QUANTUM-CHEMICAL INVESTIGATION OF THE MECHANISM OF THE SULFONATION OF PYRROLE

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A detailed quantum-chemical study of the sulfonation of pyrrole with regard to the effect of the solvent (the model of overlapping spheres) on the energy characteristics of the formation of the σ-complexes produced during attack on the α- and β-positions of the heterocycle and their possible transformation paths was made by density functional theory [the B3LYP/6-31G(d) method]. The possibility of mutual transformations between the isomeric σ-complexes by α/β-migration of the SO_3 is examined. The formation of pyrrolesulfonic acids was studied for the case of the intramolecular rearrangement of the complexes. Comparison of the activation energies shows that in contrast to the gas-phase reaction the formation of the β-sulfonic acid is preferred in methylene chloride: the solvation energy of the α-isomer of the σ-complex is higher than the energy for the transition state of its rearrangement and its product, α-pyrrolesulfonic acid, leading to an increase in the kinetic barrier and to a decrease of the energy gain on the path to the formation of the latter. The opposite variation of the energy characteristics on the path to the β-isomer with regard to solvation leads to agreement between the calculated data and the experimentally observed preferred formation of the β-pyrrolesulfonic acid.

On the whole the results of calculations [1] carried out by *ab initio* [MP2/6-31G(d)//RHF/6-31G(d)] and density functional theory [B3LYP/6-31G(d)] methods for the molecules of pyrrole, furan, thiophene, selenophene, and the corresponding benzannulated systems and hetarenium ions formed during C-protonation agree with existing experimental data on the positional selectivity not only for acid-catalyzed isotope exchange but also for other electrophilic substitution reactions of five-membered heterocycles containing one heteroatom and some of their derivatives. Disagreement with experiment is only observed for the most active and least selective molecules of pyrrole and its N-substituted derivatives. In all cases investigation of the molecules of various N-substituted pyrroles and of the hetarenium ions formed during their α- and β-protonation by the RHF/6-31G(d), MP2/6-31G(d)//RHF/6-31G(d), and B3LYP/6-31G(d) methods predicts a preference for α-substitution [2], although cases of preferred β-substitution are known in a series of reactions of similar N-substituted pyrroles and in pyrrole itself (see, in particular, the summarizing paper [3]).

In [3] it was suggested that agreement between the calculated and experimental data can be achieved if particles closer to real particles and not the proton are used as model electrophile and the effect of the solvent is taken into account. The results from MP2/6-31G(d)//RHF/6-31G(d) and B3LYP/6-31G(d) quantum-chemical

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* Dedicated to Mikhail Grigor'evich Voronkov.

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calculations for the σ-complexes formed by pyrrole, N-methylpyrrole, and N-(*tert*-butyl)pyrrole with the trimethylsilyl cation instead of a proton as model electrophile agree with experimental data on the formation of β-isomers during trimethylsilylation of pyrrole and its N-substituted derivatives with trimethylsilyl triflate even without taking into account the solvent effect [4]. However, the results from investigation of the sulfonation of the same pyrroles by the B3LYP/6-31G(p) method using the SO_3 molecule as electrophile [4] proved not so clear-cut, since they indicated a preference for the σ-complexes formed during attack at the α position but at the same time indicated greater thermodynamic preferability for the β-sulfonic acids and that it increased in the transition from pyrrole to N-methylpyrrole and then to N-(*tert*-butyl)pyrrole. In [4] to explain this contradiction it was suggested that the more stable σ-complexes formed during attack at the α position are transformed into the α-sulfonic acid more slowly than the isomeric σ-complexes formed during attack at the β-position are transformed into the β-sulfonic acid, and the amount of the minor β-intermediate is made up as a result of the reversibility of the first stage of sulfonation.

The aim of the present work was to make a more detailed quantum chemical study of the sulfonation of pyrrole with regard to the effect of the solvent on the formation and possible transformation paths of the σ-complexes **A** and **B** (Scheme 1).
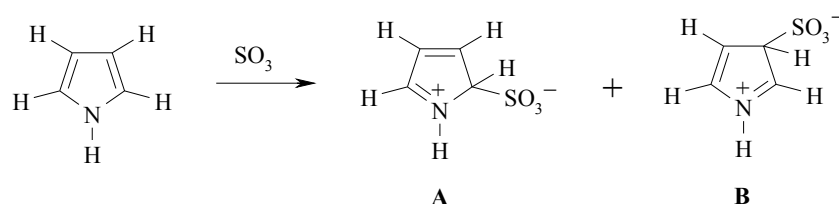
The calculations were performed within the scope of density functional theory by the B3LYP/6-31G(d) method using the Gaussian 98 software package; the solvation effect was included by means of the overlapping sphere model (DPCM) [5]. Methylene chloride was used as model solvent. In the present work we concentrated on the solvent effect, since the action of other factors requires separate special investigation. These points come up again during the study, but it can already be noted, for example, that the qualitative variation of the results presented below is not affected by some widening of the basis set of functions and the inclusion of zero-point energy corrections.

