Substrate and positional selectivity in electrophilic substitution reactions in pyrrole, furan, thiophene, and selenophene derivatives and related benzoannelated systems*

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Data on the relative reactivities (substrate selectivity) of five-membered heterocycles in electrophilic substitution reactions and positional selectivity (α : β ratio) in these reactions were analyzed. Unlike the substrate selectivity (pyrrole ≫ furan > selenophene > thiophene) determined by the position of heteroatoms in the Periodic Table, the positional selectivity decreases in the order corresponding to the change in the relative stability of the onium states of the elements ($O^+ < Se^+ \leq S^+ < N^+$) and reflects the predominant role of heteroatoms in the stabilization of σ complexes formed upon β-substitution. These differences in the positional selectivity of the parent heterocycles have a substantial effect on the orientation in electrophilic substitution reactions in their derivatives and the corresponding benzoannelated systems. This interpretation was confirmed by *ab initio* quantum chemical calculations (RHF/6-31G(d) and MP2/6-31G(d)//RHF/6-31G(d)) and density functional theory calculations (B3LYP/6-31G(d)). Quantum chemical calculations were performed by the above-mentioned methods for model *N*-R-pyrroles (R = Me, Et, Pr^i, Bu^t, $CH{=}CH_2$, C≡CH, Ph, $PhSO_2$, and 4-$O_2NC_6H_4$) and their α- and β-protonated σ complexes. The results of these calculations demonstrated that it is the steric factors and charges on the β-C, α-C, and N atoms and the substituents at the N atom (the kinetic control), as well as the nature of the electrophile, rather than the difference in the relative stabilities of the onium states of N^+ (which depends on the nature of the substituent at the N atom and reflects the role of the heteroatom in stabilization of σ complexes formed *via* β-substitution; the thermodynamic control) that are responsible for the type of orientation (α or β) that prevails.

Key words: pyrrole, furan, thiophene, selenophene, indole, benzo[*b*]furan, benzo[*b*]thiophene, benzo[*b*]selenophene, electrophilic substitution, substrate selectivity, positional selectivity, cationic σ complexes, relative stability of onium states of chalcogens, quantum chemical calculations, *ab initio* methods (RHF/6-31G(d), MP2/6-31G(d)), DFT B3LYP/6-31G(d).

Electrophilic substitution is the most important class of reactions of five-membered heterocycles with one heteroatom, which allows one to prepare compounds with various substituents. The present paper summarizes the results of theoretical studies of the features of the substrate and positional selectivities in electrophilic substitution reactions in pyrrole, furan, thiophene, and selenophene derivatives and the corresponding benzoannelated systems that have been rationalized only recently.

It is well known that the effect of the heteroatom is manifested in the higher reactivities of the α positions. This is generally interpreted as the result of higher stability of the corresponding σ complex (**A**) due to favorable charge delocalization compared to its isomer (**B**) resulting from the attack at the β position (Scheme 1).

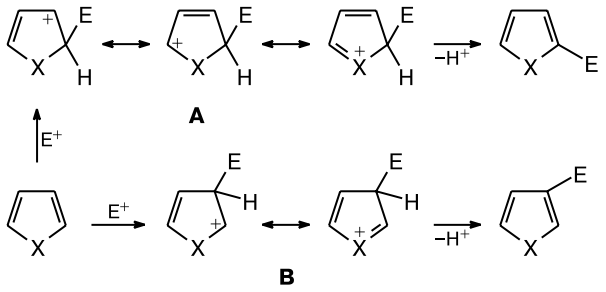
The reactivities and positional selectivities of pyrrole, furan, and thiophene and the reactivity of selenophene in electrophilic substitution reactions were studied quantitatively.[1,2] There are tremendous differences in the reactivity, which drops by approximately ten orders of magnitude in the series pyrrole ≫ furan > thiophene. This fact is attributable to the difference in the conditions of electron density delocalization over the heterocycle, resulting in the overlap of the π orbitals of the C atoms with the n orbitals of the heteroatoms belonging to different groups

* Dedicated to Academician V. I. Minkin on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 4, pp. 837—846, April, 2005.

1066-5285/05/5404-0853

Scheme 1



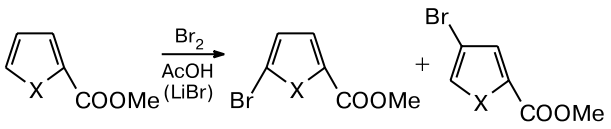
and periods of the Periodic Table. The differences in the positional selectivity are less pronounced. For example, in acetylation the difference in the α : β ratio (ratio of the α- to β-substitution products) between the most selective furan and the least selective pyrrole is "only" three orders of magnitude. It should be emphasized that this ratio changes in the series furan > thiophene > pyrrole, which does not correlate with the above series of the reactivities (substrate selectivity) in electrophilic substitution reactions.[1,2]

Positional selectivity in reactions of furan, thiophene, selenophene, pyrrole, and their derivatives with electrophiles

A hypothesis that rationalized the discrepancy between the substrate and positional selectivities of electrophilic substitution reactions in five-membered heterocycles containing one heteroatom was proposed twenty five years ago.[3,4] Its essence is that the formation of β-substituted compounds occurring through σ complexes **B** where only the heteroatom and one of the α-carbon atoms are involved in charge delocalization depends more substantially on the ability of the elements X to exist in the onium state than the formation of α-substituted derivatives where all atoms of the rings, except for the geminal C atom, are involved in charge delocalization in the cations **A**. Actually, a decrease in stability of the onium states in the series $N^+ > S^+ > O^+$ correlates well with experimental data on the formation of β-substituted pyrrole, thiophene, and furan derivatives.

