Electrophile affinity and positional selectivity in electrophilic substitution reactions of N-substituted pyrroles*

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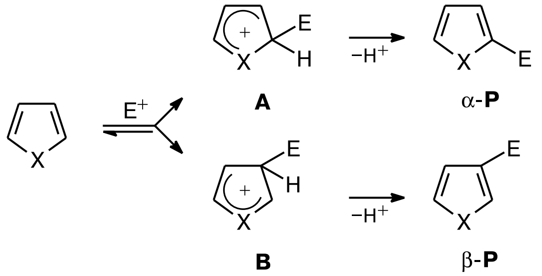
In terms of the density functional theory (DFT) using B3LYP/6-31G(d) method with full geometry optimization, gas-phase quantum chemical calculations were performed for σ-complexes formed upon the attack of electrophiles E (E = H^+, Me^+, Me_3Si^+, Br^+, NO_2^+, $MeCO^+$, SO_3) on α- and β-positions of furan, thiophene, selenophene, pyrrole, and N-substituted pyrroles (NR-pyrroles, R = Me, Bu^t, $SiMe_3$, $SiPr^i_3$, $C_6H_4NO_2$-*p*, SO_2Ph, CHO, COOMe) and for respective α- and β-substituted electrophilic substitution products. The energy differences between the α- and β-isomers of the σ-complexes characterize the preferred direction of the electrophilic attack, while the energy differences between the isomeric products make it possible to estimate the energy preference of a particular product. An analysis of the results obtained demonstrates the effect of the structure of heterocycle, the nature of electrophile, and thermodynamic and steric factors on the positional selectivity (α/β ratio) in electrophilic substitution reactions of π-electron rich five-membered heteroaromatics.

Key words: furan, thiophene, selenophene, pyrrole, N-substituted pyrroles, quantum chemical calculations, density functional theory (DFT), B3LYP/6-31G(d) method.

Predominant formation of either α- or β-isomeric product, α-**P** or β-**P**, in the electrophilic substitution in five-membered aromatic heterocycles C_4H_4X (Scheme 1) is determined by the total energy difference between the isomers **A** and **B** of the σ-complex ($\Delta E_{int} = E_A - E_B$) and between the isomers α-**P** and β-**P** of the product ($\Delta E_{prod} = E_{\alpha\text{-}P} - E_{\beta\text{-}P}$). This is indicated by agreement of the results of calculations for pyrrole, furan, thiophene, selenophene, and benzoannulated systems they form (proton was the model electrophile) with experimental data.[1]

Scheme 1



The energy difference ΔE_{int} shows which isomer of the σ-complex is more favorable and is present in a higher concentration in the equilibrium isomer mixture (the equilibrium between the σ-complex isomers can be attained both due to reversibility of addition of the electrophile and due to direct α,β-migration of the incoming group). If the isomers **A** and **B** of the σ-complex are irreversibly converted to the corresponding isomers α-**P** and β-**P** at equal rates, a higher yield of a particular isomer is due particularly to a higher concentration of the corresponding intermediate in the reaction mixture.

The second energy difference, ΔE_{prod}, determines both the energetic preference of either α- or β-isomer of the product, α-**P** or β-**P**, and the ratio of their yields under conditions of reversible proton elimination in the final step provided there is sufficiently long time for the equilibrium between the product isomers to be established (this may occur not only in the electrophilic substitution but also in acidic α,β-rearrangements of substituted heterocycles, Scheme 2).

In addition, joint consideration of the energy differences ΔE_{int} and ΔE_{prod} allows one to make assumptions about the relative kinetic stabilities of isomeric σ-complexes **A** and **B**. For instance, if both these differences are negative (ΔE_{int} and $\Delta E_{prod} < 0$), thus demonstrating that the α-isomer is preferred both for the σ-complex and for the product, one can expect that the same isomer will be

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* Dedicated to Academician of the Russian Academy of Sciences O. M. Nefedov on the occasion of his 80th birthday.

