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QUANTUM-CHEMICAL STUDY OF THE ELECTRONIC STRUCTURE AND REACTIVITY OF 2-METHYL-4H-THIENO[3,2-*b*]PYRROLE-5-CARBOXYLIC ACID METHYL ESTER

V. N. Yarovenko, S. L. Semenov, I. V. Zavarzin, N. D. Chuvylkin, and M. M. Krayushkin

We have used the MNDO approximation to carry out a quantum-chemical study showing that the selectivity of acylation of 2-methyl-4H-thieno[3,2-b]pyrrole-5-carboxylic acid methyl ester under Friedel–Crafts reaction conditions in the presence of AlCl₃ depends more on the electron density distribution in the complexes than on the structure parameters.

Keywords: thienopyrroles, molecular structure, semiempirical quantum-chemical calculations, regioselective acylation.

Thienopyrroles are analogs of indoles and so are of significant interest in synthesis of various bioactive substances. Considerable attention has been focused on designing physiologically active compounds based on 4H-thieno[3,2-*b*]pyrrole-5-carboxylic acid esters [1-3].

Considering the electron-rich nature of thienopyrroles, electrophilic processes are generally used to modify them. An attractive method for adding functional groups to thienopyrroles is to introduce acyl groups which then can be converted to various functional groups, including heterocyclic moieties. However, a serious and poorly studied problem is how to carry out regioselective reactions with thienopyrroles having free positions on both the thiophene ring and the pyrrole ring.

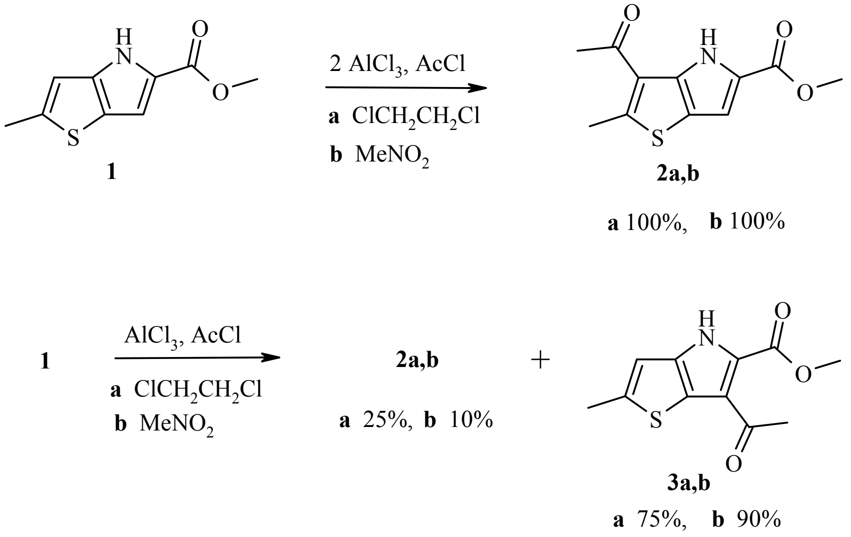
Earlier we showed that in the presence of a two-fold excess of $AlCl_3$, acylation of 2-methyl-4H-thieno[3,2-*b*]pyrrole-5-carboxylic methyl ester (**1**) occurs regioselectively at the 3 position of the diheterocycle, yielding the product **2**, while when equimolar amounts of $AlCl_3$ and thienopyrrole are used, a mixture of 3- and 6-acyl derivatives **2** and **3** is formed (Scheme 1) [4].

With the aim of estimating the effect of structural and electronic factors on the selectivity of acylation, in this paper we compare the calculated heats of reaction and the experimentally established percentages of isomers formed, and also the calculated electron density distributions in complexes of thienopyrrole with $AlCl_3$ and possible routes for electrophilic attack in nonpolar and polar solvents.

