QUANTUM-CHEMICAL INVESTIGATION OF THE 1,2-PROTON SHIFT IN PROTONATED FIVE-MEMBERED AROMATIC HETEROCYCLES

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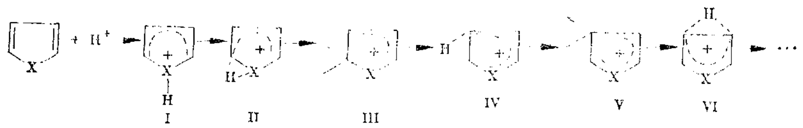
UDC 541.67:543.422'5:547.72'73'74

Calculations of the energetics of the 1,2-proton shift in protonated five-membered aromatic heterocycles — pyrrole, furan, and thiophene — have been carried out by the SCF MO LCAO method in the MINDO/3 approximation and nonempirically on the OST-3GF (OST-3GF*) basis. The general features of this process, and also the influence of solvation and of taking into account the vacant d-AOs of the sulfur atom in the protonated form of thiophene on the results of the calculation are considered. The results obtained have been used for a discussion of the activity and selectivity of the heterocycles considered in aromatic electrophilic substitution reactions.

The aromatic molecule—proton system may be considered as a model of numerous reactions of aromatic electrophilic substitution, and also of acid-catalyzed isomerization, the splitting out of substituents, etc. In a theoretical analysis of these reactions, particular interest is presented by a determination of the energy of the system according to the relative positions of the proton and the aromatic ring and, in particular, the position of structures corresponding to so-called σ- and π-complexes on the potential energy hypersurface of the system. For benzene, calculations of this type have been performed repeatedly using both nonempirical and semiempirical methods (see the reviews [1, 2], and also [3, 4]). For heteroaromatic compounds — for example, for the five-membered aromatic heterocycles furan, pyrrole, and thiophene — similar results are sporadic and nonsystematic [5-8]. In addition to this, it is precisely for these compounds that quantum-chemical calculations may have fundamental value in connection with the lower kinetic stability of the hetarenium ions, which complicates their experimental investigation by physical methods, and also with the fact that the results obtained in these calculations can be connected directly with the chemically important question of the activity and positional selectivity of aromatic heterocycles in electrophilic substitution reactions.

From the quantum-chemical point of view such an analysis amounts to calculating the changes in the energetics of the system along the reaction pathway which, by analogy with benzene derivatives, and also on the basis of the results of calculations performed earlier for some protonated heteroaromatic systems [5-7], can be illustrated schematically in the following way:



Here, structures of type (I), (III), and (V) correspond to local minima (LMs) on the potential energy hypersurface, and (II), (IV), and (VI) to transition states (TSs). The direct calculation of the structure of the TSs corresponding to this scheme by minimizing the norm of the energy gradient is difficult because of the relatively large dimensions and low symmetry of the systems under consideration, which leads to an exceptionally slow convergence of this procedure. Consequently, the change in the energy of the system when a proton moves along the reaction coordinate has been calculated. As has been shown previously for the case of the calculation of the energy of a 1,2-proton shift in the benzene—proton

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N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1186-1190, September, 1984. Original article submitted January 28, 1983; revision submitted March 5, 1984.

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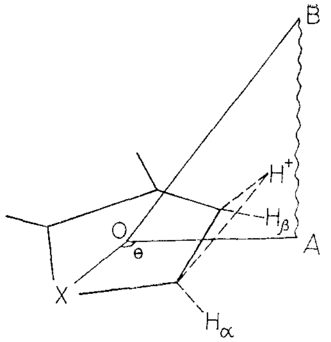

Fig. 1. For determining the reaction coordinate θ.

