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QUANTUM-CHEMICAL INVESTIGATION OF THE EFFECT OF SOLVENT POLARITY ON THE DIRECTION OF SULFONATION OF PYRROLE

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The relative stability of the isomeric σ-complexes formed in the sulfonation of pyrrole at the α- or β–position (the α-isomer is energetically more favorable) does not agree with the experimentally established positional selectivity of substitution (the formation of β-pyrrolesulfonic acid). However, quantum-chemical calculations of the energy parameters for the reaction of pyrrole and SO_3 with due regard to the solvation effect in the model solvent methylene chloride (ε = 8.93) lead to the conclusion that the calculated activation energy of the rearrangement to the more favorable β-pyrrolesulfonic acid for the less favorable β-isomer of the σ-complex is lower than on the path to the formation of the α-pyrrolesulfonic acid. It was shown that the significant increase in the polarity of the model medium in the transition to DMSO (ε = 46.7) does not lead to substantial change in the energy parameters of the reaction. The explanation for the positional selectivity during the sulfonation of pyrrole using $Py{\cdot}SO_3$, according to previous data, involves the participation of the pyridine in the transformation of the σ-complexes into the products. The calculations were made by the B3LYP/6-31G(d) and HF/3-21+G methods using the model of overlapping spheres to take account of solvation.

Keywords: quantum-chemical calculations, B3LYP/6-31G(d) method, positional selectivity of substitution, sulfonation of pyrrole.

Earlier [1] we undertook quantum-chemical calculations for the molecules of pyrrole, furan, thiophene, selenophene, and the corresponding benzannelated systems and hetarenium ions formed during their C-protonation by *ab initio* methods [MP2/6-31G(d)//RHF/6-31G(d)] and by density functional theory [B3LYP/6-31G(d)]. On the whole the results of these calculations agree with existing experimental data on the positional selectivity not only for the acid-catalyzed isotope exchange of hydrogen but also for other electrophilic substitution reactions of five-membered heterocycles with one heteroatom and their various derivatives. Only for the most active and least selective compounds (pyrrole and its N-substituted derivatives) are there discrepancies with experiment; calculations by these methods for the molecules of N-substituted pyrroles (substituents at the nitrogen atom R = Me, Et, *i*-Pr, *t*-Bu, $CH{=}CH_2$, C≡CH, Ph, $PhSO_2$, 4-$O_2NC_6H_4$) and the hetarenium ions formed during their □- and □-protonation predict a preference for □-substitution [2], although cases of preferred or even exclusive □-protonation are known for a series of reactions of similar

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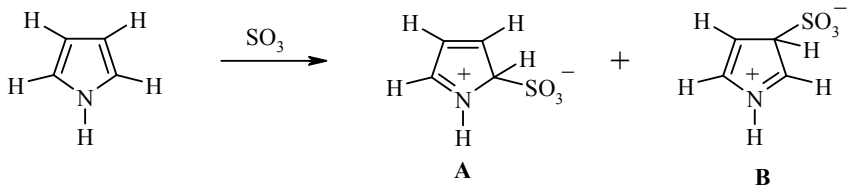
N-substituted pyrroles and of pyrrole itself, as occurs during the silylation of pyrrole [3] and the sulfonation of unsubstituted pyrrole and N-methylpyrrole with pyridinesulfotrioxide [4] (for greater detail, see the review [5]).

In [5] it was suggested that agreement between the calculated and experimental data can be achieved if particles closer to real and not the proton are used as model electrophile and the effect of the solvent is taken into account. In fact, the results of quantum-chemical calculations by the MP2/6-31G(d)//RHF/6-31G(d) and B3LYP/6-31G(d) methods for the σ-complexes formed by pyrrole, N-methylpyrrole, and N-(*tert*-butyl)pyrrole with the trimethylsilyl cation and not the proton as model electrophile [6] agree with experimental data [3] on the formation of pyrrole and its N-substituted derivatives, β-substituted during trimethylsilylation with trimethylsilyltriflate, even if the solvent effect is not taken into account.

However, investigation of the sulfonation of the same pyrroles by the B3LYP/6-31G(d) method using the SO_3 molecule as electrophile [6] did not give entirely unambiguous results. On the one hand they indicated a preference for the σ-complexes formed during attack at the α-position; on the other, they indicated greater thermodynamic preference for the β-sulfonic acids and a stronger preference in the transition from pyrrole to N-methylpyrrole and then to N-(*tert*-butyl)pyrrole. These results were interpreted as being due to the reversibility of the first stage of sulfonation and the enhanced stability of the σ-complexes formed during attack at the α-position.