These features are also pronounced in reactions of substituted five-membered heterocycles. Evidently, the presence of an electron-releasing substituent in any position of the ring should favor the electrophilic attack on the free α position. By contrast, the α-orienting effect of the heteroatom can compete with the "*meta*"-orienting effect of the substituent in compounds containing electron-withdrawing groups at position 2. The results of this competition vividly demonstrate the differences in the positional selectivity for pyrrole, thiophene, and furan derivatives. The character of these differences can be illustrated by the data on bromination of the corresponding methyl 2-carboxylates[5] (Scheme 2). Bromination of thiophene and furan derivatives affords only 5-bromo-substituted products, whereas bromination of methyl pyrrole-2-carboxylate gives rise to a mixture, with the 4-bromo-substituted ester predominating.

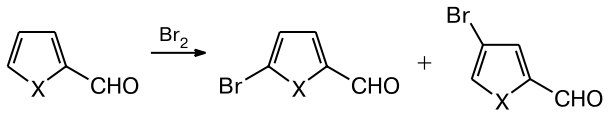
Scheme 2



X	k_{rel} (for position 5)	Resulting isomer
NH	$5.9 \cdot 10^8$	23 : 77 (α : β)
O	$1.2 \cdot 10^2$	α
S	1.0	α

As for aldehydes containing a stronger electron-withdrawing group, it is furfural that affords the 5-bromo derivative as the only product upon bromination in the absence of a catalyst.[6] Bromination of thiophene-2-carbaldehyde gives rise not only to 5-bromothiophene-2-carbaldehyde but also to a small amount of the 4-substituted isomer[7] and bromination of pyrrole-2-carbaldehyde affords, on the contrary, the 4-substituted isomer as the major product, only traces of the 5-bromo derivative being detected[8] (Scheme 3).

Scheme 3

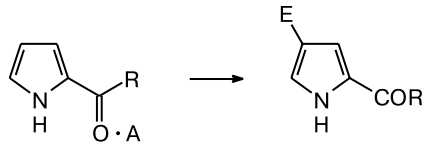


X	Products	
	2,5-isomer	2,4-isomer
NH	Traces	~99.9
O	100	—
S	97	3

The orientation in electrophilic substitution reactions in pyrrole, thiophene, and furan derivatives containing type II orienting substituents at position 2 can be changed by enhancing the electron-withdrawing ability of such substituents by complexation with protic or Lewis acids (see Refs 9—12).

Taking into account the above-mentioned ability of pyrroles to form β-substituted derivatives, it is not surprising that complexation of strong Lewis acids with virtually all 2-RCO-substituted compounds of the pyrrole series results in the electrophilic substitution exlcusivley at position 4[13—21] (Scheme 4).

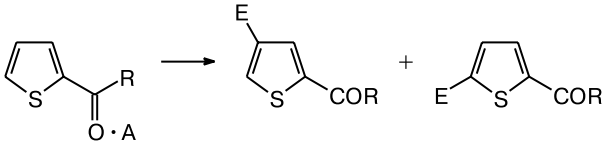
Scheme 4



A = $AlCl_3$, $AlBr_3$, $GaCl_3$; R = Alk, AlkO, AlkS;
E = Br, Ac, CHO, Alk

High positional selectivity in reactions of 2-acylthiophenes can be achieved by modifying substituents through either complexation with aluminum chloride[22—27] or protonation.[28—30] In the resulting mixture of 2,4- and 2,5-disubstituted derivatives, the content of the latter was no more than several percents (Scheme 5).

Scheme 5



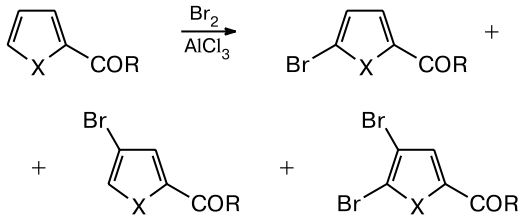
R = H, Me

A	E	Ratio of 2,4 : 2,5-isomers
$AlCl_3$	Br, CH_2Cl, Ac, $ClCH_2CO$	(99.5 : 0.5)—(94 : 6)
HCl—$SbCl_5$	Br, CH_2Cl, NO_2	(98 : 2)—(89 : 11)
H_2SO_4	Br, CH_2Cl, NO_2	(90 : 10)—(67 : 33)

At the same time, the synthesis of 4-substituted derivatives from 2-acylfurans and 2-acylselenophenes is a challenge. The predominant formation of these compounds was observed in bromination of aluminum chloride complexes with furfural and, to a lesser extent, with 2-acetylfuran.[24] Later,[31] it has been demonstrated that bromination of the selenophene-2-carbaldehyde and 2-acetylselenophene complexes with $AlCl_3$ yielded the corresponding 4-bromo derivatives as the major products (their content was higher than 70%). In all cases, substantial amounts of 4,5-dibromo derivatives were obtained (Scheme 6). Competitive reaction studies demonstrated[31] that the selenophene-2-carbaldehyde complex with aluminum chloride was brominated more rapidly than its thiophene analog.