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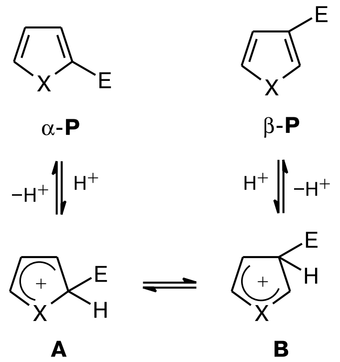
Scheme 2



preferred among the transition states $\mathbf{TS}_\alpha$ and $\mathbf{TS}_\beta$ lying on the pathway from the σ-complex to the product. In this case, apparently, the activation energies E_a^α and E_a^β, and hence the rates of transformation of the σ-complex isomers **A** and **B** into the corresponding product isomers α-**P** and β-**P** would not differ much (Fig. 1, *a*).

In another case, where different isomers are preferred for the σ-complex and for the product (for example, **A** and β-**P** if $\Delta E_{\text{int}} < 0$ and $\Delta E_{\text{prod}} > 0$), the energies of the isomeric systems inevitably approach each other as the systems move along the reaction pathway from isomeric σ-complexes **A** and **B** to products α-**P** and β-**P**, so that the energies of the transition states $\mathbf{TS}_\alpha$ and $\mathbf{TS}_\beta$ located on these pathways may be similar, whereas the activation energies E_a^α and E_a^β of the formation of product isomers α-**P** and β-**P** are fairly different (see Fig. 1, *b*).

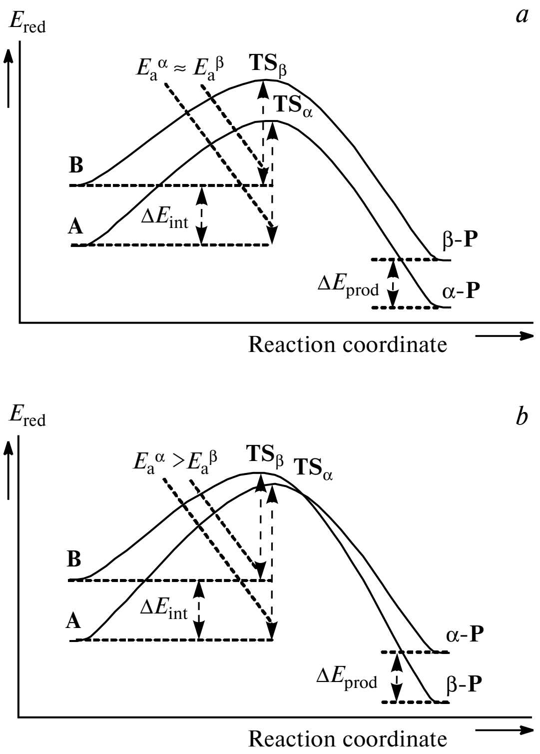


Fig. 1. Energy profiles of alternative pathways of electrophilic substitution in five-membered π-excessive heterocycles.

This means that the thermodynamically more favorable isomer **A** of the σ-complex is kinetically more stable with respect to transformation into the product than the thermodynamically less favorable isomer **B**, and the overall product accumulation is mainly due to the formation of that isomer whose precursor decomposes faster. We considered this situation in detail in relation to sulfonation of unsubstituted pyrrole.[2—4]

Previously, we demonstrated that, unlike other five-membered heteroaromatic compounds with one heteroatom including N-unsubstituted pyrrole, for N-substituted pyrroles a proton is not a versatile model electrophile in quantum chemical calculations and is only suitable for correct description of the positional selectivity of the acid-catalyzed hydrogen isotope exchange.[5,6] It was also assumed that calculations with more realistic electrophiles would be suitable for predicting the direction of electrophilic substitution in N-substituted pyrroles. More recently, the trimethylsilyl cation and the SO_3 molecule were used as model electrophiles, and the energies of the corresponding σ-complexes and the isomeric reaction products were calculated; this made it possible to interpret the positional selectivity of trimethylsilylation and sulfonation of pyrrole and N-alkylpyrroles.[2,7]

In this study, for some N-substituted pyrrole molecules bearing electron-releasing or electron-withdrawing groups at nitrogen, also with different steric requirements, we calculated the affinities of these pyrroles to various electrophiles that attack the α- or β-position in terms of the density functional theory (DFT) and using the B3LYP/6-31+G(d) method [4] without allowance for the solvent effect. These calculations were also carried out for the four first members of the series of π-electron rich five-membered heterocycles, namely, pyrrole, furan, thiophene, and selenophene.

