheme with selection of the diagonal and nondiagonal matrix elements of the F operator by the CNDO/2 method [68]; 2) the Hückel MO method – within the framework of the simple Hückel method with the parameters for coulombic and resonance integrals recommended by Streitwieser [67] (the 3d AO of the sulfur atom were disregarded).* The q_μ^π values (except, perhaps, for q_4^C for II when X = S and q_3^C and q_5^C for I when X = O) obtained by the C/PPP and Hückel MO methods are qualitatively in comparatively good agreement with the values calculated by the CNDO/2 method (see Table 2). This means that the electrons that participate in the formation of σ bonds have only a slight effect on the distribution of the π-electron density, and the extensively used π-electron approximation may be satisfactory for evaluating the distribution of charges in the π system. However, as will be demonstrated below, the distribution of charges in the π system cannot be made to satisfactorily agree with the reactivity data.

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*The formation of a protonated form, which, for convenience, we will also designate in terms of II, was modeled in the Hückel method by means of a change in the coulombic integral ($\alpha_{\dot{O}}$) of the oxygen atom, to which a proton (H^+) is added. Within the framework of perturbation theory, the Δq_μ^π values at which the electron populations of the π AO (φ_μ) change can be calculated from the expression

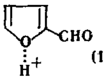
$$\Delta q_\mu^\pi = \pi_{\mu O} \Delta\alpha_{\dot{O}} \tag{3}$$

and, according to the Hückel MO method, are ($\Delta\alpha_C$ in β units): $\Delta q_1^S = 0.011\Delta\alpha_{\dot{O}}$, $\Delta q_2^C = -0.008\Delta\alpha_{\dot{O}}$, $\Delta q_3^C = 0.094\Delta\alpha_{\dot{O}}$, $\Delta q_4^C = 0.008\Delta\alpha_{\dot{O}}$, $\Delta q_5^C = 0.090\Delta\alpha_{\dot{O}}$, $\Delta q_{CHO}^C = 0.162\Delta\alpha_{\dot{O}}$, and $\Delta q_{CHO}^O = -0.356\Delta\alpha_{\dot{O}}$ for X = S; $\Delta q_1^O = 0.002\Delta\alpha_{\dot{O}}$, $\Delta q_2^C = -0.016\Delta\alpha_{\dot{O}}$, $\Delta q_3^C = 0.112\Delta\alpha_{\dot{O}}$, $\Delta q_4^C = 0.003\Delta\alpha_{\dot{O}}$, $\Delta q_5^C = 0.106\Delta\alpha_{\dot{O}}$, $\Delta q_{CHO}^C = 0.160\Delta\alpha_{\dot{O}}$, and $\Delta q_{CHO}^O = -0.367\Delta\alpha_{\dot{O}}$ for X = O. It follows from the expressions written out above that the redistribution of the electron density in the π system occurs similarly in both cases (the signs of the corresponding Δq_μ^π terms are identical), and $\Delta q_4^C > 0$, and $\Delta q_5^C > 0$. In addition, the Hückel method was used to directly calculate the q_μ^π values for $\alpha_{\dot{O}} = \alpha_{\dot{O}}^{\cdot}$ ($\Delta\alpha_O = \alpha_{\dot{O}}$), the results of which are presented in Table 2 along with the values found from the CNDO/2 method.

Comparison of the Chemical Behavior of the Examined Compounds with the Electron-Density Distribution Calculated for Them

This comparison makes it possible to judge the effectiveness of the Q_μ and q_μ^π values as reactivity indexes. Attempts to use the electron populations of the π AO (q_μ^π) as such indexes in the interpretation of the experimental data encounter a number of difficulties. Thus, from the data presented in Table 2, it can be concluded that the maximum electron density in all cases is localized in the 4 position, and electrophilic substitution reactions for both protonated and unprotonated 2-formylthiophene and furfural molecules should consequently be directed at the 4 position, which is not in agreement with the experimental data discussed above. At the same time, the total charges (Q_μ) presented in Table 1 correlate much better with the principal tendencies manifested in the reactivity of 2-formyl derivatives of thiophene and furan in electrophilic substitution reactions. In fact, calculation for the unprotonated 2-formylthiophene molecule demonstrates increased electron density in the 5 position as compared with the 3 and 4 positions and in the 4 position as compared with the 3 and 5 positions for its protonated form, which is in complete agreement with the available experimental data. The known cases of substitution of an acyl group in the chemistry of thiophene may be associated with the increased electron density (Q_2^C) in the 2 position [69, 70]. At first glance, the results of calculation for the furfural molecule are in poorer agreement with the experimental data, since, from the values presented in Table 1, it might have been concluded that the 4 position should be more active than the 5 position, not only in the protonated but even in the unprotonated molecule. However, one's attention should be directed to the calculated high negative charge on the oxygen atom of the furan ring of furfural, which is also retained in the protonated form. It seems to us that the presence of this sort of charge makes it probable that the electrophilic agent coordinates at the heteroatom of the ring with subsequent cleavage of the latter or migration of the substituent to the adjacent free α' position; i.e., as already noted, side processes and specific peculiarities of the electrophilic substitution mechanism are possible in the case of furfural.