These data confirm the known order in which the relative reactivities (substrate selectivities) change in electrophilic substitution reactions for the first members of the series of five-membered heterocycles (pyrrole ≫ furan > selenophene > thiophene[1,2]) and demonstrate that the positional selectivity decreases in the series furan > selenophene ≥ thiophene > pyrrole, which corresponds to the changes in the relative stabilities of the onium states of the elements ($O^+ < Se^+ \leq S^+ < N^+$) in

Scheme 6



X	R	Ratio of 5-Br : 4-Br : 4,5-Br_2 derivatives
O	Me	30 : 30 : 40
O	H	20 : 65 : 15
Se	Me	8 : 73 : 19
Se	H	4 : 86 : 10

accordance with the earlier hypothesis[3,4] (however, the series considered did not include selenophene and its derivatives).

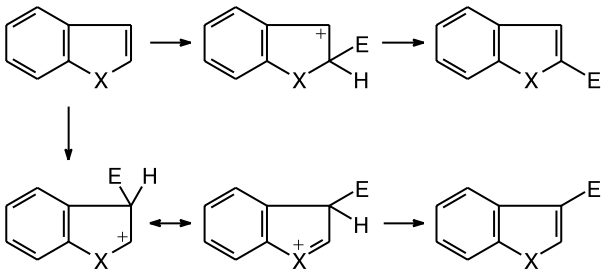
Positional selectivity in reactions of indole, benzofuran, benzothiophene, and benzoselenophene with electrophiles

Although the quantitative data obtained by kinetic measurements or the competitive reaction method are known only for benzo[*b*]thiophene and benzo[*b*]furan,[1,2] the order in which the relative reactivities of benzoannelated five-membered heterocycles containing one heteroatom change in electrophilic substitution reactions is presumably analogous to that described above (indole ≫ benzo[*b*]furan > benzo[*b*]thiophene), the position of benzo[*b*]selenophene relative to benzofuran and benzothiophene can hardly be predicted. The positional selectivity decreases in the series benzo[*b*]furan ≥ ≥ benzo[*b*]selenophene > benzo[*b*]thiophene > indole, as evidenced by the data from the α : β ratios observed in acetylation.[32—34] These data are consistent with the fact that the more stable the onium state of the heteroatom in the ring the more favorable delocalization of the positive charge in the resulting σ complexes (without the involvement of the benzene ring and, consequently, without loss of its aromaticity) for the attack at the β position (Scheme 7).

Quantum chemical studies of positional selectivity in reactions of furan, thiophene, selenophene, *N*-unsubstituted pyrrole, and related benzoannelated systems with electrophiles

Since quantitative data on the stabilities of the onium states of elements are missing (see, for example, Ref. 35); and the above-given sequence $O^+ < Se^+ \leq S^+ < N^+$ is based on purely qualitative estimates[36—38] going back to

Scheme 7



E = Ac

X	α : β Ratio	Reference
NH	0 : 100	32
S	1 : 6	33
Se	7.0 : 1	34
O	7.2 : 1	33

the pioneering study by Meerwein[39]), we studied protonation of monocyclic and the corresponding benzoannelated five-membered heteroaromatic systems containing one heteroatom by quantum chemical methods.[40,41] First semiempirical calculations at the CNDO/2 level performed about 20 years ago[42] gave the energy differences for the cations formed upon protonation of the α and β positions ($\Delta E_{\alpha\text{-}\beta}$) that agreed with the experimental data suggesting that the positional selectivity decreases in the following order: furan > thiophene > > pyrrole. However, the position of selenophene between thiophene and pyrrole predicted by these calculations was in contradiction with the more recent results.[31,43] Nor the results of calculations by the semiempirical MNDO and PM3 methods were completely consistent with the experimental data, which is, apparently, attributable to an inadequate parametrization used in these methods for the selenium atom.[43,44]

In our study,[41] the energy differences $\Delta E_{\alpha\text{-}\beta}$ were evaluated by the *ab initio* RHF/6-31G(d) and MP2/6-31G(d) quantum chemical methods (electron correlation effects were taken into account by the second-order perturbation theory using the geometry calculated by the RHF/6-31G(d) method) and by density functional theory (DFT) calculations with full geometry optimization at the B3LYP/6-31G(d) level. The principal results are given in Table 1. The energy differences $\Delta E_{\alpha\text{-}\beta}$ calculated by all three methods show qualitative agreement with the observed experimental dependences of the positional selectivity in electrophilic substitution reactions on the structure of the heteroaromatic compound: furan > selenophene > thiophene > pyrrole and benzo[*b*]furan > benzo[*b*]selenophene > benzo[*b*]thiophene > indole. It should be emphasized that $\Delta E_{\alpha\text{-}\beta}$ for indole changes the sign, which reflects the fact that the reactivity of its β position is higher than that of the α position (in reactions of indole with electrophiles, virtually no α-substitution products can be detected).