TABLE 1. Relative Energies of σ- and π-Complexes and Solvation Corrections, kJ/mole

Method of calculation	X*	Structure					
		I	II	III	IV	V	VI
MINDO/3	O	44,9	175,5	0,0	74,9	25,0	118,1
	NH	49,9	159,3	0,0	83,6	−7,1	90,7
	S	49,1	99,0	0,0	60,7	31,6	129,4
OST-3GF	O	125,5	341,5	0,0	200,9	47,4	257,9
	NH	97,3	332,0	0,0	192,6	0,0	236,3
	S	154,7	252,5	0,0	165,6	47,8	242,9
	S†	142,7	265,8	0,0	163,6	36,6	229,6
ΔE_s	O	59,9	21,6	0,0	10,0	10,0	30,0
	NH	20,0	8,3	0,0	−2,5	12,1	19,1
	S	−0,4	3,3	0,0	8,7	−0,4	−10,0

*For benzene (X = $-CH{=}CH-$) the calculated barriers of the 1,2-shift amount to 31.6 kJ/mole (MINDO/3), 133.1 kJ/mole (OST-3GF), and ΔE_S = 13.7 kJ/mole.

†On the OST-3GF* basis.

system [9], in this case it is more convenient to take angular, and not linear, coordinates as the reaction coordinates. Consequently, as the reaction coordinate we selected the angle XOA (Fig. 1) between the fixed direction OX and the plane OAB perpendicular to the plane of the heteroaromatic system in which the additional hydrogen atom H^+ was placed. The angle XOA was given by introducing the fictitious atoms O, A, and B and by the condition of the constancy of r_{OX}, which was taken as 1 Å in all calculations. The angle XOA was varied in 5° steps (2° in the region of a TS); for structures corresponding to LMs, complete optimization of the geometric parameters was carried out additionally by minimizing the energy. For each fixed value of the angle XOA an optimization of angles and bond lengths was carried out with accuracies of 0.1° and 0.001 Å, respectively. It was assumed here that all the atoms, with the exception of the migrating proton and the hydrogen atoms closest to it, were present in one plane. The calculations were performed by the MINDO/3 method [10] using a program [11] adapted for a BESM-6 computer.

As for protonated benzene [1], a σ-complex (LM) in the systems under consideration is characterized by lengthened (in comparison with the initial aromatic molecules) CC (CX) bonds of the atom at which the proton is added, with the bonds closest to it shortened (i.e., by a so-called pseudoquinoid structure). In the case of a π-complex (PC), a lengthening takes place mainly of that bond over which the migrating atom is located, and then the projection of the position of the proton on the plane of the aromatic system lies outside the ring of the latter by a distance of 0.4-0.6 Å from the corresponding bonds or atoms, and the distance from the proton to the plane amounts to approximately 1 Å.†

The values of the geometric parameters obtained corresponding to the LMs and PCs were used in the calculation of the energetics of a 1,2-proton shift by the nonempirical SFC MO LCAO method on the OST-3GF basis (and for X = S we also used the OST-3GF* basis, including

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†Information on the optimization of the values of the internal or Cartesian coordinates of the atoms of the systems under consideration can be obtained from the authors.

TABLE 2. Energies of Protonation (kJ/mole) and Ionization Potentials I (eV) of Aromatic Compounds

Method	X			
	CH=CH	O	NH	S
MINDO/3	689,3	754,2	781,7	745,5
OST-3GF	943,9	1035,8	1123,2	1060,0†
Experiment [8]	737,6	815,4	869,0	814,9
I_{exp} [18]	9,24	8,77	8,22	8,86

†In the OST-3GF* basis, 1076.6 kJ/mole.

the vacant d-AOs of the S atom). The calculations were performed by the KVANT-77 program [12] on the BÉSM-6 computer.

The influence of a polar solvent on the energetics of a 1,2-proton shift in the systems under investigation has been considered within the framework of a modification proposed by ourselves [13] (variant SG-1,2) of the solvation model [14] taking into account the interaction of the charge distribution of the solvate with the polarizable dielectric continuum of the medium (in the calculations an effective value of the dielectric constant of the medium $\varepsilon = 80$ was used) and realized by the CNDO/2 method [15].