The energy differences ΔE_{int} between the α- (**1**, **1´**) and β-isomers (**2**, **2´**) of the corresponding σ-complexes (see Fig. 1) characterize the preferred site of the electrophilic attack. We also calculated the energies of the isomeric neutral products of electrophilic substitution (in the case of sulfonation, sulfonic acid anions were also studied). The energy difference ΔE_{prod} between the α- (**3**, **3´**, **3″**) and β-isomeric (**4**, **4´**, **4″**) substitution products (see Fig. 1) can be used to estimate the energetic preference of either of them (Table 1). To shorten the computing time, no zero-point vibrational energy corrections were applied. As was demonstrated in our study of sulfonation of pyrroles, when the above-mentioned energy differences (rather than the energies *per se*) are used, the inclusion of zero-point vibrational energy corrections does not affect much the conclusions about the positional selectivity.[4]

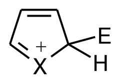
Table 1. Energy differences ΔE_{int} (kcal mol^{-1}) between α- (**1**, **1´**) and β-isomeric (**2**, **2´**) σ-complexes EC_4H_4X ($E = H^+$, Me^+, Me_3Si^+, Br^+, NO_2^+, $MeCO^+$, SO_3) formed from five-membered heterocycles and *N*-substituted pyrroles and the energy differences ΔE_{prod} (kcal mol^{-1}) between the α- (**3**) and β-isomers (**4**) of substitution products formed in reactions with the corresponding electrophiles

X	H^+		Me^+		Me_3Si^+		Br^+		NO_2^+		$MeCO^+$		SO_3		
	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}	ΔE_{int}	ΔE_{prod}[a]	ΔE_{prod}[b]
O	−13.3	0.0	−17.1	−2.5	−6.2	−0.9	−11.9	0.8	−14.4	1.3	−13.8	−0.7	—[c]	0.6	4.5
S	−10.9	0.0	−11.6	0.0	−5.2	−1.7	−8.5	2.4	−9.0	1.9	−8.4	−1.7	—[c]	1.0	2.0
Se	−12.1	0.0	−13.6	−0.9	−7.5	−5.1	−10.4	1.5	−11.5	0.1	−10.2	−3.6	—[c]	−1.5	−0.1
NH	−6.1	0.0	−8.2	−1.3	−2.2	−0.6	−6.3	0.7	−7.5	−1.2	−7.3	−4.5	−2.2	−7.6	0.8
NMe	−4.7	0.0	−6.5	−0.9	−0.1	0.8	−5.7	0.3	−5.6	1.2	−6.1	−2.2	−2.7	−6.6	4.0
NBu^t	−4.0	0.0	−3.1	3.3	4.1	7.1	−3.4	2.5	−2.5	6.6	−2.9	2.5	−1.1	−2.7	8.7
$NSiMe_3$	−5.4	0.0	−5.9	0.8	1.4	5.0	−6.7	−1.0	−6.0	−1.0	−5.6	−3.7	−3.0	−7.1	4.3
NSi^iPr_3	−5.0	0.0	−4.4	3.8	4.6	10.8	−5.3	2.3	−5.2	1.3	−4.0	−1.3	−2.5	−1.2	10.3
$NC_6H_4NO_2$-*p*	−5.4	0.0	−7.5	1.4	−0.9	3.1	−4.4	2.5	−5.5	4.9	−6.3	1.6	−1.0	−2.8	5.9
NSO_2Ph	−6.1	0.0	−6.9	0.4	−0.9	1.5	−6.2	3.4	−6.4	5.4	−6.6	7.2	1.4	1.8	0.0
NCHO	−9.1	0.0	−10.9	−0.9	−3.4	−3.4	−8.0	1.5	−8.7	2.4	−8.5	5.7	−0.7	−5.1	0.4
NCOOMe	−7.4	0.0	−9.2	0.3	−2.3	−0.5	−6.6	5.4	−8.3	9.7	−7.5	6.7	−0.4	7.9	0.6

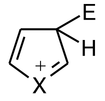
[a] The energy differences between the α- and β-isomeric sulfonic acid anions are given.

[b] The energy differences between the α- and β-isomeric neutral sulfonic acids are given.

[c] We failed to locate a minimum corresponding to the β-isomeric σ-complex on the PES.