Recently [7] we showed during quantum-chemical examination of the key stage in the formation of the α- and β-pyrrolesulfonic acids, i.e., intramolecular rearrangement of the respective isomeric intermediates (σ-complexes **A** and **B**, scheme 1), that the results of the calculations do not contradict the experimental data only if the effect of the solvent is taken into account.

Scheme 1



The activation energies of the intramolecular rearrangement of the isomeric σ-complexes in the gas phase, calculated by the B3LYP/6-31G(d) method [7], are similar while the energy barrier on the path to the formation of the α-pyrrolesulfonic acid is even somewhat lower. In terms of the model of overlapping spheres (DPCM) [8] inclusion of the effect of the model solvent (methylene chloride) led to an increase in the activation energy for the intramolecular rearrangement of intermediate **A**; its solvation energy proved larger than for the corresponding transition state of the rearrangement. On the other hand, if the solvation of the isomers of the σ-complex and the transition state was taken into account the energy barrier on the path to the formation of the β-pyrrolesulfonic acid became significantly lower than in the case of the rearrangement of the isomeric intermediate **A**. Together with the thermodynamic preference for the β-isomer of the sulfonic acid this agrees with the experimental data on the preferential formation of the β-sulfonic acid.

In so far as examination of the reaction of pyrrole with SO_3 in methylene chloride (ε = 8.93) [7] even led to a qualitatively different conclusion about the relative preference for the α- and β-substitution paths compared with the nonpolar gas phase (ε = 1), in the present work the effect of increase in the polarity of the model medium was studied. The DMSO medium (ε = 46.7) was chosen for analysis in comparison with the previously studied methylene chloride. The calculations were conducted in density functional theory by the B3LYP/6-31G(d) method using Gaussian 98 software; as before, the solvation effect was taken into account by means of the model of overlapping spheres (DPCM) [8].

TABLE 1. The Relative Energies and their Differences for the σ-Complexes **A** and **B** (E_{int} and ΔE_{int}), the Isomeric Forms of the sulfonic Acid (E_{prod} and ΔE_{prod}), the Transition States TS_α and TS_β (ΔE_{TS}), and the Activation Energy of Intramolecular Rearrangement of the σ-Complexes (Fig. 2) to the α- and β-Forms of the Sulfonic Acid (E_a), kcal/mol

Model medium	E^{α}_{int}	E^{β}_{int}	ΔE_{int}	$E_a{}^{\alpha}$	$E_a{}^{\beta}$	ΔE_{TS}	E^{α}_{prod}	$E^{®}_{prod}$	ΔE_{prod}
CH_2Cl_2 (ε= 8.93)	-20.9	-12.0	-8.9	33.5	26.2	-1.6	-25.6	-28.0	2.4
DMSO (ε = 46.70)	-23.2	-13.4	-9.8	33.7	26.1	-2.2	-27.1	-29.6	2.5

Table 1 gives the relative energies of formation of the intermediates **A** and **B** (scheme 1) from pyrrole and SO_3 (E_{int}) (the energy totals of pyrrole and SO_3 in methylene chloride and DMSO respectively were taken as zero), the activation energies of their intramolecular rearrangement (E_a) to the final α- and β-pyrrolesulfonic acids, the relative energies of the reaction products (E_{prod}), and the differences in the energies of the respective isomers (ΔE_{int}, ΔE_{TS}, and ΔE_{prod}), calculated for methylene chloride and DMSO as media.

In both media the addition of the SO_3 molecule to the pyrrole both at the α- and at the β-position leads to activation and 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** ($\Delta E_{int} < 0$, Table 1), is preferred. The energy difference ΔE_{int} between the σ-complexes **A** and **B** indicates a significant preponderance of the σ-complex **A** in the supposed equilibrium mixture of isomers. In methylene chloride the fraction of the σ-complex **B** under normal conditions must be $\sim 3 \cdot 10^{-5}$% of the total number of molecules if the ratio of the isomers is determined according to Boltzmann:

$$N_\alpha / N_\beta = \exp[-(\Delta E_{int})/RT], \quad (1)$$

where N_α and N_β are the numbers of molecules of the isomeric σ-complexes **A** and **B** in one mole of the reaction mixture; $\Delta E_{int} = E^{\alpha}_{int} - E^{\beta}_{int}$ is the difference between the energies of the isomers; R is the universal gas constant; T is the absolute temperature. In the transition to the more polar medium DMSO the gain in energy during the formation of the complexes **A** and **B** from the initial pyrrole and SO_3 is increased (E_{int}, Table 1). Here the energy advantage (ΔE_{int}) of the intermediate **A** compared with **B** increases appreciably, and the fraction of the intermediate **B** in the equilibrium mixture of **A** and **B**, determined by means of Eq. (1), decreases approximately fivefold ($6 \cdot 10^{-6}$% of the total number of molecules) compared with the methylene chloride medium.

