Quantum-chemical study of the protonation of pyrrolo[2,1-*b*]thiazole and its selenium and tellurium analogs

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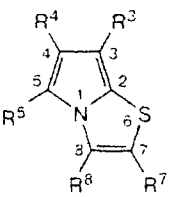
The possibility of proton attack on various centers in pyrrolo[2,1-*b*]thiazole (**1**) has been evaluated. The results of semiempirical (MNDO, AM1, and PM3) and *ab initio* (6-31G*) calculations were compared. The MNDO and 6-31G* methods give "chemically proper" and qualitatively coincident results. Analysis of the intramolecular (geometric and electronic) reorganization of molecule **1**, depending on the protonation center, has been carried out. The most probable attack centers, depending on the mechanism of electrophilic reaction, have been recognized. The energy parameters of intramolecular prototropic rearrangements in cation **1** and the "blocking" factor value of methyl groups reducing the corresponding complex stability have been evaluated. It has been established that the relative stability of the protonated forms does not change on going to pyrrolo[2,1-*b*]selenium- and telluriumazoles, but the range of variations is considerably narrowed in the series S > Se > Te.

Key words: pyrrolothiazole, protonation, quantum-chemical calculation, orbital control, transition states.

A pyrrolo[2,1-*b*]thiazole molecule (**1**)[1,2] contains formally three heterocyclic systems (pyrrole, thiazole, and thiophene), each of which plays an important role in its nature and synthetic chemistry. However, their manifestations in the general structure differ, though superficially. Although the π-system of the pyrrole fragment is presented in full measure, one of the C atoms in the thiophene part of the molecule is replaced by the N atoms. It should be expected that the electrophilic reactions of compound **1** resemble, to a great extent, similar reactions of pyrrole cycles. At the same time, the channels of electrophilic reactions depend substantially on several external factors (temperature, structure of the electrophile, medium, counterion, *etc.*), under the action of which the routes of the chemical transformations can even change.

Undoubtedly, experimental information about the relative stability of different protonated structures and character of transition states of intramolecular transformations is very important for understanding the mechanisms of electrophilic attacks and performing purposeful syntheses. However, it is difficult to obtain this information. Therefore, the preliminary quantum-chemical simulation of some possible channels of electrophilic reactions is justified and reasonable.

We used semiempirical (MNDO,[3,4] AM1,[5,6] PM3[7]) and nonempirical (6-31G* basis set) methods to reveal the sensitivity of the calculated results to the applied approximation. Most calculations were performed by the semiempirical procedures, and the key points were additionally identified in the framework of the nonempirical scheme. The saddle points on the potential energy surface (transition states in the gas phase) were determined from the presence of a single negative eigenvalue of the matrix of the secondary energy derivatives with respect to the geometric parameters. The solvation effects were taken into account by a described procedure[8–10] using two parameters: the dielectric constant (ε) of the solvent and the empirical constant *C* independent of the atomic nature. The accepted numeration of the atoms and substituents is given below.



R^3, R^4, R^5, R^7, R^8 = H, Me

Detailed studies of the mechanisms of the protonation of pyrrole and its derivatives using different quantum-chemical methods[11–16] suggested, in particular, orbital control of the regio orientation of this process.[17] Unfortunately, this conclusion cannot be extended to compound **1**, for which the semiempirical methods gave different sequences of the relative stabilities of the protonated structures under study (Table 1). All methods preferred the C_3-protonated form (Table 2)

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Table 1. Relative energies (E) of the protonated structures of molecule **1** according to the quantum-chemical data[*]

Protonation center	E/kcal mol^{-1}			
	6-31G*	AM1	PM3	MNDO
C_2	20.8	27.1	22.6	19.3
C_3	5.0	0.0	0.0	1.6
C_4	16.1	12.9	7.9	9.3
C_5	0.0	1.1	1.6	0.0
C_7	19.1	23.5	17.7	14.9
C_8	33.9	18.2	22.9	23.9
N	44.3	35.8	27.3	34.5
S	49.6	19.3	12.0	30.2

[*] In each case, the full energy (eV) of the most stable form −18568.9913 (6-31G*), −1279.5856 (MNDO), −1243.4957 (AM1), and −1143.2153 (PM3) was taken as the reference point.