According frontier orbital theory, at the beginning of the first stage of the reaction the bond between the sulfur atom of the SO_3 molecule and one of the pyrrole carbon atoms is generated preferentially at the α-atom, which has the highest HOMO coefficient (0.66 against 0.37 for the β atom for the gas phase, according to data from the B3LYP calculations). The inclusion of solvation does not change the values of the coefficients and does not at this stage correct the observed tendency.

Table 1 gives the relative energies (E_{rel}) for the formation of the intermediates **A** and **B** from pyrrole and SO_3 (ΔE_1) (in solution, in relation to solvated pyrrole and SO_3), the activation energies (E_a) of their rearrangement to the final α- and β-sulfonic acids by transfer of the *ipso* proton from a carbon atom to one of the oxygen atoms of the sulfo group, and the relative energies of the reaction products (ΔE_2). According to the results of the calculations, the addition of the SO_3 molecule to the pyrrole both at that α-position and at the β-position takes place without activation and leads to the formation of the respective σ-complexes **A** and **B** (Fig. 1). Attack at the α-position, leading to the formation of the thermodynamically more favorable intermediate **A**, is preferred (Table 1).

According to the data from the calculations for the gas phase (Fig. 1a), the difference in the energies of the σ-complexes **A** and **B** must lead to a significant preference for form **A** in the supposed equilibrium mixture of isomers, i.e., the fraction of the β-isomer **B** under normal conditions should not exceed 2% of the total number of molecules, and this does not favor the formation of the β-pyrrolesulfonic acid as a result of the
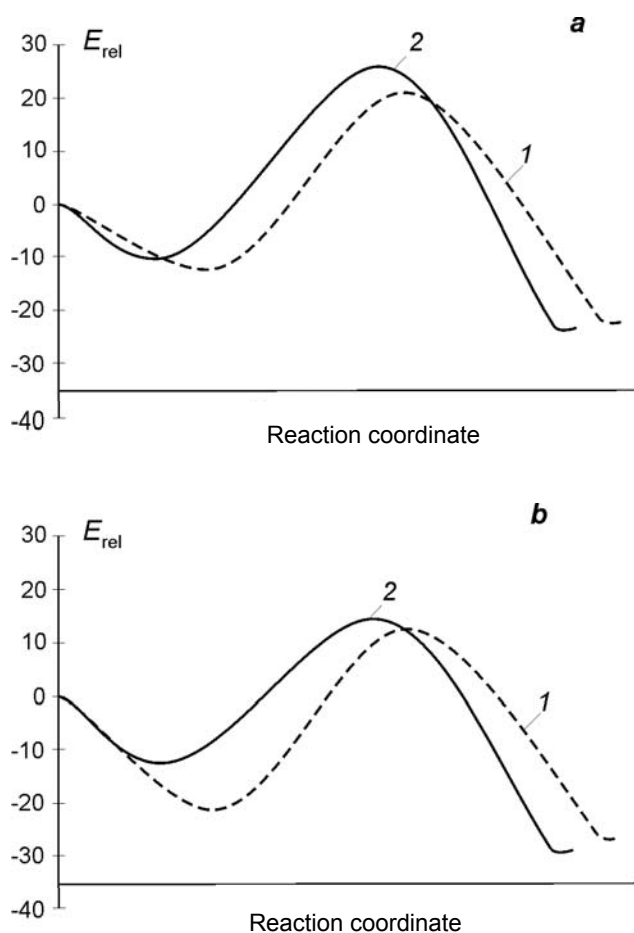
Fig. 1. The energy profiles of the alternative paths for the sulfonation of pyrrole.
The total energy of the isolated pyrrole and SO_3 molecules in the gas phase (a) and in methylene chloride (b) were taken as the zero relative energy of the system (E_{rel}, kcal/mol): 1) α path; 2) β path.

reaction in the gas phase. This ratio of isomers was estimated by the Boltzmann method on the assumption that the preexponential coefficients for the α- and β-substituted compounds and the other corresponding factors are identical:

$$N_\alpha/N_\beta = \exp[-(E^\alpha - E^\beta)/RT], \qquad (1)$$

where N_α and N_β are the numbers of molecules of the α- and β-isomers in one mole of the equilibrium mixture, E^α and E^β are the energies of the isomers, R is the universal gas constant, and T is absolute temperature.