The geometric characteristics of the systems under consideration calculated by the RHF/6-31G(d) method (Tables 2 and 3) are in good agreement with the experimental data for the neutral molecules, which were summarized in the monograph[45] and are given in the present study for pyrrole, furan, thiophene, and selenophene (see Table 2, the values in parentheses). In the 2*H*-hetarenium cations, the X(1)—C(2), C(2)—C(3), and C(4)—C(5) bonds in the monocyclic ions and the X(1)—C(2), C(2)—C(3), C(3a)—C(4), C(5)—C(6), and C(3a)—C(7a) bonds in the bicyclic ions are elongated, whereas the X(1)—C(5) and C(3)—C(4) bonds in the monocyclic ions and the X(1)—C(7a) and C(3)—C(3a) bonds in the bicyclic ions are shortened. In the 3*H*-hetarenium cations, the X(1)—C(2) and C(4)—C(5) bonds in the monocyclic ions and the X(1)—C(2) bond in the bicyclic ions are shortened, whereas the X(1)—C(5), C(2)—C(3), and C(3)—C(4) bonds in the monocyclic ions and the X(1)—C(7a), C(2)—C(3), and C(3)—C(3a) bonds in the bicyclic ions are elongated, which clearly reflects the

Table 1. Differences in the total energies of five-membered heterocycles containing one heteroatom and cationic σ complexes formed upon their protonation for the α (ΔE_α) and β positions (ΔE_β) and the energy differences $\Delta E_{\alpha\text{-}\beta} = \Delta E_\alpha - \Delta E_\beta$ (kcal mol^{-1}) calculated by the *ab initio* RHF/6-31G(d) and MP2/6-31G(d) methods and the DFT B3LYP/6-31G(d) method

Molecule (cation)	RHF/6-31G(d)			MP2/6-31G(d)			DFT B3LYP/6-31G(d)		
	ΔE_α	ΔE_β	$\Delta E_{\alpha\text{-}\beta}$	ΔE_α	ΔE_β	$\Delta E_{\alpha\text{-}\beta}$	ΔE_α	ΔE_β	$\Delta E_{\alpha\text{-}\beta}$
Pyrrole	−222.0	−214.5	−7.6	−209.0	−204.0	−5.0	−214.7	−209.1	−5.6
Furan	−207.0	−193.8	−13.2	−193.2	−181.4	−11.8	−200.7	−188.5	−12.2
Thiophene	−202.6	−191.1	−11.5	−194.0	−185.5	−8.5	−201.1	−190.8	−10.3
Selenophene	−205.3	−192.6	−12.7	−196.7	−187.0	−9.7	−205.1	−193.5	−11.6
Indole	−218.3	−222.7	4.4	−202.9	−213.0	10.1	−213.3	−218.0	4.7
Benzo[*b*]furan	−218.1	−201.2	−16.9	−202.4	−190.7	−11.7	−204.9	−197.6	−7.3
Benzo[*b*]thiophene	−206.3	−198.9	−7.4	−192.8	−192.1	−0.7	−205.3	−199.8	−5.5
Benzo[*b*]selenophene	−208.7	−198.9	−9.8	−196.8	−186.3	−10.5	−208.5	−202.4	−6.1

changes in the multiplicities of the bonds in the σ complexes compared to those in the neutral molecules. Interestingly, the C—C bond lengths in the benzene rings in the bicyclic 3*H*-hetarenium ions, unlike the corresponding values in their 2*H*-isomers, differ much less from the corresponding lengths in the neutral molecules and differ only slightly from each other; all bond lengths are in the range of 1.37—1.39 Å, which is typical of compounds of the benzene series. In our opinion, this suggests that the benzene ring in the bicyclic 3*H*-hetarenium ions is virtually not involved in the positive charge delocalization, which is rather efficient in the five-membered ring involving the heteroatom and the C(2) atom (see Scheme 7).

The total charges on atoms do not vividly reflect the changes in electron density (primarily, in the π system) in the cations compared to the neutral molecules. Apparently, the charges on the heteroatoms depend primarily on the electronegativities of the corresponding elements, and the charges on the O and N atoms are negative even in the cations.

Positional selectivity in reactions of *N*-substituted pyrroles with electrophiles

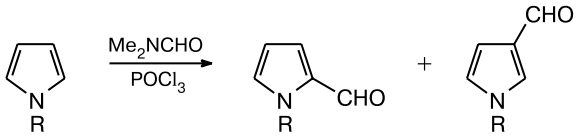
Any structural changes have a considerable effect on the direction of electrophilic substitution in the pyrrole series, which is a consequence of the above-mentioned low positional selectivity of pyrrole in reactions with electrophiles. In contrast to thiophene, selenophene and, particularly, furan analogs, a relatively weak type II orienting substituent at position 2 of the pyrrole ring can overcome the α-orienting effect of the heteroatom and directs an electrophile predominantly to position 4.[5] By contrast, *N*-(*p*-nitrophenyl)pyrrole-2-carbaldehyde is brominated only at position 5 and 4-bromo-1-(*p*-nitrophenyl)pyrrole-2-carbaldehyde is only formed upon bromination of a complex with aluminum chloride,[46] thus resembling the behavior of thiophene-2-carbaldehyde. Below we consider the reaction pathways of *N*-substituted pyrroles with electrophiles. As follows from the above discussion, the substituents at the nitrogen atom in *N*-substituted pyrroles would be expected to influence substantially the ratio of the resulting α and β isomers. It should be emphasized that a large number of semiempirical quantum chemical calculations[47] (see also references in the review[48]) suggest that σ complexes that mimic substitution at the α position of pyrroles are thermodynamically more favorable than those of the β isomers, whereas the kinetic factors (a higher negative charge) favor β substitution.