Table 2. Contributions of AO to HOMO and charges of atoms in molecule **1**

Atom	MNDO	AM1	PM3
	Contribution		
C_3	0.48	0.47	0.48
C_4	0.10	0.03	0.01
C_5	0.44	0.43	0.42
C_7	0.20	0.15	0.18
	Charge		
C_3	−0.073	−0.161	−0.101
C_4	−0.119	−0.173	−0.146
C_5	0.002	−0.129	−0.274
C_7	−0.286	−0.420	−0.284

because of the orbital property. The experimental thermodynamic preference of the C_5-structure[2] has been transmitted only by the 6-31G* method and, which is somewhat unexpected, in the MNDO variant (see Table 1).[*]

The question arises: Due to which electron factors is the C_5-cation most stable in the MNDO model of the isolated system? The influence of the frontier occupied MO on the regio orientation of protonation can be excluded (the gap between the energy levels of the HOMO and the preceding occupied MO is 0.79, 1.18, and 0.83 eV in the MNDO, AM1, and PM3 variants, respectively). Apparently, the reason for the correct MNDO transmission should be searched for in the changes in the electron parameters, which occur in molecule **1** upon the addition of a proton.

These changes can be examined in detail by interrelation of the structural reorganization due to the effect of H^+ and the corresponding electron transformation. Excluding the source of structural deformations (proton) from the calculation with unchanged geometry of molecule **1**, we can elucidate the influence of the pure geometric reorganization in the electron distribution. In the general case, this problem is very labor-consuming if we take into account the multiprofile character of the reaction routes. Therefore, we considered only the initial and final points of the studied protonation routes. The deformation degree (ΔE_{X_i}) was estimated as the difference between the energies of two neutral structures (with optimized geometric parameters (E_{opt}) and those inherent in the stationary protonated state ($E_{X_i}^{\Phi}$))

$$\Delta E_{X_i} = E_{opt} - E_{X_i}^{\Phi}.$$

The changes in some electron parameters due to the structural reorganization are presented in Tables 3 and 4. Naturally, the transformations of the HOMO and charge distributions in different fragments of the molecule are of interest. When the C atom is attacked, the contribution of the AO of this atom prevails in the rearranged HOMO (see Table 4). Comparison of the competing C_5- and C_3-centers shows an explicit loss in the increase in the contribution of the AO of the C(3) atom as compared to that of C(5). This is most pronounced in the MNDO method (for C(5) the contribution increases from 0.44 to 0.58, and that for C(3) increases from 0.48 to 0.54, see Table 4). A similar tendency is observed in the AM1 and PM3 variants (for C(5) from 0.43 to 0.53 and from 0.42 to 0.47; for C(3) from 0.47 to 0.54 and from 0.48 to 0.51, respectively).

Thus, the MNDO variant is the most adequate among semiempirical methods used by us. The data obtained by this method indicate that the compounds of type **1** during their protonation are orbital-controlled. However, unlike pyrroles, for which the most probable protonation center can be chosen already by the composition of the HOMO of the neutral optimum structure,[17] for molecule **1** this factor begins to appear only in the dynamics of structural transformation (see Table 4).

Table 3. Deformation energies (ΔE_{X_i}), dipole moments (μ), and energies of HOMO (E) of neutral molecule **1** with optimized geometry and corresponding to the protonation of different centers (MNDO)

Protonation center	ΔE_{X_i} /kcal mol^{-1}	μ /D	$-E$ /eV
*	0.0	2.02	8.26
C_2	37.4	2.54	8.13
C_3	39.6	2.90	7.94
C_4	39.5	2.77	8.03
C_5	38.2	1.70	7.94
C_7	42.6	2.81	8.09
C_8	41.2	1.54	8.17
S	0.7	2.02	8.29
N	15.1	1.95	8.52

* Geometry optimum.

[*] The calculations in the 3-21G and 6-21G* basis sets do not explicitly prefer the C_5-protonated form because of the relative stability.