Solvation substantially affects the energy and structural characteristics of the participants in the reaction. Table 2 gives the solvation energies ΔE_{solv} of the intermediates **A** and **B**, the transition states $\mathbf{TS_\alpha}$ and $\mathbf{TS_\beta}$ in the transfer of the *ipso*-proton, the transition state of α/β-migration of the SO_3 group $\mathbf{TS_{\alpha/\beta}}$ and the isomeric pyrrolesulfonic acids, and the corresponding dipole moments. The geometric parameters are given in Table 3. In comparison with the gas phase, for both intermediates **A** and **B** in solution the "double bonds" ($C_{(3)}$–$C_{(4)}$ and $C_{(4)}$–$N_{(1)}$ in molecule **A**, $N_{(1)}$–$C_{(2)}$ and $C_{(4)}$–$C_{(5)}$ in molecule **B**) are shortened and the "ordinary" bonds (($N_{(1)}$–$C_{(2)}$, $C_{(2)}$–$C_{(3)}$, $C_{(4)}$–$C_{(5)}$ and $C_{(2)}$–$C_{(3)}$, $C_{(3)}$–$C_{(4)}$, $C_{(5)}$–$N_{(1)}$ in **A** and **B**, respectively) are lengthened while the C–S bonds are significantly shortened, indicating an increase in the stability of the σ-complexes if solvation is taken into account.

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The energy gain during the formation of complexes **A** and **B** from the initial pyrrole and SO_3 is increased in the transition to the solution (Table 1), and the thermodynamic preference for the more polar α-isomer **A** (Table 2) is increased significantly (Fig. 1b). In comparison with the gas phase the fraction of the intermediate **B** in the equilibrium mixture of **A** and **B**, determined by means of Eq. (1), is negligibly small (~$3 \cdot 10^{-5}$% of the total number of molecules), and this does not make it possible to explain the preferential formation of the β-substituted product by the solvent effect at this stage of the reaction.

In the simplest case the second stage of the formation of the sulfonic acid can be reduced to intramolecular rearrangement of the σ-complex, i.e., transfer of the *ipso*-proton to one of the oxygen atoms of the sulfo group through a four-membered transition state (Fig. 2, Table 3). As in the case of the intermediates **A** and **B**, the transition state of the α-isomer rearrangement **TS$_α$** is energetically more favorable than that for its β analog **TS$_β$** (Fig. 1). During examination of the system in the gas phase (Fig. 1a) the numerical expression for this advantage is comparable with the difference between the energies in the σ-complexes **A** and **B**. In total this leads to close values for the activation energies of the rearrangement processes of the α- and β-isomers in the gas phase (E_a, Table 1). The energy barrier on the path to the formation of α-pyrrolesulfonic acid is nevertheless lower than for the β-isomer. If the ratio of rate constants for the rearrangement of the β- and α-isomers of the σ-complex is determined by analogy with Eq. (1) using the formula:

$$k_β/k_α = \exp[-(E_a^β - E_a^α)/RT], \tag{2}$$

where $k_α$ and $k_β$ are the rate constants of the rearrangements of the α and β-isomers, respectively, of the σ-complex to the sulfonic acids and $E_a^α$ and $E_a^β$ are the activation energies of these processes, then for normal conditions the ratio amounts to 0.02. Consequently, the parameters determined for the gas phase favor the α-substitution path.