The calculations were performed using the MOPAC program [5] by the standard semiempirical quantum-chemical method MNDO with full optimization of the geometry for the molecules of thienopyrrole **1**, monoketones **2, 3**, complexes with aluminum chloride **4-8**, and σ-complexes **9, 10** (Scheme 2).

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow 119991; e-mail: yarov@ioc.ac.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 291-298, February, 2006. Original article submitted July 1, 2004.

Scheme 1



DISCUSSION OF RESULTS

The optimized geometric parameters of structures **1-10** obtained by the MNDO method are shown in Tables 1 and 2; the structural formulas for the indicated compounds, together with the numbering of the atoms we used, are shown in Scheme 2.

As shown by our quantum-chemical calculations, going from the free thienopyrrole molecule **1** to the complex **4** is associated with slight shortening of the C(7)-C(8) bond (from 1.48 Å to 1.46 Å) and a little lengthening of the C(8)=O bond (from 1.23 Å to 1.26 Å).

The coplanarity characteristic of the isolated thienopyrrole molecule is practically preserved in all the complexes with $AlCl_3$. The angle of deviation of the C=O bond of the carboxyl group from the plane of the ring of the diheterocycle is within the range from -11° to -17°, i.e., essentially there is no disruption of the conditions ensuring effective conjugation with the aromatic system for the carbonyl group that has been modified by complexation.

Table 3 shows the ethalpies of formation (ΔH_f), the dipole moments (μ), the frontier molecular orbital energies (ε_f, ε_v) and the differences between them, and also the charges on the atoms (Q) as calculated in the MNDO approximation.

Complexation of thienopyrrole **1** with $AlCl_3$ (structure **4**) is accompanied by substantial transfer of electron density from the donor molecular moiety (thienopyrrole) to the acceptor ($AlCl_3$), where the charges on the carbon atoms at the 3 and 6 positions of the diheterocycle, as we go from the isolated thienopyrrole molecules **1** to its complex with AlCl3 **4**, vary from -0.05 to -0.07 and from 0.03 to 0.10. Complexation with $AlCl_3$ is accompanied by a substantial increase in the dipole moment of the system compared with the starting reagents, and the forming complexes **6-8** have the highest dipole moments (Table 3).

When a proton is added to complex **4**, the 3 and 6 positions in compounds **9-10** as a whole become more accessible to electrophilic attack by the acylating agent. The calculated enthalpy of reaction for the isolated molecule **1** with the acylating complex $MeCOCl{\cdot}AlCl_3$ (Scheme 3, Tables 2-4) suggest that in the gas phase, formation of complex **5** as the end product should be preferred. At the same time, we may expect that when the reactions are carried out in a polar solvent, according to the Onsager solvation model for spherical, electrically neutral systems [6], the isomeric complex **7** proves to be more stable since its dipole moment is substantially