The calculated values of the relative energies of the LMs and PCs of the protonated heterocycles obtained by various methods, and also the corresponding relative solvation corrections ΔE_S, are given in Table 1. It can be seen that, in all cases with the exception of X = NH, on calculating by the MINDO/3 method protonation at the α position is energetically most favorable and the β-protonated forms are energetically less favorable, while the activation energy of the α,β-proton shift is the lowest among the activation energies of shifts into other positions (an exception is thiophene, for which the activation energy of the X,α-proton shift is smaller). The forms protonated at the heteroatom are energetically the least favorable among the structures corresponding to the LMs on the potential energy hypersurface, but under certain conditions (for example, when substituents are present in the α positions) they may apparently be stabilized as the result of a comparatively large value of the energy barrier of the X,α-shift. The calculations by the OST-3GF method agree qualitatively with the results of the MINDO/3 method, but the scale of the change in the energies of the various forms in the nonempirical calculations is 2.5-3 times greater than in the calculations by the MINDO/3 method. This may be connected both with defects in the minimal basis and, also, partially with the use of geometric parameters optimized by the MINDO/3 method.

On comparing the calculated results obtained for heterocycles with experiment, as a criterion it is customary to use the α,β-selectivity of the electrophilic substitution reaction (or the difference in the α,β-ionic affinity), which, as has been established fairly clearly at the present time (see, for example [16]), decreases relatively sharply in the sequence X = O > S > NH. It actually follows from a comparison of the calculated values of the relative energies of the corresponding σ-complexes (III) and (V) (Table 1) that for pyrrole the selectivity in these processes should be the minimum. However, for furan and thiophene calculations by the MINDO/3 and OST-3GF methods predict an order of selectivity that is the opposite of that found experimentally.

To a certain extent, this may be connected with the influence of solvation. In actual fact, as can be seen from the figures given in Table 1 for the solvation energies ΔE_S, the α- and β-protonated forms of thiophene in a polar solvent are stabilized almost identically (the β-form even somewhat more strongly), while for furan the opposite situation exists — the α-protonated form is stabilized more strongly. This is in harmony with the available experimental results indicating that in solution the difference in the selectivities of furan and thiophene is greater than in the gas phase [8, 16].

A second factor causing an additional stabilization of the β-protonated form of thiophene as compared with the corresponding form of furan may be the participation of the d-AOs of the sulfur atom in the delocalization of the positive charge of the hetarenium ion. The importance of this factor for stabilizing β-protonated forms of type (V) has been shown in a previous paper [17], from the results of which it follows that the higher the percentage of the π-charge in the β-protonated form that is localized on the heteroatom the more relatively stable is this structure.

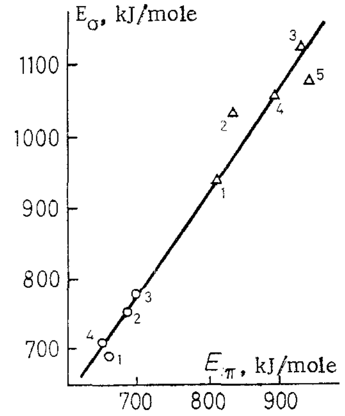

Fig. 2. Correlation between the calculated energies of protonation with the formation of σ- (E_σ) and π- (E_π) complexes: 1) benzene; 2) furan; 3) pyrrole; 4) thiophene (sp basis); 5) thiophene (spd basis); ○ — MINDO/3; Δ — OST-3GF (OST-3GF*).

The calculations of the protonated forms of thiophene on the OST-3GF* basis performed in the present work taking into account the vacant 3d-AOs of the sulfur atom, which were not included in the calculation scheme of the MINDO/3 and OST-3GF methods, showed that in this case the selectivity of thiophene actually becomes lower than that of furan (Table 1). Then the π-charge on the sulfur atom for the β-protonated forms rose from 0.497 (OST-3GF basis) to 0.643 (OST-3GF* basis).