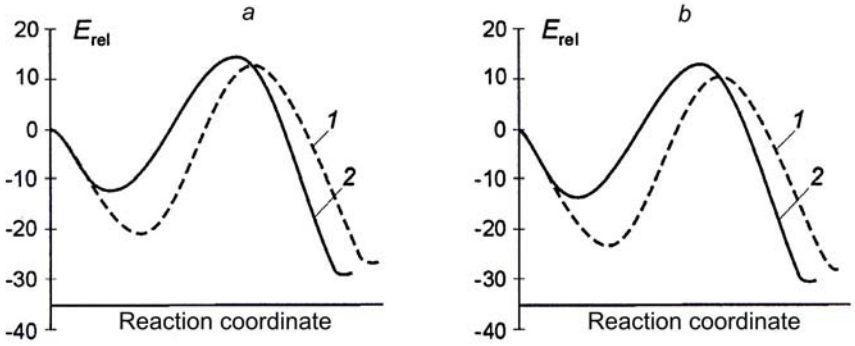
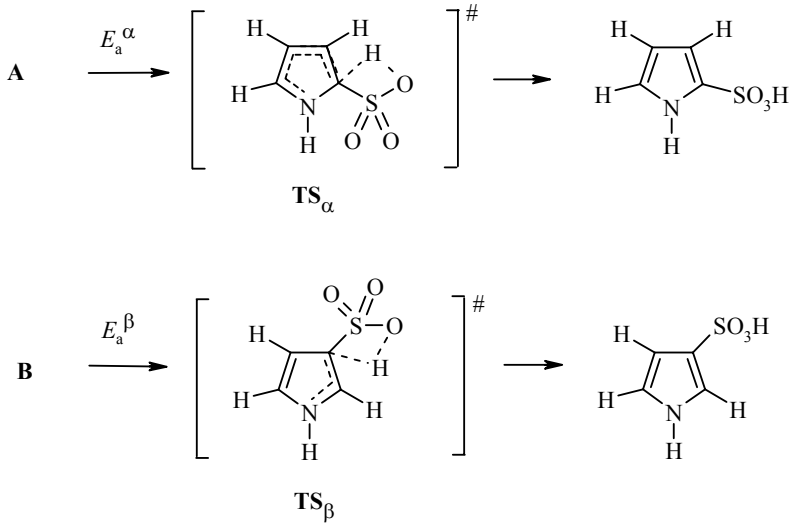


Fig. 1. The energy profiles of the alternative paths for the sulfonation of pyrrole. The total energy of the initial pyrrole and SO_3 in methylene chloride (*a*) and DMSO (*b*) was taken as the zero relative energy of the system (E_{rel}, kcal/mol): 1) α-path; b) β-path.

In the simplest case the second stage in the formation of the sulfonic acid can amount 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 (scheme 2).

Scheme 2



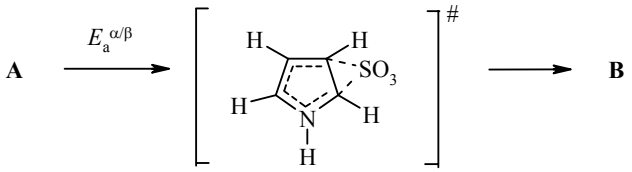
Both in methylene chloride and in DMSO the transition state $\mathbf{TS}_{\alpha}$ of the rearrangement leading to the α-isomer of the sulfonic acid is energetically more favorable than its β-analog $\mathbf{TS}_{\beta}$ (Fig. 1; $\Delta E_{TS} < 0$, Table 1). Here the difference in the energies of the transition states $\mathbf{TS}_{\alpha}$ and $\mathbf{TS}_{\beta}$ ΔE_{TS} is insignificant compared with the thermodynamic advantage of the intermediate **A** in relation to **B** (ΔE_{int}, Table 1), and the less favorable β-isomer of the σ-complex **B** is closer in energy to the transition state $\mathbf{TS}_{\beta}$ than the α-isomer is to the isomeric analog $\mathbf{TS}_{\alpha}$. As a result the activation barrier E_a on the path to the formation of the β-pyrrolesulfonic acid is substantially lower than for the α-isomer (Table 1). If the ratio of the rate constants for the rearrangement of the β- and α-isomers of the σ-complex is determined according to the equation