1



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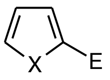

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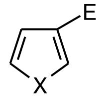

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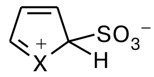
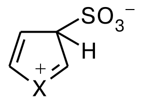


1′



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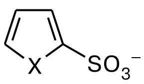

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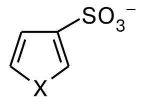

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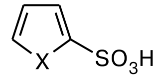
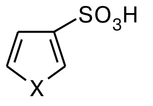


3″

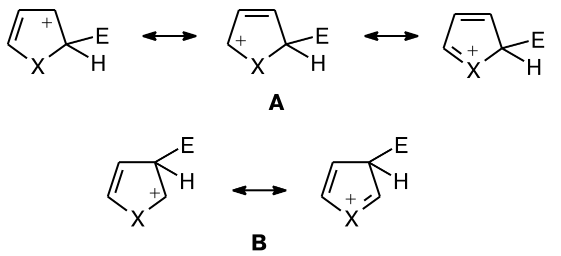


4″

The differences ΔE_{int} presented in Table 1, which characterize the positional selectivity of substitution for 84 reactions involving 12 heterocycles and 7 electrophiles, are in reasonably good agreement with the available experimental data. As was shown,[5,6] the results of calculations are in excellent agreement with the experimental results[8] for a number of *N*-substituted pyrroles having a deactivating group (Ac, PhCO, $MeSO_2$, CF_3SO_2, $PhSO_2$, Me_3N^+, Me_2NH^+) at nitrogen in the hydrogen isotope exchange in which the cationic σ-complexes studied correctly model the intermediates. The exchange rate in the α-position is always more than an order of magnitude higher than that in the β-position.

The simplest cationic σ-complexes of aromatic five-membered heterocycles are formed upon protonation of the α- and β-positions of pyrrole, furan, thiophene, and selenophene. In all cases, α-protonation is preferred ($\Delta E_{\text{int}} < 0$, see Table 1), which is attributable to better delocalization conditions of the positive charge in the α-isomer **A** of the σ-complex compared with its β-isomer **B** (Scheme 3).

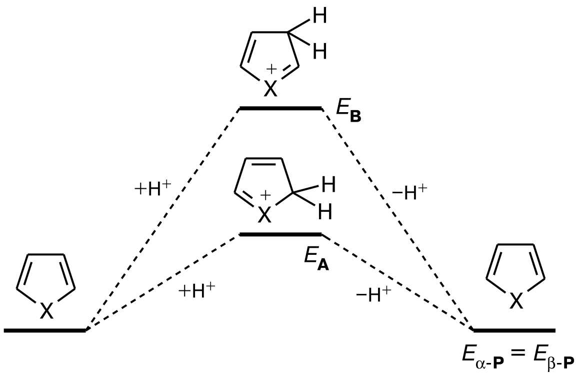
Scheme 3



The energetic preference of the α-isomer increases in the series pyrrole < thiophene < selenophene < furan. This corresponds to the relative stability series of the onium states of heteroatoms $N^+ > S^+ \geq Se^+ > O^+$ and can be related to their predominant role in the stabilization of the β-isomers **B** (charge delocalization involves, besides the heteroatom, two ring carbon atoms in the α-isomers and only one α-carbon atom in the β-isomers).[9–15]

The results obtained for *N*-substituted pyrroles support this view. The advantage of the α-isomer of the σ-complex with the proton is more pronounced when nitrogen bears electron-withdrawing groups and is less pronounced in the case of electron-releasing substituents (see Table 1).

Naturally, the energy differences between the α- (**3**) and β-isomers (**4**) of the substitution products formed in



X = O, S, Se, NH, NMe, NBu^t, $NSiMe_3$, $NSiPr^i{}_3$, $NC_6H_4NO_2$-*p*, NSO_2Ph, NCHO, NCOOMe

Fig. 2. Specific features of proton exchange as a model reaction.

the reactions with proton as a model electrophile are equal to zero (Fig. 2). Hence, strictly speaking, the results of calculations do not allow one to estimate the probability of formation of α- or β-isomeric final substitution products with electrophiles other than proton.