Scheme 2

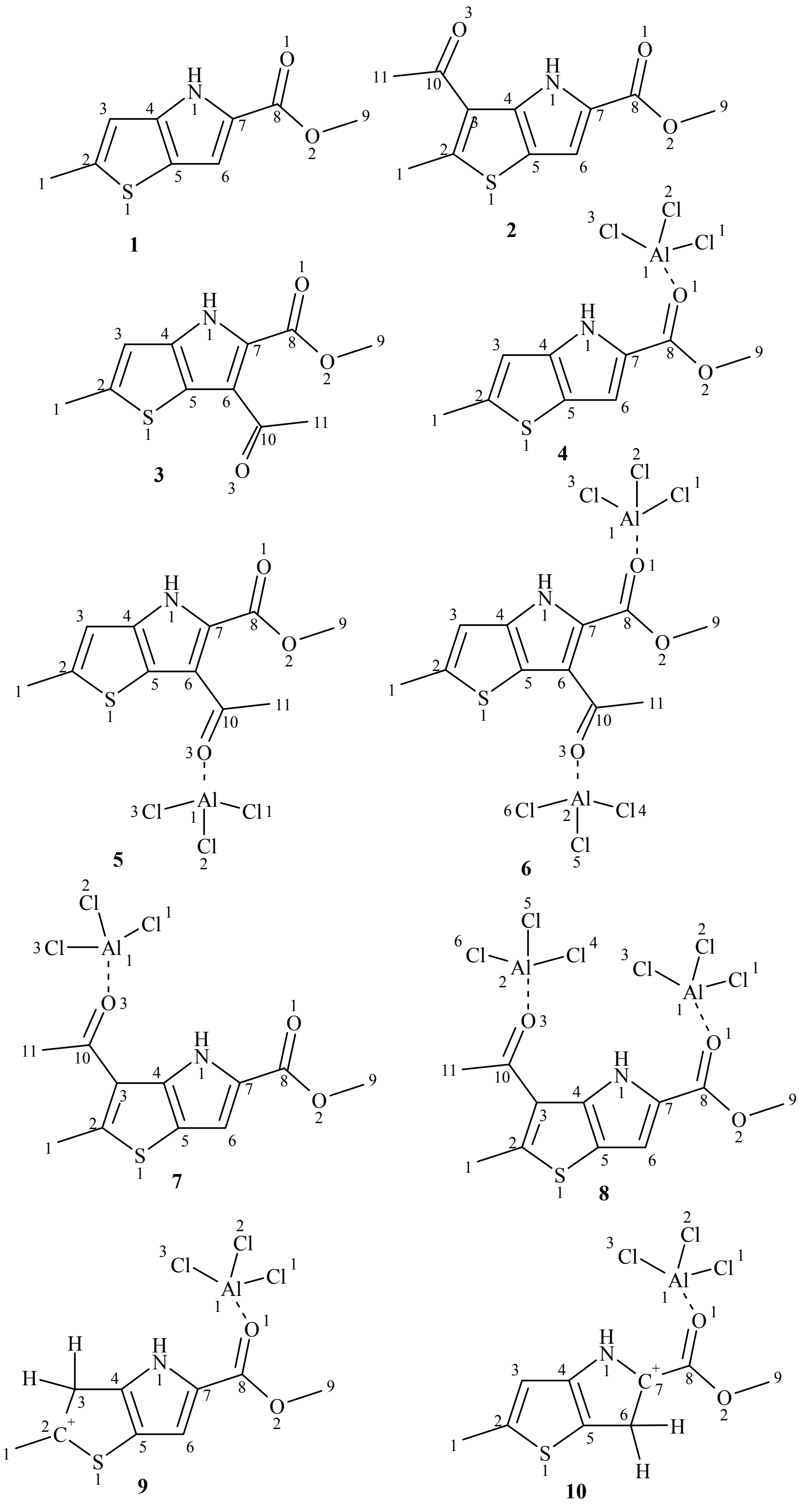


TABLE 1. Bond Lengths (*d*) in Structures **1-10**, Optimized by the MNDO method

Bond	*d*, Å									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
C(1)–C(2)	1.49	1.49	1.49	1.49	1.53	1.49	1.50	1.49	1.49	1.50
C(2)–C(3)	1.38	1.39	1.38	1.38	1.40	1.38	1.40	1.38	1.52	1.39
C(3)–C(4)	1.44	1.45	1.44	1.45	1.45	1.44	1.45	1.45	1.50	1.43
C(4)–N(1)	1.38	1.38	1.38	1.37	1.38	1.38	1.37	1.37	1.38	1.41
C(4)–C(5)	1.43	1.43	1.42	1.44	1.43	1.43	1.43	1.44	1.43	1.42
C(5)–S(1)	1.67	1.66	1.67	1.67	1.66	1.67	1.66	1.67	1.66	1.64
C(5)–C(6)	1.42	1.42	1.42	1.41	1.42	1.43	1.42	1.42	1.42	1.49
C(6)–C(7)	1.41	1.41	1.42	1.43	1.41	1.42	1.42	1.43	1.36	1.54
C(7)–C(8)	1.48	1.48	1.48	1.46	1.48	1.50	1.47	1.47	1.49	1.51
C(8)–O(1)	1.23	1.23	1.23	1.26	1.23	1.23	1.26	1.26	1.26	1.23
C(8)–O(2)	1.36	1.36	1.38	1.34	1.36	1.36	1.33	1.33	1.33	1.32
O(2)–C(9)	1.41	1.41	1.41	1.42	1.41	1.40	1.42	1.42	1.43	1.43