Table 4. Contributions of AO to HOMO and charges of atoms in molecule **1** with optimized geometry and corresponding to the protonation of different centers (MNDO)

Protonation center	Contribution of AO								Charge							
	C_8	C_7	C_5	C_4	C_3	C_2	S	N	C_8	C_7	C_5	C_4	C_3	C_2	S	N
*	0.30	0.20	0.44	0.10	0.48	0.35	0.53	0.16	0.065	−0.286	0.002	−0.119	−0.073	−0.204	0.331	−0.200
C_2	0.20	0.03	0.49	0.21	0.31	0.51	0.38	0.04	0.031	−0.234	0.028	−0.152	−0.017	−0.239	0.279	−0.177
C_3	0.13	0.35	0.35	0.05	0.54	0.36	0.41	0.21	−0.061	−0.309	−0.027	−0.083	−0.129	−0.190	−0.378	−0.188
C_4	0.11	0.11	0.50	0.53	0.07	0.42	0.29	0.19	0.043	−0.258	0.031	−0.179	−0.036	−0.238	0.330	−0.177
C_5	0.20	0.09	0.58	0.14	0.37	0.37	0.38	0.09	0.061	−0.305	−0.085	−0.056	−0.110	−0.196	0.378	−0.165
C_7	0.36	0.52	0.24	0.11	0.44	0.11	0.49	0.27	0.097	−0.320	0.002	−0.080	−0.096	−0.144	0.271	−0.213
C_8	0.50	0.18	0.45	0.07	0.44	0.36	0.46	0.15	0.010	−0.286	0.001	−0.134	−0.051	−0.278	0.441	−0.181
S	0.29	0.19	0.44	0.07	0.49	0.36	0.54	0.16	0.071	−0.280	0.006	−0.119	−0.073	−0.195	0.311	−0.204
N	0.25	0.19	0.33	0.07	0.46	0.29	0.49	0.16	0.039	−0.266	0.007	−0.102	−0.047	−0.199	0.310	−0.220

* Geometry optimum.

Then all quantum-chemical parameters obtained in the semiempirical approximation are attributed to the MNDO variant, unless otherwise specified.

As a result of the deformation of molecule **1**, the interaction between the vacant orbital of the electrophile and its HOMO enhances the energy level of the latter (see Table 3). This occurs only for C_i-carbon centers. The sequence of the relative increase in the energy of the HOMO ($C_5 \approx C_3 > C_4 > C_7 > C_2 > C_8$) corresponds to the series of stability of the cationic σ-complexes (see Tables 1 and 3). Another correlation between the stabilities of different C_i-protonated structures of compound **1** and the degree of HOMO transformation is observed: the greater an increase in the contribution of the AO of the corresponding carbon center to the HOMO during geometric reorganization, the higher the stability of the protonated form (see Tables 1 and 4).

It is reasonable to expect that the structural rearrangement results in the maximum increase in the electron population (q) of the attacked carbon center. This occurs to a greater extent for the C_5- and C_8-centers ($\Delta q = 0.087$ and 0.065, respectively) and to a less extent for C_7 and C_2 (0.034 and 0.038, respectively). However, unlike the orbital parameters, a correlation between the Δq_i and the sequence of the relative stability of the cationic σ-complexes is not found.

The changes in the dipole moments related to the charge redistributions (see Table 3) stipulate a decrease in the polarity of molecule **1** upon the protonation at the C_5- and C_8-centers, whereas it increases in all other variants. This suggests that for the potential-competing C_3- and C_5-centers of protonation the polar medium can change their ratio. Quantitative estimations of the deformation degree of molecule **1** for the C_i-carbon forms lie in a wide interval (~6 kcal mol^{-1}) and do not correlated to the series of their stability (see Tables 1 and 3). As should be expected from the electron redistributions (see Table 4), the calculations of the neutral deformed structures that took into account the solvent effect ($C = 1.2$, $\varepsilon = 20$) gave a decrease in the stability of the C_5- and C_8-forms by 1.3 and 2.8 kcal mol^{-1}, respectively, and an increase in the stability of the C_7-, C_4-, C_3-, and C_2-structures by 2.5, 2.1, 3.3, and 2.0 kcal mol^{-1}, respectively. This confirms the assumption on the opposite influence of the medium polarity on the probabilities of the protonation of the C_3- and C_5-centers.