On going from the proton to other electrophiles, the above-described trends are generally retained; however, specific electronic and steric features of the electrophiles also start to play a role. The ΔE_{int} differences for the σ-complexes formed by electrophiles with unsubstituted pyrrole and chalcogenide heterocycles show (see Table 1) that for the Br^+ and $NO_2{}^+$ cations, the preference of the formation of α-isomer **A** is approximately the same as with the proton, while for Me^+ it is more pronounced. The $SiMe_3{}^+$ cation and a neutral Lewis acid SO_3 are, conversely, less selective, although the attack on the α-position still remains favored. These features are manifested in the complexes with *N*-substituted pyrroles (see Table 1), although the steric interactions of the electrophilic moieties and substituents at the nitrogen atom considerably destabilize the α-isomeric σ-complexes, which is particularly pronounced for the addition of the bulky $SiMe_3$ group.

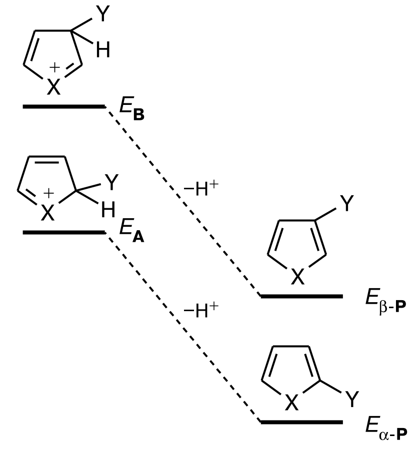
The steric effect on the energy ratio of the α- and β-isomers becomes generally prevailing for the electrophilic substitution products (see Table 1), which is indicated by the lack of clear-cut α,β-preference for substituents E in the heterocycles EC_4H_3X (except for $SO_3{}^-$). This is evidenced by the differences ΔE_{prod} for the products devoid of substituents at the ring heteroatom. Moreover, in α-isomeric *N*,*C*-substituted pyrroles α-**P**, the substituents are more crowded than in analogous σ-complexes **A** in which the electrophilic moiety bonded to an sp^3-hybridized carbon atom is remote from the ring plane near which the N-substituent resides. Consequently, the β-isomer β-**P** is most often a more favorable electrophilic substitution product.

An interesting exception is the considerable energetic preference of α-isomeric α-**P** for pyrrolesulfonic acid anions, especially as compared with neutral pyrrolesulfonic acids (see Table 1). It is observed in almost all cases except for those where α-isomeric anions are destabilized due to the inevitable proximity of the COOMe or SO_2Ph oxygen atoms and the $SO_3{}^-$ group (conversely, the corresponding α-pyrrolesulfonic acids are stabilized by intramolecular hydrogen bonds). Considering the charges found in our calculations, in most α-isomeric pyrrolesulfonic acid anions, the electrostatic interaction of the $SO_3{}^-$ group and the substituent at the nitrogen atom is energetically favorable.

Under real conditions of pyrrole sulfonation with pyridinesulfotrioxide, the direct products are contact ion pairs resulting from deprotonation of the intermediate σ-complexes with pyridine. The detected differences in the α,β-preferences are characteristic of isomeric pyrrolesulfonic acids and the acid anions call for more precise consideration taking into account the formation of pyrrole sulfonation products as salts.

For electrophiles other than protons, according to our calculations (see Table 1), intermediates resulting from the α-attack (Fig. 3) are also preferred ($\Delta E_{\text{int}} < 0$) in most cases: in 80 out of 84 reactions presented in Table 1, cationic σ-complexes **A** formed upon the α-attack predominate. Nevertheless, for many of the reactions in question, β-isomeric final products β-**P** are favored from the thermodynamic standpoint.

If the 12 reactions where proton is the electrophile are excluded, the formation of α-isomeric final products is thermodynamically more favorable only in 23 out of the remaining 72 reactions (see Fig. 3). If we neglect the reac-



Y	X
Me^+	O, S, Se, NH, NMe, NCHO
Me_3Si^+	O, S, Se, NH, NCHO, NCOOMe
Br^+	$NSiMe_3$
$NO_2{}^+$	NH, $NSiMe_3$
SO_3	Se, NH, NMe, NBu^t, $NSiMe_3$, $NSiPr^i{}_3$, $NC_6H_4NO_2$-*p*, NCHO

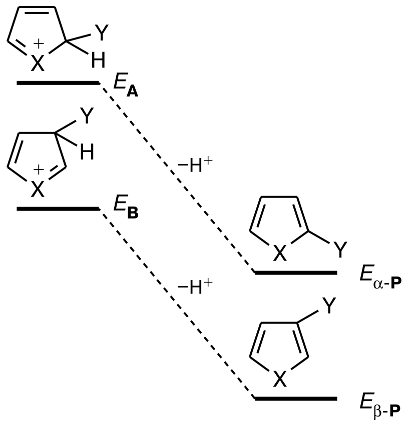
Fig. 3. Rearomatization steps of reactions with predominant α-substitution (intermediates **A** and products α-**P** are energetically preferred).

tions of the first members of the series the results for which were reported previously, restricting ourselves to the *N*-substituted pyrroles, there will be only 11 reactions in which the formation of isomers α-**P** is energetically preferred.