C(3)–C(10)	—	1.50	–	—	—	—	1.49	1.49	—	—
C(6)–C(10)	—	–	1.50	—	1.48	1.49	—	—	—	—
C(10)–C(11)	—	1.52	1.53	—	1.53	1.53	1.53	1.52	—	—
C(10)–O(3)	—	1.23	1.22	—	1.25	1.24	1.25	1.24	—	—
O(1)–Al(1)	—	—	—	1.80	—	1.82	—	1.84	1.85	1.89
Al(1)–Cl(1)	—	—	—	2.11	—	2.11	—	2.11	2.12	2.11
Al(1)–Cl(2)	—	—	—	2.12	—	2.12	—	2.11	2.08	2.07
Al(1)–Cl(3)	—	—	—	2.13	—	2.13	—	2.12	2.13	2.13
O(3)–Al(2)	—	—	—	—	1.83	1.84	1.83	1.81	—	—
Al(2)–Cl(4)	—	—	—	—	2.11	2.11	2.11	2.12	—	—
Al(2)–Cl(5)	—	—	—	—	2.12	2.11	2.11	2.12	—	—
Al(2)–Cl(6)	—	—	—	—	2.12	2.12	2.12	2.13	—	—

higher (Table 3), leading to formation of a mixture of products. Thus competition between electronic factors (charges on the atoms) and solvation effects (dipole moments) does not rule out the possibility of reaction occurring between **1** and the acylating complex MeCOCl·$AlCl_3$ at the two reaction centers, resulting in the formation of a mixture of products in a ratio that is difficult to predict.

