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Dedicated to Full Member of the Russian Academy of Sciences N.S. Zefirov on His 70th Anniversary

Quantum-Chemical Study on Positional Selectivity in the Trimethylsilylation and Sulfonation of Pyrrole and *N*-Alkylpyrroles

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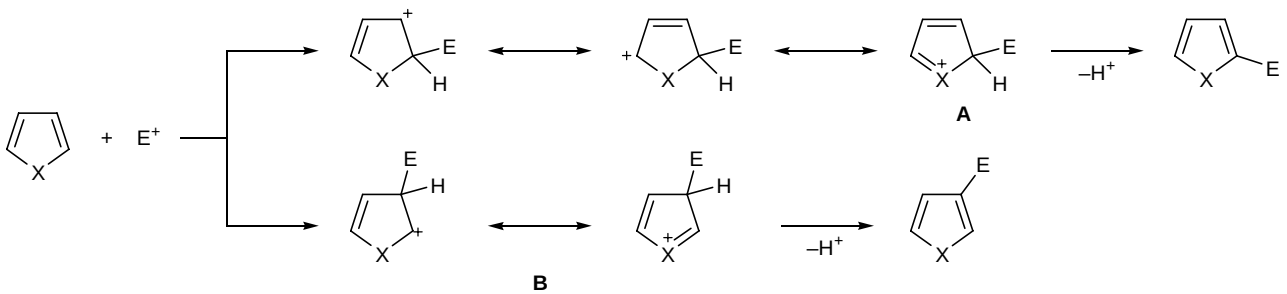
Abstract—Positional selectivity (α:β ratio) of electrophilic substitution in pyrrole, *N*-methylpyrrole, and *N*-*tert*-butylpyrrole was analyzed by *ab initio* [RHF/6-31G(*d*), MP2/6-31G(*d*)//RHF/6-31G(*d*)] and DFT [B3LYP/6-31G(*d*)] calculations of some σ-complexes derived from the substrates. The results of calculations with the use as model electrophilic species of trimethylsilyl cation [MP2/6-31G(*d*)//RHF/6-31G(*d*) and B3LYP/6-31G(*d*)] and SO_3 molecule [B3LYP/6-31G(*d*)] instead of proton are fairly consistent with the experimental data, according to which trimethylsilylation of pyrrole and its *N*-substituted derivatives with trimethylsilyl trifluoromethanesulfonate, as well as sulfonation with pyridine–sulfur trioxide complex, gives the corresponding β-substituted products.

We previously performed a quantum-chemical study on positional selectivity in electrophilic substitution in derivatives of pyrrole, furan, thiophene, selenophene, and their benzo-fused analogs [1]. Our results allowed us to rationalize the absence of correlation between the reactivity (substrate selectivity) and positional selectivity (ratio of the α- and β-substituted products). Very strong differences in the reactivity (in the series pyrrole >> furan > selenophene > thiophene the reactivity decreases by about 10 orders of magnitude) may be interpreted in terms of different conditions for electron density delocalization over the ring atoms in intermediate σ-complexes (primarily in more thermodynamically favorable ionic species like **A**), which involves overlap of carbon π-orbitals with *n*-orbitals of heteroatoms belonging to different groups and periods of the Periodic Table (Scheme 1) [2, 3]. However, the selectivity (α:β) conformed to a different series: furan > selenophene > thiophene > pyrrole, which was not rationalized so far. The results of our *ab initio* [RHF/6-31G(*d*), MP2/6-31G(*d*)//RHF/6-31G(*d*)] and DFT [density functional theory; B3LYP/6-31G(*d*)] calculations of pyrrole, furan, thiophene, and selenophene molecules, as well as of the corresponding benzo-fused systems and hetarenium ions formed upon protonation (E = H) [1], were consistent with our previous hypothesis [4, 5] implying predominant contribution of heteroatoms to the stabilization of σ-com-

Scheme 1.



plexes like **B** (which give rise to β-substituted products). This hypothesis substantiates the series furan > selenophene > thiophene >> pyrrole, which is based on the relative stabilities of the corresponding onium states ($O^+ < Se^+ \leq S^+ < N^+$).