TABLE 1. The Relative Energies of the σ-Complexes **A** and **B** (ΔE_1) and the Isomeric Pyrrolesulfonic Acids (ΔE_2) and the Activation Energies of the Intramolecular Rearrangement (E_a) through Transition States TS$_α$ and TS$_β$ (Fig. 2)

Model medium	ΔE_1, kcal/mol		E_a, kcal/mol		ΔE_2, kcal/mol	
	A	**B**	**TS$_α$**	**TS$_β$**	α-Sulfonic acid	β-Sulfonic acid
Gas phase	-1.8	-9.6	32.5	34.9	-21.5	-22.3
CH_2Cl_2	-20.9	-12.0	33.5	26.2	-25.6	-28.0

TABLE 2. The Solvation Energies of the σ-Complexes **A** and **B**, the Transition States TS$_α$ and TS$_β$ (Fig. 2), the Transition State TS$_{α/β}$ (Fig. 3), and the Isomeric α- and β-Sulfonic Acids (ΔE_{solv}) and their Dipole Moments in the Gas Phase and in Methylene Chloride

Property	**A**	**B**	**TS$_α$**	**TS$_β$**	**TS$_{α/β}$**	α-Sulfonic acid	β-Sulfonic acid
ΔE_{solv}, kcal/mol	-13.5	-6.8	-12.6	-15.5	-5.0	-8.5	-10.1
μ (gas), D	6.45	4.77	8.19	10.20	4.05	3.99	5.43
μ (solution), D	11.15	9.42	10.24	12.69	5.85	5.47	6.20

TABLE 3. The Bond Lengths (*l*) of the Pyrrole Ring and C–S in the Pyrrole Molecule, the σ-Complexes **A** and **B**, the Transition States TS$_\alpha$ and TS$_\beta$ (Fig. 2), the Transition State TS$_{\alpha/\beta}$ (Fig. 3), and the α- and β-Sulfonic Acids in the Gas Phase and in Methylene Chloride

Bond	*l*, Å							
	Pyrrole	**A**	**B**	TS$_\alpha$	TS$_\beta$	TS$_{\alpha/\beta}$	α-Sulfonic acid	β-Sulfonic acid
Gas phase								
N(1)–C(2)	1.375	1.404	1.358	1.402	1.339	1.368	1.376	1.363
C(2)–C(3)	1.378	1.420	1.390	1.420	1.410	1.390	1.380	1.380
C(3)–C(4)	1.425	1.380	1.430	1.390	1.450	1.420	1.410	1.420
C(4)–C(5)	1.378	1.400	1.370	1.400	1.360	1.370	1.380	1.370
C(5)–N(1)	1.375	1.340	1.380	1.340	1.400	1.370	1.360	1.380
C(2)–S(6)	—	2.240	—	1.870	—	2.790	1.740	—
C(3)–S(6)	—	—	2.610	—	1.890	2.830	—	1.740
Methylene chloride								
N(1)–C(2)	1.374	1.429	1.331	1.403	1.332	1.363	1.376	1.359
C(2)–C(3)	1.379	1.450	1.420	1.430	1.420	1.400	1.380	1.380
C(3)–C(4)	1.425	1.360	1.450	1.380	1.450	1.420	1.410	1.420
C(4)–C(5)	1.379	1.420	1.350	1.400	1.350	1.370	1.380	1.370
C(5)–N(1)	1.374	1.320	1.400	1.330	1.390	1.370	1.360	1.370
C(2)–S(6)	—	1.990	—	1.840	—	2.670	1.730	—
C(3)–S(6)	—	—	2.200	—	1.840	2.700	—	1.730

In the transition to methylene chloride as medium the energies of the transition states **TS$_\alpha$** and **TS$_\beta$** decrease appreciably on account of solvation (Table 2), whereas the geometric parameters remain largely similar to those calculated for the gas phase (Table 3). In contrast to the intermediates **A** and **B**, the β-isomer of the transition state **TS$_\beta$** is more polar, and its energy decreases to a greater degree if solvation is taken into account, but it is no less polar that the α-isomer of **TS$_\alpha$** (Table 2). Here the difference in the energies of the transition states **TS$_\alpha$** and **TS$_\beta$** becomes insignificant compared with the thermodynamically preferred intermediate **A** in solution (Fig. 1b), and the less favorable β-isomer of the σ-complex **β** is closer in energy to the transition state **TS$_\beta$** than the α-isomer **A** is to the isomeric analog **TS$_\alpha$**. As a result of this the activation barrier E_a on the path to the formation of β-pyrrolesulfonic acid is substantially lower (Table 1) and the ratio of the rate constants of the rearrangement of the β- and α-isomers of the σ-complex (k_β/k_α), determined by means of Eq. (2), is no longer 0.02 (see above) but is approximately $2.5 \cdot 10^5$.
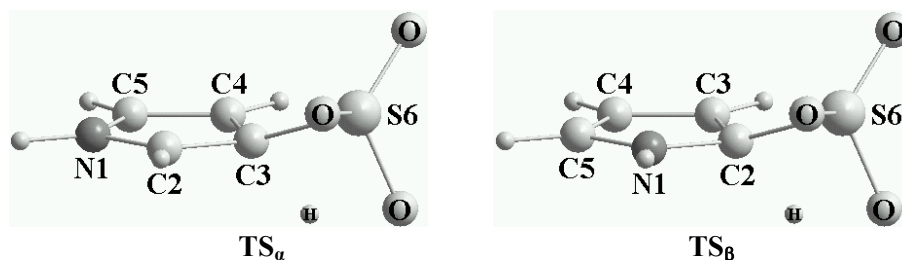