It should be noted that the ratio of the α to β isomers depends on such factors as the nature and steric requirements of the substituent at the nitrogen atom and the nature of the electrophile, which, in turn, can depend even on the solvent used. The difficulties of the interpretation of the available data are associated with the simultaneous influence of different factors. Nevertheless, the major effect can be distinguished in many cases.

For example, it was hypothesized[49] that the formation of β-substituted *N*-(triisopropylsilyl)pyrroles is associated with steric shielding of the α positions with the triisopropylsilyl group. The Br^+, I^+, NO_2^+, and RCO^+ cations belong to electrophiles that are directed by the 1-Pr^i_3Si substituent to position 3. The Vilsmeier formylation of 1-(triisopropylsilyl)pyrrole also occurs at position 3. The nitrogen atom can be quantitatively deprotected under the action of the fluoride anion.[49]

The fact that the percentage of β-aldehydes derived from *N*-alkylpyrroles upon the Vilsmeier formylation increases from *N*-methyl- to *N*-(*tert*-butyl)pyrrole[50] (Scheme 8) is also attributable to the increase in steric shielding of the α positions by the *N*-alkyl group.

Scheme 8



R	Ratio α : β
Me	*
Et	11.5 : 1
Pr^i	1.9 : 1
Bu^t	1 : 14

* Only the α-isomer is formed.

However, the reaction of *N*-(phenylsulfonyl)pyrrole, which also contains a bulky substituent at the N atom, produces exclusively α-aldehyde.[51] We suggested[41,43,46,52] that this effect can be partially attributed to stabilization of the onium state of the heteroatom by electron-releasing substituents and, to the contrary, destablization of this state by electron-withdrawing substituents.

The orientation of the electrophilic substitution in the pyrrole series strongly depends also on the nature of the electrophile, as evidenced by the results of reactions of the same electrophile with pyrroles containing various substituents at the nitrogen atom or of different electrophiles with the same *N*-substituted pyrrole. The electrophilic H—D exchange for a series of substituted pyrroles containing a deactivating group (Ac, PhCO, $MeSO_2$, CF_3SO_2, $PhSO_2$, Me_3N^+, or Me_2NH^+) at the N atom was studied.[53] In all cases, the rate of exchange at the α position is higher than that at the β position by more than an order of magnitude. Allylation of *N*-methylpyrrole occurs predominantly at the α position (the α to β ratio is 4 : 1),[54] whereas silylation occurs exclusively at the β position.[55] The influence of the *N*-phenylsulfonyl substituent, which has been proposed as a protective group simultaneously

Table 2. Geometry (RHF/6-31G) of the pyrrole, furan, thiophene, and selenophene molecules (experimental data[45] are given in

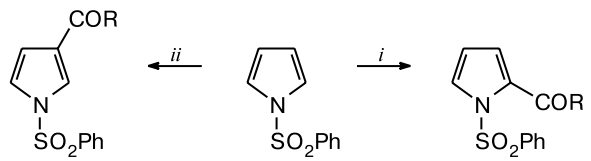
Molecule (cation)	Bond length/Å							
	X(1)—C(2)	X(1)—C(5)	C(2)—C(3)	C(3)—C(4)	C(4)—C(5)	C(sp^3)—H	C(sp^2)—H	N—H
Pyrrole	1.36 (1.37)	1.36 (1.37)	1.36 (1.38)	1.43 (1.42)	1.36 (1.38)	—	1.07 (1.08)	1.07
Furan	1.34 (1.36)	1.34 (1.36)	1.34 (1.36)	1.44 (1.43)	1.34 (1.36)	—	1.07 (1.08)	—
Thiophene	1.73 (1.71)	1.73 (1.71)	1.35 (1.37)	1.44 (1.43)	1.35 (1.37)	—	1.07 (1.08)	—
Selenophene	1.86 (1.86)	1.86 (1.86)	1.34 (1.37)	1.44 (1.43)	1.34 (1.37)	—	1.07 (1.07—1.08)	—
2*H*-Pyrrolium	1.46	1.29	1.49	1.34	1.44	1.084	1.070—1.074	1.00
2*H*-Furanium	1.44	1.26	1.49	1.34	1.42	1.082	1.070—1.075	—
2*H*-Thiophenium	1.81	1.66	1.48	1.35	1.42	1.086	1.072—1.076	—
2*H*-Selenophenium	1.94	1.79	1.48	1.35	1.41	1.085	1.072—1.075	—
3*H*-Pyrrolium	1.27	1.44	1.49	1.50	1.32	1.088	1.069—1.073	1.00
3*H*-Furanium	1.24	1.43	1.48	1.50	1.31	1.089	1.067—1.076	—
3*H*-Thiophenium	1.62	1.77	1.48	1.50	1.32	1.091	1.071—1.075	—
3*H*-Selenophenium	1.75	1.91	1.48	1.50	1.32	1.091	1.071—1.075	—

Table 3. Geometry (RHF/6-31G) of the indole, benzo[*b*]furan, benzo[*b*]thiophene, benzo[*b*]selenophene, and the related