In going to N-substituted pyrroles, it should be emphasized that any structural variations should strongly affect the direction of electrophilic substitution in the pyrrole series due to high reactivity (low positional selectivity) of these compounds. As follows from published data (for review, see [6]), the ratio of α- and β-substituted products depends on such factors as the nature and size of substituent on the nitrogen atom, electrophile nature, and solvent properties. Simultaneous action of different factors complicates interpretation of the available data.

We presumed in [1, 7–9] that substituent on the nitrogen atom could affect the α:β ratio via stabilization (electron-donor groups) or destabilization (electron-withdrawing groups) of the corresponding onium species. This is confirmed by the following examples. Unlike thiophene, selenophene, and especially furan analogs, even such a relatively weak electron-withdrawing substituent as ester group in position *2* of the pyrrole ring is capable of overcoming α-orienting effect of the heteroatom and directing electrophile mainly at position *4* [10]. On the other hand, the bromination of *N*-(4-nitrophenyl)pyrrole-2-carbaldehyde occurs at position *5*, while 4-bromo-1-(4-nitrophenyl)pyrrole-2-carbaldehyde is obtained only from a complex with aluminum chloride [7], by analogy with thiophene-2-carbaldehyde.

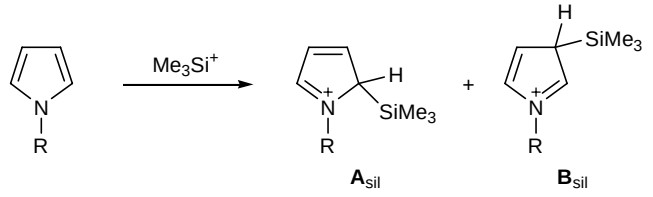
However, the results of our RHF/6-31G(*d*), MP2/6-31G(*d*)//RHF/6-31G(*d*), and B3LYP/6-31G(*d*) calculations [11] of molecules of various N-substituted pyrroles (R = Me, Et, *i*-Pr, *t*-Bu, $CH{=}CH_2$, C≡CH, Ph, $PhSO_2$, $4\text{-}O_2NC_6H_4$) and hetarenium ions formed upon protonation at the α- and β-position do not support the above assumption: in all cases, α-substitution is more favorable. Nevertheless, comparison of the $\Delta E_{\alpha-\beta}$ values indicates that the presence of an alkyl group on the pyrrole nitrogen atom makes β-substitution relatively more advantageous (less unfavorable), as compared to unsubstituted pyrrole, and that other substituents should favor formation of α-substituted products approximately to the same or greater extent. According to semiempirical quantum-chemical calculations (for reviews, see [12, 13]), σ-complexes corresponding to α-substitution are thermodynamically more favorable than their isomers giving rise to β-substituted products, while kinetic factors (greater negative charge) favor β-substitution.

We can conclude that, in the general case, calculations of 2*H*- and 3*H*-pyrrolium ions could not predict the direction of electrophilic attack on N-substituted pyrroles. An exception is isotope exchange of hydrogen, where the examined σ-complexes fairly reliably simulate the real intermediates, and the results of calculations are fully consistent with the experimental data demonstrating predominant α-substitution in the series of N-substituted pyrroles [14]. It should be noted that earlier semiempirical (CNDO/2) study [15] in terms of so-called pseudoatom formalism revealed a relation between the direction of electrophilic substitution in the series of five-membered heterocycles and such electrophile parameters as electronegativity and ionic and covalent radii. It was concluded that β-substitution in pyrrole is more probable when parameters of electrophile are similar to those of silicon atom. Therefore, we anticipated that modern quantum-chemical calculations performed for real (rather than model) electrophiles with account taken of solvent effect should predict the direction of electrophilic substitution in N-substituted pyrroles with an acceptable reliability. The first results showed that agreement with experimental data may be achieved even without taking into account solvent effect.