Fig. 2. The transition states in the intramolecular transfer of the *ipso*-proton to the oxygen atom of the sulfo group.

Consequently, the kinetic parameters for the transformation of the σ-complexes **A** and **B** into the reaction products calculated with allowance for the solvation effect make it possible to provide an explanation for the preferential formation of the β-isomer of pyrrolesulfonic acid. However, the very possibility of the rearrangement leading to the observed product must be secured by the presence of at least a small amount of its precursor, i.e., the thermodynamically less favorable intermediate **B**, in the reaction mixture.

As mentioned above, the existence of a certain amount of the σ-complexes **B** in the course of the reaction may be achieved as a result of the reversibility of the first stage of sulfonation. More likely, however, is the possibility that the concentration of the intermediate **B** is maintained by means of α/β migration of the SO_3 group in the σ-complex **A** through the transition state $TS_{\alpha/\beta}$ (Fig. 3). Actually, the calculated activation energy for the transformation of the complex **A** into the isomer **B** in the gas phase amounts to only 2.5 kcal/mol, whereas the dissociation of **A** into the initial pyrrole and SO_3 requires the expenditure of 11.8 kcal/mol (Table 1). The solvent does not have such a significant effect on the energy of the transition state $TS_{\alpha/\beta}$ as in the case of the σ-complex **A** (Table 2), and as before the ratio of the energy expenditures needed to realize either the isomerization or dissociation favors α/β-migration: 11.0 against 20.9 kcal/mol, respectively. Consequently, α/β-migration is capable of securing the presence of the necessary amount of the intermediate **B** in the reaction mixture and kinetic control of the formation of the β-isomer of the sulfonic acid at the stage of proton transfer (rearrangement) in the σ-complexes.

The thermodynamic characteristics of the concluding stage of the reaction also indicate a preference for β-substitution. According to the results of the calculations for the gas phase, the energy gain during the transformation of the thermodynamically less favorable intermediate **B** into the β-pyrrolesulfonic acid, which is more stable than the α-isomer (Fig. 1a), prevents α-substitution (Table 1). In solution the energies of both isomers of the sulfonic acid are appreciably reduced (Table 2), unlike their geometric parameters, which remain practically unchanged (Table 3), and the difference in energies here (Fig. 1b) is increased on account of the predominant solvation of the more polar β-isomer (Table 2). Together with the changes in the relative energies of the σ-complexes (Fig. 1b) the significant decrease in the energy of the β-pyrrolesulfonic acid with inclusion of the solvent effect leads to an even more clearly defined energy preference for β-substitution compared with the gas phase (Table 1).

Thus, examination of the calculated energy characteristics for the reaction of pyrrole with SO_3 in the model methylene chloride medium clearly favors the preferred formation of the β-pyrrolesulfonic acid. By comparing the results obtained for the solution and the gas phase it is possible to clarify the role of the solvent. The solvation energy of the α-intermediate is greater than for the transition state of its rearrangement TS_{α} and the α-pyrrolesulfonic acid, leading to an increase in the activation barrier and a decrease in the thermodynamic energy gain on the path to the production of this form. On the other hand, the opposite ratio of the solvation energies for the corresponding three β-isomers (the σ-complexes, **TS**, and the final products) facilitates the formation of the β-pyrrolesulfonic acid. At the same time a closer understanding of the effect of the polarity of the medium on the sulfonation paths of pyrrole requires further investigation.
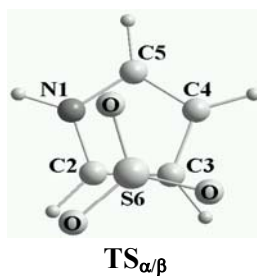

$TS_{\alpha/\beta}$

Fig. 3. The transition state for the α/β-migration of the sulfo group.

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