Scheme 3

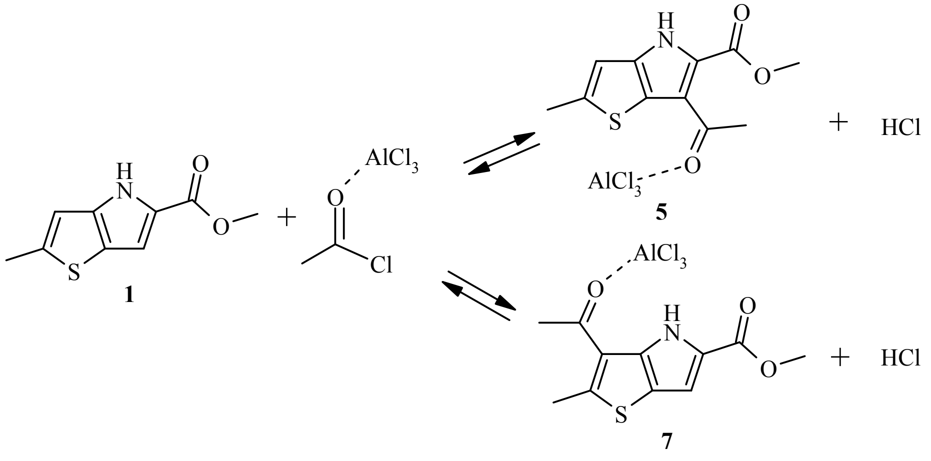


TABLE 2. Bond Angles (ω) in Structures **1-10**, Optimized by the MNDO method

Bond angle	ω, deg									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
C(1)–C(2)–C(3)	127	129	127	127	128	127	129	126	120	125
C(2)–C(3)–C(4)	109	109	110	109	109	109	109	109	99	110
C(3)–C(4)–C(5)	113	113	113	113	113	113	113	113	123	115
C(4)–C(5)–S(1)	110	110	110	111	111	110	111	110	111	112
C(4)–C(5)–C(6)	108	108	108	107	108	108	108	107	105	112
C(5)–C(6)–C(7)	107	107	106	107	107	106	107	107	107	97
C(5)–C(4)–N(1)	108	108	108	109	108	108	108	109	111	108
C(4)–N(1)–C(7)	109	108	108	109	108	108	108	109	110	111
N(1)–C(7)–C(8)	120	120	119	122	120	120	121	121	128	124
C(7)–C(8)–O(1)	126	126	126	126	126	123	124	125	139	121
O(1)–C(8)–O(2)	120	120	120	118	121	115	120	119	114	121
C(8)–O(2)–C(9)	125	125	125	128	125	127	128	128	125	124
C(8)–O(1)–Al(1)	—	—	—	174	—	169	—	179	147	144
O(1)–Al(1)–Cl(1)	—	—	—	103	—	101	—	104	97	107
O(1)–Al(1)–Cl(2)	—	—	—	104	—	103	—	102	168	111
O(1)–Al(1)–Cl(3)	—	—	—	104	—	105	—	102	108	111
C(2)–C(3)–C(10)	—	128	—	—	—	—	127	127	—	—
C(3)–C(10)–C(11)	—	117	—	—	—	—	119	120	—	—
C(3)–C(10)–O(3)	—	121	—	—	—	—	122	118	—	—
C(10)–O(3)–Al(2)	—	—	—	—	155	157	158	160	—	—
O(3)–Al(2)–Cl(4)	—	—	—	—	103	102	102	101	—	—
O(3)–Al(2)–Cl(5)	—	—	—	—	102	103	103	103	—	—
O(3)–Al(2)–Cl(6)	—	—	—	—	105	102	104	103	—	—
C(5)–C(6)–C(10)	—	—	126	—	125	119	—	—	—	—
C(6)–C(10)–C(11)	—	—	117	—	121	119	—	—	—	—
C(6)–C(10)–O(3)	—	—	121	—	118	119	—	—	—	—

In the case of reaction of complex **4** with the acylating agent $\text{MeOCl}\cdot\text{AlCl}_3$ (Scheme 4, Tables 3 and 4), we may expect formation of only complex **6**, since the substantial difference in charges on the carbon atoms in positions 3 and 6 in complex **4** directs the electrophilic attacking agent to position 3. (Enthalpies of formation, calculated in the MNDO approximation: for the complex $\text{MeCOCl}\cdot\text{AlCl}_3$, $\Delta H_f = -210.1$ kcal·mol^{-1}; for the HCl molecule, $\Delta H_f = -15.3$ kcal·mol^{-1}.

Scheme 4

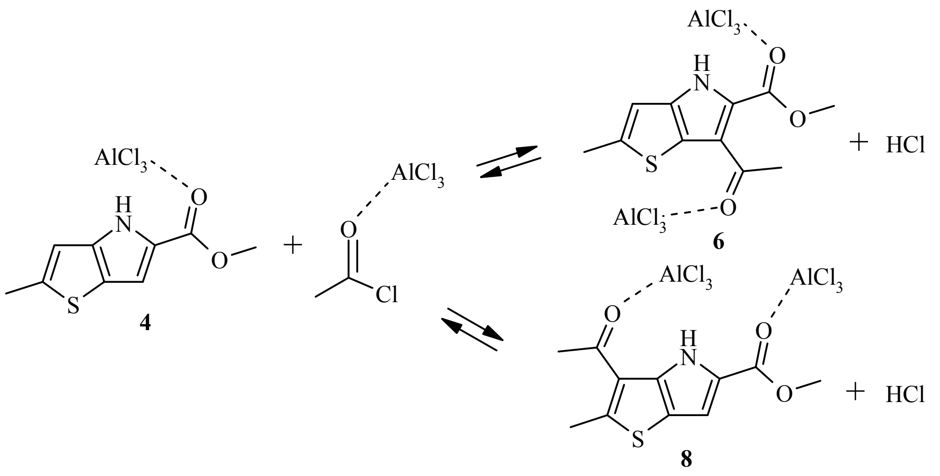


TABLE 3. Characteristics of Thienopyrrole **1**, Monoketones **2, 3**, Their Complexes with AlCl3 **4-8** and σ-Complexes **9, 10**, Calculated in the MNDO Approximation*