Preferred formation of cationic σ-complexes **B** corresponding to the β-attack and the subsequent formation of β-substituted products β-**P** (Fig. 4) was found only in four reactions: silylation of *N*-(*tert*-butyl)-, *N*-(trimethylsilyl)-, and *N*-(triisopropylsilyl)pyrrole and sulfonation of *N*-phenylsulfonylpyrrole.

The formation of β-substituted products is consistent with experimental data and can be attributed to steric effects.[16,17] These effects are especially clearly manifested for the most bulky of the studied groups, $(Pr^i)_3Si$. Indeed, almost exclusive formation of β-substitution products was reported for bromination, iodination, nitration, acylation, and formylation of *N*-(triisopropylsilyl)pyrrole.[16] The crucial role of particularly the steric effects in reactions of *N*-(triisopropylsilyl)pyrrole is clearly seen by considering the acylation with *N*-aroylbenzotriazoles (ArCO = = 4-MeC_6H_4CO, $4\text{-O}_2NC_6H_4CO$, $4\text{-Et}_2NC_6H_4CO$, 2-furoyl, pyridine-2-carbonyl, indole-2-carbonyl, pyrrole-2-carbonyl) in the presence of $TiCl_4$. Under these conditions, pyrrole and *N*-methylpyrrole are converted to 2-acylpyrroles, and *N*-(triisopropylsilyl)pyrrole gives 3-acylpyrroles.[18]

Apart from the steric shielding of the α-positions by bulky N-substituents, polar effects favoring β-substitution can also be noted: the electron-donor Bu^t, Me_3Si, and $(Pr^i)_3Si$ groups at nitrogen should enhance the basic properties of the heteroatom, and this increases the relative stability of the cationic σ-complex resulting from the β-attack of the electrophile.[1,6,9,10]

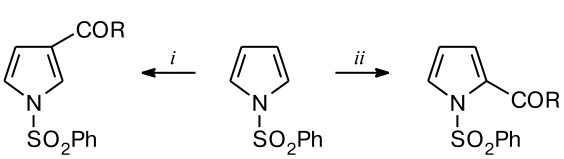


$Y = Me_3Si^+$; $X = NBu^t$, $NSiMe_3$, $NSiPr^i_3$
$Y = SO_3$; $X = NSO_2Ph$

Fig. 4. Rearomatization steps of reactions with predominant β-substitution (intermediates **B** and products β-**P** are energetically preferred).

Unlike electron-releasing substituents, electron-withdrawing groups at the N atom should reduce the ability of the heteroatom to stabilize the onium state and thus facilitate the α-substitution (see Refs 11—14). The effect of the *N*-phenylsulfonyl substituent was studied in most detail.[19—22] The reactions of *N*-(phenylsulfonyl)pyrrole such as the Riche[19,20] or Vilsmeier[19] formylation and cyanation with cyanogen bromide or chlorosulfonyl isocyanate[19,22] yield only 2-substituted products. Of particular interest are the results of Friedel—Crafts acylation of *N*-phenylsulfonylpyrrole:[19—26] in the presence of boron trifluoride etherate, 2-acyl-substituted pyrroles are formed, while with aluminum chloride, the reaction gives the 3-isomers (Scheme 4).

Scheme 4



i. $(RCO)_2O$ or RCOCl, $AlCl_3$, $(CH_2Cl)_2$, −20°C. *ii*. $(RCO)_2O$ or RCOCl, BF_3, OEt_2, $(CH_2Cl)_2$, ~20 °C.