Parameter	Indole	Benzo[*b*]-furan	Benzo[*b*]-thiophene	Benzo[*b*]se-lenophene	2*H*-Indolium	2*H*-Benzo[*b*]-furanium
Bond			*d*/Å			
X(1)—C(2)	1.37	1.35	1.74	1.87	1.45	1.42
X(1)—C(7a)	1.37	1.35	1.75	1.88	1.31	1.29
C(2)—C(3)	1.35	1.33	1.33	1.33	1.49	1.49
C(3)—C(3a)	1.44	1.45	1.45	1.45	1.34	1.35
C(3a)—C(4)	1.40	1.39	1.40	1.40	1.45	1.44
C(4)—C(5)	1.37	1.38	1.37	1.38	1.34	1.34
C(5)—C(6)	1.40	1.40	1.40	1.40	1.45	1.44
C(6)—(7)	1.37	1.38	1.38	1.38	1.35	1.37
C(7)—C(7a)	1.39	1.38	1.39	1.39	1.42	1.40
C(3a)—C(7a)	1.40	1.39	1.40	1.40	1.45	1.44
C(sp^3)—H	—	—	—	—	1.085	1.083
C(sp^2)—H	1.07	1.07	1.07—1.08	1.07—1.08	1.07	1.075
N—H	0.99	—	—	—	1.00	—
Angle			ω/deg			
C(2)—X(1)—C(7a)	109.0	106.5	90.8	87.0	111.4	109.2
X(1)—C(2)—C(3)	110.0	112.6	113.4	113.0	102.1	104.0
C(2)—C(3)—C(3a)	106.7	105.5	112.8	115.1	109.9	108.7
C(3)—C(3a)—C(7a)	106.7	104.9	111.8	113.8	107.2	105.8
C(3a)—C(7a)—X(1)	107.5	110.4	111.2	111.09	109.4	112.2
H—C(sp^3)—H	—	—	—	—	108.5	109.4

by two research teams,[51,56—58] has been studied in most detail. Due to the electron-withdrawing effect, this group deactivates predominantly the α position, thus providing the formation of a β derivative, and the $PhSO_2$ group can be easily removed by alkaline hydrolysis.[57] The effect of the $PhSO_2$ group is best examined for the Friedel—Crafts acylation.[51,56—62] The role of the nature of the reagent is most clearly manifested in the fact that 3-acyl derivatives are obtained in the presence of aluminum chloride, whereas the reactions in the presence of boron trifluoride etherate produce 2-isomers[57] (Scheme 9).

Scheme 9



Reagents and conditions: *i*. $(RCO)_2O$ or RCOCl, $BF_3 \cdot OEt_2$, $(CH_2Cl)_2$, ~20 °C. *ii*. $(RCO)_2O$ or RCOCl, $AlCl_3$, $(CH_2Cl)_2$, ~20 °C.

parentheses) and the related 2*H*- and 3*H*-hetarenium ions

Bond angle/deg					
C(2)—X(1)—C(5)	X(1)—C(2)—C(3)	C(2)—C(3)—C(4)	C(3)—C(4)—C(5)	C(4)—C(5)—X(1)	H—C(sp^3)—H
109.5 (109.8)	108.2 (107.7)	107.1 (107.4)	107.1 (107.4)	108.2 (107.7)	—
107.1 (106.5)	110.8 (110.7)	105.6 (106.1)	105.6 (106.1)	110.8 (110.7)	—
91.3 (92.2)	111.8 (111.5)	112.5 (112.5)	112.5 (112.5)	111.8 (111.5)	—
87.3 (87.8)	111.7 (111.6)	114.7 (114.6)	114.7 (114.6)	111.7 (111.6)	—
111.1	101.2	110.3	106.5	110.8	109.0
109.3	102.7	109.3	105.1	113.7	110.1
91.6	106.0	115.2	111.2	115.9	107.9
87.7	105.9	117.3	113.2	115.9	108.7
111.8	109.3	101.7	109.1	108.0	106.9
109.8	112.2	100.2	108.6	109.2	106.9
93.3	114.1	106.6	114.4	111.6	105.8
89.3	114.3	108.6	116.6	111.3	105.5

2*H*- and 3*H*-hetarenium ions

2*H*-Benzo[*b*]-thiophenium	2*H*-Benzo[*b*]-selenophenium	3*H*-Indolium	3*H*-Benzo[*b*]-furanium	3*H*-Benzo[*b*]-thiophenium	3*H*-Benzo[*b*]-selenophenium
		d/Å			
1.81	1.95	1.27	1.24	1.62	1.75
1.72	1.85	1.43	1.43	1.77	1.90
1.48	1.48	1.50	1.49	1.49	1.47
1.35	1.36	1.51	1.51	1.50	1.50
1.44	1.44	1.38	1.38	1.38	1.38
1.35	1.35	1.39	1.39	1.39	1.39
1.43	1.43	1.39	1.39	1.39	1.39
1.37	1.38	1.39	1.39	1.38	1.38
1.39	1.39	1.37	1.37	1.38	1.38
1.44	1.44	1.38	1.37	1.39	1.39
1.086	1.084	1.087	1.089	1.090	1.090
1.075	1.075	1.074	1.075	1.075	1.075
—	1.00	—	—	—	
		ω/deg			
91.8	88.0	112.2	109.9	93.8	89.9
106.9	106.8	110.8	113.8	115.5	115.5
115.6	117.7	101.4	100.0	106.5	108.5
112.2	114.2	108.5	107.6	133.3	115.4
113.5	113.3	107.1	108.7	110.9	110.7
107.7	108.5	107.2	107.0	106.2	106.0