Table 2 gives the calculated values of the energies of protonation (proton affinities) of the heterocycles investigated, and also of benzene, obtained by various methods. They are all in good qualitative and fairly satisfactory quantitative agreement with experiment [8]. At the same time, the results obtained by the MINDO/3 method are somewhat low and those by the OST-3GF (OST-3GF*) method somewhat high in comparison with experiment, but quantitatively the results of the semiempirical approach to this case, on the whole, agree better with the latter.

Heidrich and Grimmer [5] have shown the existence of a linear correlation between the calculated values of the energies of formation of the most stable σ-complex with a proton (arenium or hetarenium ion) and the energies of the formation of the π-complex corresponding to the transition state of a 1,2-shift leading to the σ-complex next in energy. As can be seen from Fig. 2, a similar relationship is satisfactorily followed also for the systems considered in the present paper (correlation coefficient r = 0.978), the points calculated by the MINDO/3 and OST-3GF methods lying on the same straight line.† As a formal explanation of such relationships we may apparently use, on the one hand, the symbaticity in the changes of proton affinity [8] and of ionization potential [18] that has been reported in a number of publications (see, for example [8]) and also exists in this case (Table 2), and, on the other hand, the symbaticity between the barrier to the 1,2-shift (from the α- to the β-position) and the ionization potentials of the corresponding compounds (Tables 1 and 2). The physical reason for the existence of these correlations lies considerably deeper and is connected with the intermediate formation of states with charge transfer in the interaction of an aromatic molecule with an electrophile [19].

In conclusion, we may mention that the mathematical results obtained in the present work may serve as a definite confirmation of the hypothesis of the influence of vacant d-orbital of atoms of period III on the reactivities of chemical compounds. Their relative role in the processes considered may be comparable with the corresponding influence of a polar solvent.

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†The substantiation of this is connected with features of the charge distributions and, as a consequence of the energies of Coulomb interactions for the σ- and π-complexes calculated by the MPNDO/3 and OST-3GF methods, which are not discussed in the present paper.

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A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES.

41.* SYNTHESIS AND SPATIAL STRUCTURE OF 3a-ALKYL-4,7-DICHLORO-1,2-DIOXOOXAZOLIDINO[3,2-f]PYRIDO[2,3-b][1,4]THIAZINES

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UDC 543.51:422.25:541.634:547.836

The structure of the products of the chlorination of oxazolidino[3,2-f]pyrido-[2,3-b][1,4]-thiazines has been studied with the aid of spectral methods. It has been shown that the chlorine atom substitutes position 4 of the tricyclic system (in the thiazine ring). It has been established on the basis of PMR and ^{13}C NMR spectra that in solution the compounds obtained exist in the form of mixtures of two diasteromers with the cis and trans orientations of the substituents at the $C_{(3a)}$ and $C_{(4)}$ carbon atoms of the tricyclic system in each case. The configurations of the diastereomers have been determined from the chemical shifts in the ^{13}C NMR spectra and from the relaxation times in the PMR spectra. It has been shown that the isomer with the transoid arrangement of the substituents on the $C_{(3a)}$ and $C_{(4)}$ atoms of the tricyclic system, which are included in a thiazine ring present in the "half-chair" conformation, is energetically the more favorable.

We have previously developed a method for the synthesis of derivatives of the tricyclic system oxazolidino[3,2-f]pyrido[2,3-b][1,4]thiazine (Ia-c) among which substances possessing antitumoral activity have been found [2, 3].

With the aim of a further search for new biologically active compounds in the 1,4-thiazine series, in the present investigation we have made an attempt to synthesize the 4-halogen derivatives (IIa-c). It has been shown that when substances (Ia-c) are heated in a mix-

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*For communication 40, see [1].

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