In the present article we describe the results of our calculations performed for trimethylsilylation (for preliminary communication, see [16]) and sulfonation of pyrrole, *N*-methylpyrrole, and *N*-*tert*-butylpyrrole. In keeping with published data, the silylation of *N*-methylpyrrole with trimethylsilyl trifluoromethanesulfonate $Me_3SiOSO_2CF_3$ in triethylamine [17] and sulfonation of unsubstituted pyrrole and *N*-methylpyrrole with pyridine–sulfur trioxide complex [18] occur exclusively at the β-position.

Insofar as the nucleophilicity of trifluoromethanesulfonate ion and electronegativity of silicon atom are low, as model electrophile we used trimethylsilyl cation. We calculated the total energies of σ-complexes $\mathbf{A}_{sil}$ and $\mathbf{B}_{sil}$ arising from attack by trimethylsilyl cation on the α- and β-positions, respectively, in pyrrole derivatives (Scheme 2). As previously [1, 11], the calculations were performed by the RHF/6-31G(*d*), MP2/6-31G(*d*)//RHF/6-31G(*d*), and B3LYP/6-31G(*d*) methods. It is seen (Table 1) that the three methods predict preferential α-orientation of the electrophile in trimethylsilylation of unsubstituted pyrrole and β-orientation in the reaction with *N*-*tert*-butylpyrrole.

Scheme 2.



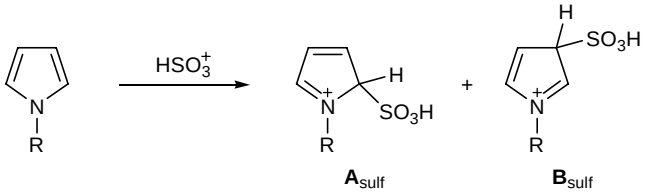
R = H, Me, *t*-Bu.

In the case of *N*-methylpyrrole, only the MP2/6-31G(*d*) and B3LYP/6-31G(*d*) data indicate some preference of β-substitution, in agreement with the experimental results [17].

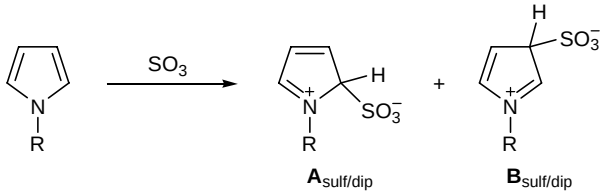
It should be noted that the differences in the energy of isomeric σ-complexes arising from attack by trimethylsilyl cation on the α- and β-positions are clearly smaller than the corresponding differences for the complexes formed by protonation of pyrrole, *N*-methylpyrrole, and *N*-*tert*-butylpyrrole. This means that the probabilities for formation of α- and β-substituted isomers in the trimethylsilylation are closer to each other than in the protonation; moreover, in the first case the dependence on solvation effects may be stronger. As follows from the total energies of σ-complexes, increase in the size of the substituent on the nitrogen atom stabilizes the corresponding onium state and increases the probability for formation of σ-complex via attack at the β-position.

Possible intermediates in the sulfonation reaction were calculated only in terms of the density functional theory [B3LYP/6-31G(*d*)], taking into account that this procedure gives the results similar to those obtained by the nonempirical MP2/6-31G(*d*)//RHF/6-31G(*d*) method but is considerably less time-consuming. In order to reduce computer time, no correction for zero-point vibration energy (ZPE) was introduced. In doing so, we kept in mind that ZPE correction increases $\Delta E_{\alpha-\beta}$ values for a wide series of N-substituted pyrroles [11] by 0.4–0.7 kcal/mol (in most cases, by 0.5 kcal/mol). Specific features of the sulfonation mechanism include reversibility of the process and possible participation of both conventional σ-complex formed by addition of HO_3S^+ ion ($\mathbf{A}_{sulf}$ and $\mathbf{B}_{sulf}$ in Scheme 3; the subsequent deprotonation gives sulfonic acid), and dipolar σ-complex ($\mathbf{A}_{sulf/dip}$ and $\mathbf{B}_{sulf/dip}$ in Scheme 4; their deprotonation leads to sulfonate anion) [19–21]. The formation of dipolar σ-complex in the reaction with $Py \cdot SO_3$ seems to be more probable.