It should be emphasized that the Rieche formylation of 1-(phenylsulfonyl)pyrrole with alkyl dichloromethyl ethers,[51,56] the Vilsmeier formylation in the DMF—$POCl_3$ system,[51] and cyanation with cyanogen bromide in the presence of $AlCl_3$ or chlorosulfonyl isocyanate afford only 2-substituted derivatives,[51,58] whereas nitration (HNO_3—Ac_2O) occurs almost exclusively at position 3.[57] Recently, it has been found[63] that even sulfonation of unsubstituted pyrrole and *N*-methylpyrrole with pyridine sulfotrioxide occurs at the same position. The above differences in the orientation are usually explained in terms of the hard and soft acids and bases principle: the direction of the attack of the "hard" electrophile is determined predominantly by the charge, whereas the substitution at position 2 in reactions with "softer" electrophiles is the result of the orbital control.[56]

These examples are, undoubtedly, attributed to the influence of the nature of the electrophile. However, an essential role of the size of electrophilic species is also documented. For instance, 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 derivatives (with Pr^iCl), up to the predominant (80%) formation of the β-substituted derivatives (with Bu^tCl).[58]

Quantum chemical studies of positional selectivity in reactions of *N*-substituted pyrroles with electrophiles

We performed quantum chemical studies of model *N*-R-pyrroles (R = Me, Et, Pr^i, Bu^t, $CH{=}CH_2$, $C{\equiv}CH$, Ph, $PhSO_2$, or 4-$O_2NC_6H_4$) and their α- and β-protonated σ complexes using the RHF/6-31G(d), MP2/6-31G(d)//RHF/6-31G(d), and B3LYP/6-31G(d) methods.[64,65] The energy differences for the cations formed upon protonation of the α and β positions ($\Delta E_{\alpha\text{-}\beta}$) are given in Table 4. These differences characterize the positional selectivity in electrophilic substitution reactions. The energy differences $\Delta E_{\alpha\text{-}\beta}$ estimated by the above three methods do not provide evidence that the β positions in the molecules under consideration are more favorable for the electrophilic attack. A comparison of $\Delta E_{\alpha\text{-}\beta}$ shows that the substitution at the β position is relatively more favorable in the presence of the alkyl substituent at the nitrogen atom of the ring than in *N*-unsubstituted pyrrole, whereas all other substituents should facilitate the formation of α-substituted derivatives to approximately the same extent (or even to a larger extent) as in the case of pyrrole.

Therefore, the calculated total energies of the cationic σ complexes formed upon protonation of the α and β positions of the model *N*-phenylsulfonyl- and *N*-(4-nitrophenyl)pyrrole molecules agree with the experimental evidence for the higher activities of their α positions, whereas the role of steric factors and charges on atoms should be considered to account for an increase in the percentage of β-substituted derivatives in the formylation products of *N*-alkylpyrroles in the series Me < Et < Pr^i < Bu^t.

Here, we do not give the main geometric characteristics and charges on atoms calculated by us earlier.[64] Let us only note that the geometry of the neutral *N*-isopropylpyrrole and *N*-(*tert*-butyl)pyrrole molecules is indicative of the presence of steric strain. In the former, the N(1)—C(2) bond length differs substantially from the N(1)—C(5) bond length. In the latter, the distances between the center of the hydrogen atom at position 2 and the centers of the nearest H atoms of two methyl groups (2.39 Å) are smaller than, or equal to, the sum of the van der Waals radii (2.4 Å), whereas the distance from the center of the H atom at position 5 to the nearest H atom of the methyl group is 2.33 Å, which is smaller than the sum of the van der Waals radii.[66] The molecular geometry of these compounds is distorted, as evidenced also by the bond angles. Thus the differences in the pairs of the bond angles, *viz.*, N(1)—C(2)—C(3) *vs.* C(4)—C(5)—N(1) and C(2)—C(3)—C(4) *vs.* C(3)—C(4)—C(5), are equal to 0.2° and 0.1—0.2°, respectively.

The charges on the atoms in the *N*-isopropylpyrrole and *N*-(*tert*-butyl)pyrrole molecules are also distributed non-symmetrically, which can be considered as a result of violation of the molecular symmetry. An analogous charge distribution in *N*-vinylpyrrole is attributable to the nearly coplanar arrangement of the ring and the vinyl group, which is favorable for conjugation of the latter with the pyrrole system. On the whole, the C atoms in the β positions of the pyrrole ring have marked negative charges, whereas the charges on the C atoms in the α positions are close to zero. The atomic charges can account for the formation of β products, but not for the fact that the reactions sometimes afford α-substitution products.

