SYNTHESIS AND TRANSFORMATION OF SULFIDES OF THE THIOPHENE SERIES. 34.* QUANTUM-CHEMICAL STUDIES OF THE SPECIFICITY OF ELECTROPHILIC ATTACK AND ISOMERIZATION UNDER C-PROTONATION CONDITIONS IN THE ALKYLMERCAPTOTHIOPHENE SERIES

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UDC 547.732.07

2-Methoxy-5-methylthiothiophene, 2,5-bis(methylthio)thiophene, and all of their possible C-protonated forms (σ complexes) were subjected to calculations by the self-consistent-field (SCF) MO LCAO method within the CNDO/2 (complete neglect of differential overlap/2) valence approximation. The results obtained were used to explain the peculiarities of the behavior of these compounds in electrophilic-substitution reactions (Vilsmeier formylation and acetylation). It is shown that the most preferred sites of electrophilic attack in both compounds are the 3 and 5 positions, while the least active site is the 2 position in 2-methoxy-5-methylthiophene, as a result of which one should not observe either migration or splitting out of an OCH_3 group, in agreement with the available experimental data. The energetics of the secondary transformations of the σ complexes formed in the reaction, viz., isomerization and elimination of the SCH_3^+ group, were estimated.

As demonstrated in [2], isomeric 2,4-bis(sulfides) are formed as a result of α-C-protonation of 2,5-bis(alkylmercapto)thiophenes; this process involves intermolecular disproportionation, in the course of which the RS^+ group is converted to a neutral sulfide molecule from the corresponding thiophenium ion (the σ complex). Migration and elimination of alkylmercapto groups also occur under electrophilic substitution conditions, viz., Vilsmeier formylation and acetylation of 2,5-bis(alkylmercapto)thiophenes [3].

As demonstrated in [4], the transformations of the protonated forms (the σ complexes) of mono- and bis(methylmercapto)thiophenes that are due to their different thermodynamic stabilities can be adequately described within the framework of the CNDO/2 (complete neglect of differential overlap/2) method. Let us note here that the thermodynamic stabilities of the C-protonated forms (the σ complexes) of aromatic molecules calculated by any quantum-chemical method can be used as reactivity indexes in aromatic electrophilic-substitution reactions (for example, see [5]). From this point of view it seems of interest to make a comparative study of the orienting effects of methylmercapto and methoxy groups, which, as demonstrated by recent experimental studies [1, 3], are manifested substantially differently in the case of electrophilic substitution in the alkylmercaptothiophene series (I). Thus a product of the IVA type, the formation of which is associated with migration of an SCH_3^+ group to the 4 position, was isolated in appreciable amounts (up to 20-25%) in the Vilsmeier formylation of 2-methoxy-5-methylthiothiophene (IA) [1], whereas under similar conditions in the case of 2,5-bis(methylthio)thiophene (IB) the amount of this sort of product does not exceed 5%, but up to 20% of the product of replacement of one of the SCH_3^+ groups of IIIb is formed.

A number of possible transformations of sulfides I during electrophilic substitution based on the data in [1, 3] are presented in the following scheme:

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*See [1] for Communication 33.

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1035-1039, August, 1981. Original article submitted January 9, 1981.

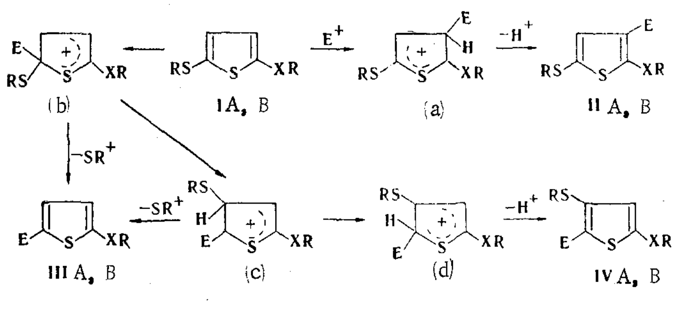
0009-3122/81/1708-0763$07.50

TABLE 1. Calculated Protonation Energies ($-\Delta E^+$, au)