Scheme 3.



Scheme 4.



The results of calculations (Table 2) clearly indicate that σ-complexes $\mathbf{A}_{sulf/dip}$ arising from attack on the α-position are more favorable; on the other hand, β-substituted pyrrolesulfonic acids are thermodynamically more stable, and their stability increases in going from unsubstituted pyrrole to *N*-methylpyrrole and then to *N*-*tert*-butylpyrrole. Apparent inconsistency of these data may be rationalized in terms of reversibility of the first sulfonation stage and increased stability of σ-complexes like $\mathbf{A}_{sulf/dip}$ (α-substitution). In fact, the differences $E_{\alpha\text{-SA}} - E_{\alpha}$ and $E_{\beta\text{-SA}} - E_{\beta}$, which charac-

Table 1. Total energies of cationic σ-complexes derived from pyrrole, *N*-methylpyrrole, and *N*-*tert*-butylpyrrole via addition of trimethylsilyl cation at the α- (E_{α}, a.u.) and β-positions (E_{β}, a.u.) and the differences $\Delta E_{\alpha-\beta}$ (kcal/mol) characterizing the predominant reaction direction

Substrate	RHF/6-31G(*d*)//RHF/6-31G(*d*)			MP2/6-31G(*d*)//RHF/6-31G(*d*)			B3LYP/6-31G(*d*)//B3LYP/6-31G(*d*)		
	E_{α} [a]	E_{β} [a]	$\Delta E_{\alpha-\beta}$	E_{α} [a]	E_{β} [a]	$\Delta E_{\alpha-\beta}$	E_{α} [b]	E_{β} [b]	$\Delta E_{\alpha-\beta}$
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*-Butylpyrrole	–772.24888	–772.25774	5.6	–773.92688	–773.93396	4.4	–776.18328	–776.19123	5.0

[a] The energies are given with correction for zero-point vibration energy: $E = E_{calc} + kZPE$, where *ZPE* is the above correction and *k* is a coefficient ($k = 0.8929$).

[b] $E = E_{calc} + kZPE$, $k = 0.980$.

Table 2. Calculated [B3LYP/6-31G(*d*)//B3LYP/6-31G(*d*)] total energies of initial pyrroles (E_{HetH}, a.u.), intermediate σ-complexes derived from pyrrole, *N*-methylpyrrole, and *N*-*tert*-butylpyrrole via addition of sulfur trioxide at the α- (E_α, a.u.) and β-positions (E_β, a.e.), and final sulfonic acids ($E_{\alpha\text{-SA}}$ and $E_{\beta\text{-SA}}$, a.u.) and the differences $E_\alpha - E_\beta$ ($\Delta E_{\alpha-\beta}$, kcal/mol) and $E_{\alpha\text{-SA}} - E_{\beta\text{-SA}}$ ($\Delta Q_{\alpha-\beta}$, kcal/mol) characterizing preferential structure of the σ-complex and sulfonic acid, respectively.

Substrate	E_{HetH}	E_α	E_β	$\Delta E_{\alpha-\beta}$	$E_{\alpha\text{-SA}}$	$E_{\beta\text{-SA}}$	$\Delta Q_{\alpha-\beta}$
Pyrrole	–210.08326	–833.94399	–833.93209	–7.5	–833.95940	–833.96073	0.8
N-Methylpyrrole	–249.36718	–873.25874	–873.24334	–9.7	–873.27075	–873.27351	1.7
N-*tert*-Butylpyrrole	–367.22609	–991.20215	–991.18787	–9.0	–991.20746	–991.21877	7.1

terize the energy gain in the transformation of σ-complex into sulfonic acid (SA), differ considerably (by a factor of 2 to 6) for the α- (9.7, 7.5, and 3.3 kcal/mol) and β-positions (18.0, 18.9, and 19.4 kcal/mol) in the series pyrrole–*N*-methylpyrrole–*N*-*tert*-butylpyrrole. Using the calculated total energy of sulfur trioxide (E_{tot} = –623.68391 a.u.) we estimated the heat effects (kcal/mol) of the sulfonation at the α- and β-positions of pyrrole (120.5, 121.4), *N*-methylpyrrole (137.7, 139.5), and *N*-*tert*-butylpyrrole (186.5, 193.6).