In this connection, one's attention should also be directed to the fact that the literature contains assumptions regarding the formation of protonated furfural molecules (IIC) in which the protons add to the oxygen atom of the heterocycles [27].


(IIC)

There are several reasons to expect that the formation of the IIC form through direct addition of the proton to the O_1 atom of the ring or as a result of migration from the carbonyl oxygen might lead to that redistribution of the electron density in the furan ring which would promote subsequent attack of the electrophilic reagent at the 5 position of the IIC form. However, calculation by the CNDO/2 method (Table 1) demonstrates that the protonated form (IIC) is considerably less favorable from an energy point of view than the IIA and IIB forms ($\Delta E_t \simeq 40$ kcal/mole). It can therefore be assumed that the protonated furfural molecules are capable of existing practically exclusively in the IIA and IIB forms, while the IIC form should be considered to be only a model of an unstable particle that is formed during cleavage of the furan ring in acidic media or transformed to stable 5-substituted compounds, which was discussed above. In addition, from the calculated data (Table 1), the IIC structure should be less active in electrophilic substitution reactions than IIA and IIB, since all of the ring atoms in it are positively charged. In contrast to total charges Q_2^C and Q_5^C, the q_2^C and q_5^C charges of the π AO are negative in the case of structure IIC (Table 2), which is in agreement with the qualitative concepts relative to the redistribution of the charges in the π-electron system.

The absence of a correlation between the Q_μ and q_μ^π values in some cases renders impossible and, in others, places under doubt the interpretation of the reactivities of the conjugated molecules within the framework of the π-electron approximation. It is known [71, 72] that the π-electron populations (q_μ^π) are often unsatisfactory reactivity indexes; however, by analogy, one should not suppose that the total charges (Q_μ) are also ineffective in this plan. The results of the correlation of the reactivities of molecules with the Q_μ values found by the CNDO/2 method with allowance for all of the valence electrons [39, 42], as well as the results of this study, make it possible to hope to retain the calculated total charge of an isolated center as a "good" index of its reactivity. When making a comparison with the experimental values, it is also necessary to bear in mind that the effects of the molecule's interaction with the medium (protonation, complexing, etc.) may also substantially affect the distribution of charges. Thus, for example, according to the CNDO/2 calculation, both electronic populations of the C_2 atom (Q_2^C and q_2^C) for the IB form for X = S are considerably lower in absolute value than the corresponding populations of the oxygen atom (Q_{CHO}^O and q_{CHO}^O). However, $Q_2^C \simeq Q_{CHO}^O$ for protonated forms IIA and IIB, although $q_2^C \simeq (1/5)q_{CHO}^O$, as before.

Thus the schemes of calculation with allowance for all of the valence electrons may lead to conclusions relative to the charge distribution in the molecule that differ qualitatively from those obtained in the π-electron approximation and, for this reason, presuppose a fundamentally different interpretation of the experimental data. In this connection, the π-electron approximation may be inadequate for the examination of problems of the reactivities of molecules. As demonstrated in the present paper, the charges on the atoms calculated with allowance for all of the valence electrons make it possible to uncover the reasons for the experimentally known changes in the reactivities of molecules associated with their interaction with the medium (with a protic acid, in our case). It should be emphasized that the protonated forms that we examined are of interest not only in themselves but also as model systems. The results obtained for them make it possible to judge the principal tendencies in the redistribution of the electron density caused by interaction of a carbonyl compound with Lewis acids. The latter is especially important for furfural, since there are no data on the effect of protonation on the specificity of electrophilic substitution in the furan series because of the acidophobic character of furan compounds. The calculation of complexes of furfural and 2-formylthiophene with aluminum chloride would certainly be of definite interest. This problem, which is substantially more complex than the calculation performed in this paper, will be the subject of our subsequent investigations.

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