Compound	Protonation site	A/B basis			
		spd	sp	spd	sp
I	2	0,4777	0,4902	0,5524	0,5352
	3	0,4989	0,5226	0,4823	0,5098
	4	0,4793	0,5060	0,4823	0,5098
	5	0,5630	0,5416	0,5524	0,5332
III	2	—	—	0,5415	0,5167
	3	—	—	0,4802	0,5036
	4	—	—	0,4611	0,4777
	5	—	—	0,5012	0,5249
IV	2	0,4646	0,4670	0,5445	0,5167
	3	0,5029	0,5201	0,4868	0,5077
	4	0,5014	0,4927	0,5046	0,4970
	5	0,5311	0,5546	0,5194	0,5494

TABLE 2. Charges of the Atoms of the Thiophene Ring and Overall Charges on the Substituents

Compound	Basis	S_1	C_2	C_3	C_4	C_5	2-SCH_3 or 2-OCH_3	5-SCH_3 or 4-SCH_3
IA	spd	−0,076	0,158	−0,053	0,072	−0,032	−0,061	−0,034
	sp	−0,058	0,186	−0,082	−0,016	0,048	−0,077	−0,030
IB	spd	−0,020	−0,017	0,044	0,044	−0,017	−0,097	−0,097
	sp	−0,022	0,059	−0,032	−0,032	0,059	−0,046	−0,046
III(E)B	spd	−0,034	−0,036	0,028	0,047	−0,018	−0,099	—
	sp	−0,017	0,068	−0,041	−0,007	−0,005	−0,046	—
IV(H)A	spd	−0,102	0,157	−0,027	0,072	−0,046	−0,062	−0,041
	sp	−0,048	0,198	−0,097	0,076	−0,047	−0,073	−0,048
IV(H)B	spd	−0,050	−0,020	0,073	0,050	−0,026	−0,097	−0,115
	sp	−0,012	0,074	−0,049	0,056	−0,035	−0,041	−0,062



I—IV A X=O; B X=S

To ascertain the difference in the reactivities of IA and IB we made model quantum-chemical calculations of IA and IVA ($E^* = H^*$), as well as all of their possible C-protonated forms (see the scheme presented above). Similar calculated data for IB, IIIB, and IVB were taken from [4]. The calculations were made by the self-consistent-field (SCF) MO LCAO method within the CNDO/2 valence approximation [6, 7] with and without allowance for the vacant d AO on the surface atom and with the aid of the modified CNINCO program [8]. The geometrical parameters of the thiophene rings, the SCH_3^+ groups, and the σ complexes were selected as in [4], and an S,O-cis conformation with $\angle COC = 109.5°$, $r_{OC_{ring}} = 1.36$ Å, $r_{OCCH_3} = 1.43$ Å, and a resular tetrahedral structure of the CH_3 group were assumed for the methoxy substituent in all cases. The protonation energies, the charges on the S and C atoms of the thiophene ring, and the overall charges of the substituents are presented in Tables 1 and 2, respectively.

It is apparent from the data presented in the tables that replacement of the SCH_3 group by an OCH_3 group leads to greater activation of the 3 and 5 positions (in analogy with the ortho and para positions of the benzene ring) and deactivation of the 4 (meta) position. This is also apparent from data on the charge distribution (Table 2): The charges on the C_3 and C_5 atoms in IA are more negative, while the charge on the C_4 atom is more positive as compared with IB, regardless of the basis selected. This is in agreement with the known data that the methoxy group is primarily a good π donor and, as a consequence, is a stronger ortho,para-orienting group than the SCH_3 group (for example, see [9]).