Quantum-chemical studies on regioselectivity in reactions of compounds of the pyrrole series with electrophiles other than proton are now in progress.

REFERENCES

1. Belen'kii, L.I., Suslov, I.A., and Chuvylkin, N.D., *Khim. Geterotsikl. Soedin.*, 2003, p. 38.
2. Marino, G., *Adv. Heterocycl. Chem.*, 1971, vol. 13, p. 235.
3. Marino, G., *Khim. Geterotsikl. Soedin.*, 1973, p. 579.
4. Belen'kii, L.I., *IIIrd Int. Symp. on Furan Chemistry. Collection of Papers*, Smolenice, Czechoslovakia, 1979, p. 4.
5. Belen'kii, L.I., *Khim. Geterotsikl. Soedin*., 1980, p. 1587.
6. Belen'kii, L.I., Kim, T.G., Suslov, I.A., and Chuvylkin, N.D., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2005, p. 837.
7. Baum, E., Belen'kii, L.I., Kul'nevich, V.G., and Goldovskaya, T.E., *Khim. Geterotsikl. Soedin.*, 1982, p. 662.
8. Belen'kii, L.I., *Heterocycles*, 1994, vol. 37, p. 2029.
9. Belen'kii, L.I., Abstracts of Papers, *16th Int. Congr. on Heterocyclic Chemistry*, OP-V-20. August 10–15, 1997, Montana State University–Boseman, USA.
10. Linda, P. and Marino, G., *J. Chem. Soc. B*, 1968, p. 392.
11. Belen'kii, L.I., Kim, T.G., Suslov, I.A., and Chuvylkin, N.D., *Arkivoc*, 2003, part xiii, p. 59.
12. Abronin, I.A., Belen'kii, L.I., and Gol'dfarb, Ya.L., *New Trends in Heterocyclic Chemistry*, Mitra, R.B., Ayyangar, N.R., Gogte, V.N., Acheson, R.M., and Cromwell, N., Eds., Amsterdam: Elsevier, 1979, p. 154.
13. Sigalov, M.V. and Trofimov, B.A., *Russ. J. Org. Chem*., 1995, vol. 31, p. 741.
14. Gilow, H.M., Hong, Y.H., Millins, P.L., Snyder, R.C., and Casteel, W.J., *J. Heterocycl. Chem*., 1986, vol. 23, p. 1475.
15. Abronin, A.I., Belen'kii, L.I., Zhidomirov, G.M., and Gol'dfarb, Ya.L., *Zh. Org. Khim*., 1981, vol. 17, p. 1134.
16. Belen'kii, L.I., Chuvylkin, N.D., Kim, T.G., and Suslov, I.A., Abstracts of Papers, *Chemistry Biology Interface: Synergistic New Frontiers*, New Delhi, India, November 21–26, 2004, IL92.
17. Majchrzak, M.W. and Simchen, G., *Tetrahedron*, 1986, vol. 42, p. 1299.
18. Mizuno, A., Kan, Y., Fukami, H., Kamei, T., Miyazaki, K., Matsuki, S., and Oyama, Y., *Tetrahedron Lett*., 2000, vol. 41, p. 6605.
19. Cerfontain, H., *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, New York: Interscience, 1968.
20. Kort, C.W.F. and Cerfontain, H., *Recl. Trav. Chim. Pays–Bas*, 1969, vol. 88, p. 860.
21. Salov, B.V. and Gershenovich, A.I., *Poluchenie i svoistva organicheskikh soedinenii sery* (Preparation and Properties of Organic Sulfur Compounds), Belen'kii, L.I., Ed., Moscow: Khimiya, 1998, p. 260.