The nitration (HNO_3—Ac_2O) involves position 3 almost exclusively (see Ref. 21). Chlorosulfonation of 1-(R-phenylsulfonyl)pyrroles (R = H, *p*-Me, *p*-NO_2, *p*-CF_3) with chlorosulfonic acid in acetonitrile produces the corresponding pyrrole-3-sulfonyl chlorides.[27] *N*-Tosylpyrroles are smoothly converted to 2-acylpyrroles with no 3-isomer impurity by the reaction with a mixture of carboxylic acids and trifluoroacetic anhydride.[28]

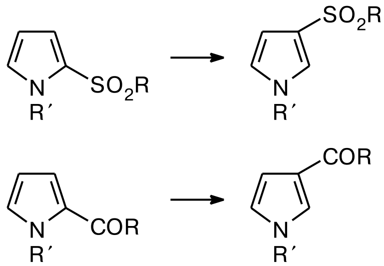
These differences in the direction are usually interpreted resorting to the principle of hard and soft acids and bases (HSAB): the site of attack of a hard electrophile is mainly dictated by the charge, while 2-substitution observed for softer electrophile is due to the orbital control.[20] In our opinion, in many cases where the electrophile attacks predominantly the α-position and the thermodynamically more stable β-isomer is formed as the reaction product, the initially formed α-isomer is probably isomerized.[15]

The presented examples are evidently explained by the nature of the electrophile; however, some facts attest to a considerable role of the size of the electrophilic species. Thus the positional selectivity of alkylation of *N*-(phenylsulfonyl)pyrrole in the presence of $AlCl_3$ varies from the predominant α-substitution (with EtBr) to the formation of a 1 : 1 mixture of α- and β-substituted products (with Pr^iCl) and then to the predominant (80%) formation of the β-substituted product for Bu^tCl (see Ref. 22).

Thus, one can conclude that the quantum chemical data on the sulfonation of *N*-phenylsulfonylpyrrole presented in Table 1 are not only exceptions to the results of calculations but also do not agree with known experimental facts. The calculation results in the case of pyrrole and *N*-methylpyrrole sulfonation point to higher stability of σ-complex **A**, which corresponds to α-substitution, whereas the obtained products proved to be β-sulfonic acids. Considering the higher thermodynamic stability of pyrrole-3-sulfonic acid predicted by calculations, one can suggest that the initially formed 2-sulfonic acid rearranges to the β-isomer.[2]

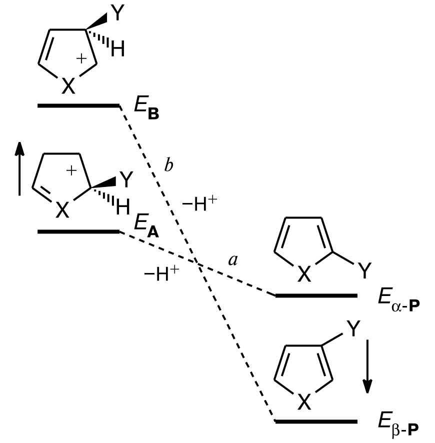
A similar process probably takes place in the acylation of *N*-phenylsulfonylpyrrole. It was already mentioned above that in the presence of BF_3 etherate, the reaction gives α-acylated pyrrole, while in the presence of $AlCl_3$, β-acylated product is formed. The acid-catalyzed rearrangements of 2-sulfonyl-substituted pyrroles[29] and 2-acylpyrroles[30—32] to 3-isomers are well known (Scheme 5). In particular, the formylation and acylation of *N*-pentafluorophenylpyrrole involve mainly position 2. The resulting 2-acylated pyrroles can be selectively converted to the 3-isomers in high yields by treatment with trifluoromethanesulfonic acid, which was proposed as a general synthesis of 3-acylpyrroles.[32]

Scheme 5



This type of rearrangement is usually interpreted as being due to *ipso*-protonation of the α-carbon atom bearing a substituent to give the corresponding cationic σ-complex, which then undergoes a 1—2-rearrangement to the β-*H*-hetarenium ion, which is deprotonated to give neutral β-substituted product. Meanwhile, the intermediate arising upon the α-attack of the *N*-substituted pyrrole is exactly the cationic σ-complex that rearranges to the β-*H*-hetarenium ion, which is facilitated by specific features of the primarily formed α-*H*-hetarenium ion that can be regarded as steric hindering of the re-aromatization step.[33]

This type of steric hindrances was observed[33] in an attempt of *tert*-butylation of 2-*tert*-butyl-4-methylthiophene where the resulting rather stable σ-complex (detected by ^1H and ^{13}C NMR) cannot be deprotonated, apparently due to steric interaction of the *tert*-butyl and methyl groups. In the case of *N*-substituted pyrrole, a similar steric interaction may occur between the N-substituent and the electrophile in the α-position; however, the absence of substituent in the β-position creates conditions for deprotonation and subsequent α to β migration of the electrophile.