The data obtained in this research make it possible to evaluate the orienting effect of the OCH_3 and SCH_3 groups in the thiophene ring. In particular, we observed a linear correlation between the σ_m^+ and σ_p^+ constants of the OCH_3 and SCH_3 substituents in the benzene ring [10] and the $\Delta\Lambda^+$ values for the 4 and 5 positions of IA and IB (relative to the corresponding 3 and 2 positions in the III molecule); this correlation is described by the equation $\sigma^+ = 0.13 + 33.98\ \Delta\Lambda^+$ ($r = 0.96$) for the spd basis or $\sigma^+ = 0.25 + 30.82$ ($r = 0.91$) in the case of the sp basis (the $\Delta\Lambda^+$ values are expressed in atomic units). This may serve as definite evidence in favor of the possibility of the use of the σ^+ constants of the benzene ring also in the case of thiophene compounds, as was pointed out in [11]. However the pronounced deactivation of the ipso-(2) position when X = O is the most substantial difference in the orienting effects of the OCH_3 and SCH_3 groups. This result is in agreement with the experimental fact that neither migration nor splitting out of an OCH_3 group, which could be associated with the formation of a σ complex precisely in this position, was observed for IA under the conditions described [1].

Thus from the examined data in Tables 1 and 2 it may be concluded that in the case of both IA and IB the most preferred sites of electrophilic attack are the 3 and 5 positions; the somewhat smaller gain in energy in the case of attack at the 3 position is compensated by the steric hindrance to attack at the energically more favorable but hindered (by the bulky SCH_3 substituent) 5 position, as a result of which, as follows from the experimental data, the principal product in both cases will be II. As regards side products III and IV (see the scheme presented above), their formation in the case of electrophilic attack on IA and IB may evidently be determined by the different ratios of the elimination and isomerization processes involving the substituents in the σ complexes.

First of all let us examine the energetics of the isomerization process (during which, of course, we should not forget that this process most likely takes place via intermolecular disproportionation [2]; however, this is not essential for the examination of its thermodynamics). The calculated values of the energies of the isomeric (c) and (d) σ complexes relative to the (b) σ complex [the (—) sign corresponds to a gain in energy] are presented in Table 3. It is apparent from these data that the transition from (b) to (c) involves substantial energy expenditures; however, in the case of the (c)→(d) transition these expenditures are partially compensated, as a result of which the entire series of transformations associated with the isomerization of σ complex (b) proceed either with relatively small energy expenditures (for the spd basis) or even with a gain in energy (for the sp basis). As demonstrated in [4], the energic results of calculations within the sp basis describe the experimental data more adequately. The second item to which our attention should be directed in Table 3 is the fact that for both X = S and X = O the energetics of the (b)→(d) transition are approximately the same, whereas the (b)→(c) is preferable in the first case.

Thus the data presented in Table 3, although they do make it possible to substantiate the development of products of the IV type in the case of electrophilic substitution of sulfides I, do not explain the different percentages of this product in the reaction mixture in the formylation of IA and IB. Let us therefore examine the competitive process, viz., elimination.

It has become customary to attribute the tendency for elimination of a cation from the σ complex to its kinetic instability. In [12] it was proposed that the charges on the leaving (in the form of a proton) hydrogen atom and on the C atom bonded to it in the σ complex be used as a measure of the kinetic instability for the splitting out of a proton; it was assumed that if they have the same sign, the given σ complex is kinetically unstable relative to the elimination of a proton. This index is hardly suitable in the case of splitting out of a polyatomic group, since the charge on it is delocalized over several atoms, and each makes a different contribution to the interaction. In the present research for the determination of the tendency of σ complex (b) to undergo elimination of the SCH_3^+ group we therefore used the integral characteristics such as the energy of stabilization of the SCH_3^+ group ($\Delta E_{SCH_3^+}$), which is defined as $\Delta E_{SCH_3^+} = E_b - E_{III} - E_{SCH_3^+}$, where E_b is the total energy of σ complex (b), E_{III} is the energy of III, and $E_{SCH_3^+}$, is the energy of the

TABLE 3. Relative Energies of the Isomeric σ Complexes (in atomic units)

X	σ-complex	Basis	
		spd	*sp*
O	(c)	0,0773	0,0449
	(d)	0,0476	−0,0170
S	(c)	0,0633	0,0349
	(d)	0,0485	0,0175