Thus, in the general case, the results of calculations for the 2*H*- and 3*H*-pyrrolium ions do not predict the

Table 4. Differences in the total energies (kcal mol^{-1}) of *N*-substituted pyrroles and cationic σ complexes formed upon their protoination for the α (ΔE_α) and β positions (ΔE_β) and the energy differences $\Delta E_{\alpha\text{-}\beta} = \Delta E_\alpha - \Delta E_\beta$

Molecule	RHF/6-31G(D)//RHF/6-31G(D)			MP2/6-31G(D)//RHF/6-31G(D)			B3LYP/6-31G(D)//B3LYP/6-31G(D)		
	$-\Delta E_\alpha$	$-\Delta E_\beta$	$-\Delta E_{\alpha\text{-}\beta}$	$-\Delta E_\alpha$	$-\Delta E_\beta$	$-\Delta E_{\alpha\text{-}\beta}$	$-\Delta E_\alpha$	$-\Delta E_\beta$	$-\Delta E_{\alpha\text{-}\beta}$
N-Methylpyrrole	226.0	221.6	4.4	214.1	210.5	3.6	221.2	216.0	5.2
N-Ethylpyrrole	228.0	223.0	5.0	215.2	211.8	3.4	221.6	217.6	4.0
N-Isopropylpyrrole	128.7	124.4	4.3	115.8	113.2	2.6	222.9	219.6	3.3
N-*tert*-Butylpyrrole	231.6	227.1	4.5	218.7	215.8	2.9	225.4	221.9	3.5
N-Vinylpyrrole	218.7	212.5	6.2	206.6	202.2	4.4	216.9	212.5	4.4
N-Ethynylpyrrole	215.8	207.7	8.1	204.5	198.5	6.0	211.4	204.3	7.1
N-Phenylpyrrole	226.4	221.8	4.6	217.1	213.4	3.7	221.5	217.1	4.4
N-(Phenylsulfonyl)-pyrrole	217.1	209.1	8.0	207.4	202.1	5.3	215.8	210.4	5.4
N-(4-Nitrophenyl)-pyrrole	216.5	210.5	6.0	205.8	201.9	3.9	211.5	206.7	4.8

Table 5. Total energies of cationic σ complexes formed by pyrrole, *N*-methylpyrrole, and *N*-(*tert*-butyl)pyrrole as a result of addition of the trimethylsilyl cation at the α (E_α) and β positions (E_β) and the energy differences $\Delta E_{\alpha\text{-}\beta}$ characterizing the preferable direction of the attack

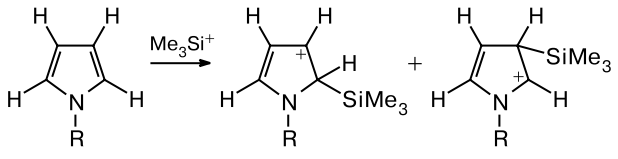
Starting molecule	RHF/6-31G(d)//RHF/6-31G(d)			MP2/6-31G(d)//RHF/6-31G(d)			B3LYP/6-31+G(d)//B3LYP/6-31+G(d)		
	$-E_\alpha$*	$-E_\beta$*	$\Delta E_{\alpha\text{-}\beta}$ /kcal mol^{-1}	$-E_\alpha$*	$-E_\beta$*	$\Delta E_{\alpha\text{-}\beta}$ /kcal mol^{-1}	$-E_\alpha$**	$-E_\beta$**	$\Delta E_{\alpha\text{-}\beta}$ /kcal mol^{-1}
	a.u.			a.u.			a.u.		
Pyrrole	616.22001	616.21437	−3.5	617.35609	617.35567	−0.3	619.03341	619.03012	−2.1
N-Methylpyrrole	655.22789	655.22665	−0.8	656.49820	656.49965	0.9	658.32118	658.32156	0.2
N-(*tert*-Butyl)pyrrole	772.24888	772.25774	5.6	773.92688	773.93396	4.4	776.18328	776.19123	5.0

* The energies were calculated with zero-point energy (ZPE) correction according to the equation $E_0 = E_{calc} + k\text{ZPE}$, where k is the normalization factor (0.8929).
** The energies were calculated with ZPE correction according to the equation $E_0 = E_{calc} + k\text{ZPE}$, $k = 0.980$.

direction of electrophilic attack on *N*-substituted pyrroles. The exception is the hydrogen isotope exchange reaction, for which the known σ complexes serve as an adequate model of an intermediate and the results of calculations are in complete agreement with the experimental data for the *N*-substituted pyrrole series.[53] It should be noted that the earlier study[67] by the semiempirical CNDO/2 method using the pseudoatom formalism revealed the dependence of the direction of the electrophilic substitution in five-membered heterocycles on the characteristics of the electrophile, such as the electronegativity and ionic and covalent radii. It was concluded that the predominant formation of β-substitution products is highly likely in the reactions of pyrrole with electrophiles, whose characteristics are similar to those of silicon. One would expect that modern quantum chemical calculations for real rather than model electrophiles with consideration for the solvent effect will predict the predominant positions of electrophilic substitution in *N*-substituted pyrroles. The first results of such calculations demonstrated that the agreement with the experimental data can be achieved even without considering the solvent effect.

We carried out[68] calculations for the cationic σ complexes resulting from the attack of the trimethylsilyl cation at the α and β positions of the pyrrole, *N*-methylpyrrole, and *N*-(*tert*-butyl)pyrrole molecules (Scheme 10).

Scheme 10



The data in Table 5 show that all three methods predict that the α substitution is favorable for pyrrole, whereas the β orientation is the major one for *N*-(*tert*-butyl)pyrrole. For *N*-methylpyrrole, only the results obtained by the MP2/6-31G(d) and B3LYP/6-31G(d) methods agree with the experimental data.[55] Quantum chemical studies of the positional selectivity in reactions of compounds of the pyrrole series with electrophiles other than the proton are presently underway.

This study was financially supported by the International Science and Technology Center (ISTC, Grant 2117).

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Received October 15, 2004;
in revised form December 21, 2004