Y	X
Me^+	NBu^t, $NSiMe_3$, $NSiPr^i_3$, $NC_6H_4NO_2$-*p*, NSO_2Ph, NCOOMe
Me_3Si^+	NMe, $NC_6H_4NO_2$-*p*, NSO_2Ph
Br^+	$NSiMe_3$, NSO_2Ph
NO_2^+	NH, $NSiMe_3$, NSO_2Ph
SO_3	O, S, NH, NMe, NBu^t, $NSiMe_3$, $NSiPr^i_3$, $NC_6H_4NO_2$-*p*, NCHO, NCOOMe

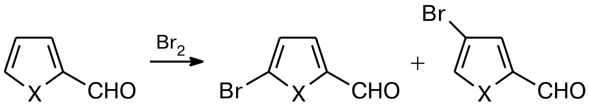
Fig. 5. Steps of the reaction to give β-substituted β-**P** products with energetically preferred α-isomer **A** of the σ-complex.

Thus, two options can be considered for the transformation of thermodynamically more favorable σ-complex **A** resulting from the α-attack to thermodynamically more favorable β-substitution product β-**P** (Fig. 5): (*a*) deprotonation to give α-substituted product α-**P** followed by its rearrangement to the β-isomer β-**P** and (*b*) α/β-isomerization (**A** → **B**) followed by deprotonation to the β-isomer β-**P**.

Note in conclusion that due to the low positional selectivity of the reactions of pyrrole with electrophiles, any structural variations have a pronounced effect on the direction of electrophilic substitution in the pyrrole series. For example, *meta*-directing aldehyde group in position 2 of the pyrrole ring, unlike thiophene, selenophene, and especially furan rings, can overcome the α-directing effect of the heteroatom and directs the electrophile mainly to position 4 (see Ref. 34). However, *N*-(*p*-nitrophenyl)-2-pyrrolecarbaldehyde is brominated in position 5, and only when complexed with aluminum chloride, it is converted to 4-bromo-1-(*p*-nitrophenyl)-2-pyrrolecarbaldehyde,[35] thus resembling 2-thiophenecarbaldehyde (Scheme 6).

Thus, we used the results of our quantum chemical calculations revealed the effect of the nature of the ring heteroatom (O, S, Se, and NR, where R = H, Me, Bu^t, $SiMe_3$, Si^iPr_3, $C_6H_4NO_2$-*p*, SO_2Ph, CHO, COOMe), the nature of the electrophile (H^+, Me^+, Me_3Si^+, Br^+, NO_2^+, $MeCO^+$, SO_3), and thermodynamic and steric factors on the positional selectivity (α/β-ratio) in the electrophilic

Scheme 6



X	Isomer	
	2,5	2,4
NH	Traces	Major product
$NC_6H_4NO_2$-*p*	100%	—

substitution of π-excessive five-membered heteroaromatic compounds. In relation to bulky N-substituents (Bu^t, $SiMe_3$, Si^iPr_3) and electrophiles (Me_3Si^+, SO_3), the pathways to the final β-substituted products were studied. It was shown that the thermodynamic factors are favorable for the β-attack of the *N*-(*tert*-butyl)-, *N*-(trimethylsilyl)-, and *N*-(triisopropylsilyl)pyrroles with the trimethylsilyl cation to give *N*-substituted 3-(trimethylsilyl)-2*H*-pyrrolium ions. In the case of reactions such as bromination, nitration, acylation, and sulfonation, the formation of α-substituted σ-complexes is preferred. These complexes can further rearrange to β-substituted products *via* either the 2*H*-pyrrolium ion or the deprotonation step, resulting in 2-substituted pyrrole, which then isomerizes to the thermodynamically favored 3-isomer. The enhanced stability of the β-substituted σ-complex observed for sulfonation of *N*-(phenylsulfonyl)pyrrole may be attributed to the lack of stability of its α-isomer caused by the Coulomb repulsion between the oxygen atoms of the *N*-sulfonyl group and the SO_3^- anion (when sulfur trioxide is used as the reagent, the intermediate is a bipolar ion).

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