Compound	ΔH_f, kcal·mol^{-1}	μ, D	ε_f, eV	ε_v, eV	$\varepsilon_v - \varepsilon_f$, eV	*Q*, a. e.	
						C(3)	C(6)
1	-43.9	0.8	-8.8	-0.6	8.2	-0.05	0.03
2	-81.8	2.4	-9.0	-0.8	8.2	-0.12	0.03
3	-82.1	3.3	-9.0	-0.8	8.2	-0.04	-0.06
4	-210.7	9.9	-9.7	-1.9	7.8	-0.07	0.10
5	-237.8	14.2	-9.9	-2.0	7.9	-0.05	-0.14
6	-393.6	12.1	-10.5	-2.8	8.3	-0.08	-0.07
7	-243.9	9.9	-9.6	-1.9	7.7	-0.20	-0.03
8	-406.8	14.7	-10.6	-2.6	8.0	-0.20	0.09
9	-23.4	—	-14.0	-7.2	6.8	0.04	0.13
10	-19.1	—	-13.9	-7.0	6.9	0.00	0.08

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*ΔH_f = enthalpy of formation, μ = dipole moment, ε_f = HOMO energy, ε_v = LUMO energy, *Q* = charge on the atom.

Analogously, if we compare the calculated enthalpies of reaction and dipole moments of complexes **6** and **8**, we may conclude that in this case, only complex **6** will be formed (Tables 3, 4; Scheme 4). Consequently, the concerted effect of the electronic factors (charges on the atoms) and the solvation effects (dipole moments) make occurrence of the reaction favorable only at the 3 position of the thienopyrrole.

Thus from the results of our quantum-chemical calculations, we may conclude that the process of acylation of 2-methyl-4H-thieno[3,2-*b*]pyrrole-5-carboxylic acid under Friedel–Crafts reaction conditions in the presence of $AlCl_3$ is determined more by the electron density distribution in the considered systems, while the role of structure parameters is less significant. The electronic structure of the isolated thienopyrrole molecule **1** and its complexes with $AlCl_3$ indicates that regioselective acylation in the 3 position of thienopyrrole should occur when excess $AlCl_3$ is used; and when equimolar amounts of thienopyrrole and $AlCl_3$ are used, a mixture of monoketones **2** and **3** should be formed.

TABLE 4. Enthalpies of Reaction Calculated by the MNDO Method

Reaction	$\Delta H_r(3)$, kcal·mol^{-1}	$\Delta H_r(6)$, kcal·mol^{-1}	$\Delta H_r(6) - \Delta H_r(3)$, kcal·mol^{-1}	$\mu_{(3)}$, D	$\mu_{(6)}$, D	Δμ, D
Scheme 3	-5.3 (**5**)	0.8 (**7**)	6.1	9.9	14.2	4.3
Scheme 4	1.3 (**6**)	11.9 (**8**)	10.6	14.7	12.1	2.6

$\Delta H_r(3)$ = enthalpies of reaction at the position 3 of the thienopyrrole, $\Delta H_r(6)$ = enthalpies of reaction at the position 6 of the thienopyrrole, $\Delta H_r(6) - \Delta H_r(3)$ = difference between enthalpies of reaction at the positions 6 and 3, μ(3) = dipole moment of the complex when attacked at the position 3, μ(6) = dipole moment of the complex when attacked at the position 6 of the diheterocycle.

The conclusions drawn on the basis of quantum-chemical calculations for the thienopyrrole molecule and its complexes with aluminum chloride are consistent with experimental data, and consequently this calculation method can be used to estimate the selectivity of thienopyrrole acylation processes.

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