$$k_{\beta}/k_{\alpha} = \exp[-(E_a^{\beta} - E_a^{\alpha})/RT], \quad (2)$$

where k_{α} and k_{β} are the rate constants for the rearrangement of the respective α- and β-isomers of the σ-complexes to the sulfonic acids and E_a^{α} and E_a^{β} are the activation energies of these processes, according to the calculation for methylene chloride under normal conditions it amounts to $\sim 2.5 \cdot 10^5$. In the transition to DMSO as medium the increase in the difference between the energies of the transition states $\mathbf{TS}_{\alpha}$ and $\mathbf{TS}_{\beta}$ ΔE_{TS} is comparable with the increase in the difference between the energies of the intermediates **A** and **B** ΔE_{int} (Table 1). Here the activation barrier E_a on the path to the formation of the β-sulfonic acid decreases somewhat, while the ratio of the rate constants for the rearrangement of the β- and α-isomers of the σ-complex (k_{β}/k_{α}), determined by means of Eq. (2), amounts to $\sim 4 \cdot 10^5$ against $2.5 \cdot 10^5$ for methylene chloride.

The presence of at least a small amount of the less favorable intermediate **B** in the reaction mixture, which makes it possible for the reaction to take place by the less hindered path to the formation of β-pyrrolesulfonic acid, can be ensured as a result of the reversibility of the first stage of sulfonation [6] or of the α/β migration of the SO_3 group in the σ-complex (scheme 3).

Scheme 3



$\mathbf{TS}_{\alpha/\beta}$

It seems more likely that α/β-migration, which requires less energy, will occur both in methylene chloride and in DMSO. Thus, the activation energy $E_a^{\alpha/\beta}$ for the isomerization of the complex **A** to the isomer **B**, calculated for a solution in methylene chloride amounts to only 11.0 kcal/mol, whereas the dissociation of **A** into the initial pyrrole and SO_3 requires 20.9 kcal/mol ($-E^{\alpha}_{int}$, Table 1). In the case of DMSO the activation energy $E_a^{\alpha/\beta}$ increases little compared with the calculated value for methylene chloride, amounting to 12.6 kcal/mol, and as before the ratio of the energy expenditures on the isomerization and dissociation paths of complex **A** (12.6 against 23.2 kcal/mol respectively) suggests α/β-migration.

The calculated thermodynamic characteristics of the concluding stage both for methylene chloride and for DMSO indicate a preference for the formation of β-pyrrolesulfonic acid (see Fig. 1, E_{prod}, Table 1); unlike the less favorable β-isomer **B** of the intermediate, the β-sulfonic acid has a lower energy than its α-isomer ($\Delta E_{prod} > 0$). With some decrease of the relative energies E^{α}_{prod} and E^{β}_{prod} the quantitative expression for the thermodynamic advantage of the β-form of the sulfonic acid (ΔE_{prod} remains practically unchanged in the transition from methylene chloride to DMSO.

On the whole, comparison of the energy parameters for the reaction of the pyrrole and SO_2 molecules, calculated for the model media methylene chloride and DMSO, shows that the significant difference in the polarity of the solvent does not have a substantial effect on the quantitative ratios of the thermodynamic and kinetic characteristics of the α- and β-substitution paths and, consequently, on the qualitative result. The preferential formation of the β-pyrrolesulfonic acid, observed in both polar media in contrast to the gas phase, is slightly more clearly defined in the case of DMSO. The quantum-chemical calculations that include the solvent effect describe its role in the determination of the energy parameters of the mechanism of sulfonation quite adequately.

Apart from solvation, it is important to consider the role of the base in the approximation of the calculated model of the reaction to the real conditions for the sulfonation of pyrrole. The most important factor determining the energy preference for one of the reaction paths is the possibility that the products are formed as a result of deprotonation of the α- and β-intermediates **A** and **B**. Here the pyridine released as a result of interaction of the $Py \cdot SO_3$ and pyrrole during the formation of the σ-complexes can act as base. This time during study of the deprotonation of the α- and β-intermediates by pyridine in the gas phase we obtained the preliminary results by the HF/3-21+G method [8]. The calculated activation energies (5.2 against 9.3 kcal/mol for the β- and α-isomer respectively) and the ratio of the constants ($k_\beta/k_\alpha \approx 1.0 \cdot 10^3$), determined by means of Eq. (2), indicate a preference for the β-path to the sulfonation of pyrrole with the use of $Py \cdot SO_3$. A more detailed study of the role of the base, including solvation effects, will be the subject of future investigations.

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