TABLE 4. Energy of Stabilization of the SCH_3^+ Group and Two-Center Components of the Energy (in atomic units) in σ Complex (b)

X	Basis	$\Delta E_{SCH_3^+}$	E_{SC}
O	*spd*	0,3675	−0,6882
	sp	0,1956	−0,5117
S	*spd*	0,3567	−0,6847
	sp	0,1799	−0,5081

SCH_3^+ cation and the two-center component of total energy E_{SC} [13] in the geminal node of σ complex (b). These values for σ complex (b) when X = O and S are presented in Table 4. It should be noted that the elimination of an SCH_3^+ group is also possible from σ complex (c). The calculations show that it should take place even more readily than in the case of (b) and virtually identically for X = S and O. However, in this case one must take into account the fact that whereas in the case of σ complex (b) elimination competes with the endothermic (b)→(c) isomerization, for σ complex (c) the (c)→(d) isomerization is substantially exothermic, and it can therefore be stated with certainty that the process will be directed precisely to favor this transformation.

In turning to a discussion of the quantitative data on electrophilic substituion in the I series [1, 3] we should point out that, for example, in the case of IB the very fact of the formation of formylation ($E^+ = CHO^+$) side products III and IV is in agreement with the existence in an acidic medium of σ complexes (b) and (d) — the precursors ($E^+ = H^+$) of III and IV, respectively [2, 14]. From this point of view, the use of the data on the C-protonation of sulfides IA and IB obtained in the present research for the discussion of other electrophilic substitution reactions is completely valid. Thus the principal product in the Vilsmeier formylation of sulfides IA and IB is II (A and B, respectively), and the difference between them consists in the fact that whereas the chief side product in the case of IA is IVa, the chief side product in the case of IB is IIIB, and the amount of IVB does not exceed 3-5% [1]. This difference could be determined by the difference in the energies of stabilization of the SCH_3^+ group in σ complex (b). It is apparent from the data in Table 4 that when X = S, the SCH_3^+ group is stabilized to a somewhat lesser degree than when X = O; however, the absolute difference in the stabilization energies is small ($\Delta E_{st} \approx 0.01$ au or 6 kcal/mole) but can completely explain the difference in the yield of IV and the development of III when X = S, even taking into account the elevated energy scale of the CNDO/2 method. On the other hand, the low ΔE_{st} value should suggest its relatively great sensitivity to the external conditions, the nature of the attacking reagent, etc., as a result of which the ratio of the side products should change relatively easily as a consequence of the change in the ratio of the energetics of the isomerization and elimination of the SCH_3^+ group. Precisely this fact may also serve as an explanation of the fact that in the acetylation of IB in the presence of $AlCl_3$ and $SnCl_4$ the principal side product is not IIIB (3-5% in the mixture) but rather IVB (20-40% in the mixture) [3].

In conclusion, let us note that this research is one of the first attempts to arrive at a complete quantum-chemical analysis of the mechanism of aromatic electrophilic substitution by means of an index approach. As we demonstrated above, a task of this type can be broken down into two components. The first component, viz., the prediction of the preferred sites of attack by the electrophile, has been tested quite thoroughly in quantum chemistry, and there are reliable methods for its solution. In fact, the data obtained in this research regarding the preferred specificity of electrophilic attack in the 3 and 5 positions in the investigated compounds and regarding the exceptional disadvantageousness of the formation of a σ complex in the position to which the OCH_3 substituent is bonded (and, consequently, the absence of products of migration or splitting out of this substituent) are in complete agreement with the available experimental data. The second component of the problem, which entails the analysis of the secondary transformations of the intermediates, does not have such an unambigous solution, and the data obtained on the energetics of the isomerization and elimination processes in the σ complexes are more qualitative in character, although they do to a certain extent also explain the experimental data. From this point of view the subsequent verification of the computation approaches used in this research in the case of the analysis of a larger number of specific reactions could be of substantial benefit.

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