The direct attack of a proton at the S atom is associated with insignificant structural distortions ($\Delta E_S = 0.7$ kcal mol^{-1}, see Table 3) and has almost no effect on the charge distribution and HOMO structure (see Table 4). This indicates the possibility of the low-activation fast proton exchange between the prototropic medium and S-center of compound **1**. Two routes of intramolecular rearrangement are possible within this exchange under the condition that the lifetime of the protonated S-form is sufficient. The first route involves 1,3- or 1,2-rearrangement* to form a more stable C_3 or C_7 cationic σ-complex, which requires substantial structural changes (see Tables 3 and 5). In this case, the subsequent proton migration with energy gain cannot be excluded (Table 6).

The second route assumes the deprotonation of the C_3- or C_7-center to form a bipolar structure. Preference for the deprotonation of one of the centers can be judged by the difference between the formation enthalpies, which is 4.9 kcal mol^{-1} in favor of the C_3-form. The E_{act} value of the subsequent migration of a proton to position 7 or 3 is 29.8 and 26.1 kcal mol^{-1}, respectively, which at least does not exceed the energy expenditures for intramolecular rearrangements. According to the used model, the C_7-center should be preferred in the first mechanism, and the position C_3 is preferential in the second mechanism.

To reveal the role of alkyl substituents, we calculated the relative stability of the cationic σ-complexes with different positions of the methyl groups and with their number varying. Based on a broad data scatter of the

* E_{act} for the centers C_3 and C_7 is 31.4 and 28.7 kcal mol^{-1}, respectively.

Table 5. Main geometric parameters of the neutral and protonated structures of molecule **1**

Parameter	Neutral	Protonation center							
		C_2	C_3	C_4	C_5	C_7	C_8	S	N
Bond					l_{ij}/Å				
N—C_2	1.427	1.509	1.381	1.464	1.385	1.475	1.431	1.436	1.512
C(2)—C(3)	1.388	1.515	1.511	1.363	1.459	1.366	1.411	1.390	1.363
N—C(5)	1.401	1.350	1.447	1.336	1.496	1.493	1.383	1.407	1.498
C(4)—C(5)	1.395	1.463	1.363	1.552	1.524	1.326	1.417	1.395	1.362
N—C(8)	1.414	1.445	1.409	1.440	1.408	1.370	1.470	1.407	1.492
S—C(2)	1.675	1.752	1.646	1.681	1.649	1.674	1.651	1.686	1.683
C(8)—C(7)	1.366	1.360	1.380	1.364	1.379	1.512	1.514	1.368	1.356
Angle					φ_{ijk}/deg				
C(2)—N—C(8)	109.2	110.9	110.9	111.3	111.2	108.1	109.1	108.6	104.1
C(2)—N—C(8)	110.0	108.6	107.4	108.2	100.6	106.5	107.4	107.1	108.1
N—C(2)—C(3)	107.8	101.7	108.8	108.5	108.6	107.4	107.5	108.1	108.6
N—C(2)—S	110.0	104.0	112.2	109.8	111.9	110.5	111.3	110.2	110.1
N—C(5)—C(4)	106.8	112.7	113.2	112.2	113.2	115.2	114.5	113.4	105.6
N—C(8)—C(7)	110.5	109.8	109.0	109.6	109.2	112.0	102.8	110.7	110.8

Table 6. Activation barriers (E_a/kcal mol^{-1}), interatomic distances (l/Å), and charges of atoms (q/au) in the transition states of 1,2-prototropic shifts $i \rightarrow j$

Shift	E_a	$l_{C_iC_j}$	l_{HC_i}	l_{HC_j}	q_{C_i}	q_{C_j}	q_H
$C_4 \rightarrow C_5$	39.1	1.49	1.37	1.24	0.05	0.11	0.12
$C_4 \rightarrow C_3$	40.7	1.50	1.35	1.22	−0.03	−0.02	0.17
$C_5 \rightarrow C_7$	37.4	1.48	1.36	1.24	−0.04	−0.07	0.22

relative stability of the protonated forms (see Table 1), it is difficult to assume that the insertion of methyl substituents into specific positions can substantially change the series found for the nonsubstituted structures. However, we may draw some conclusions about the shift of the equilibrium for the most stable C_5-, C_3-, C_4-, and C_7-protonated derivatives (Table 7). For example, the insertion of Me into position 5 results in the inversion of the relative stability of the C_5- and C_3-cations, whereas the sequence of the other two cations remains unchanged. The alternative substitution of the hydrogen atoms in positions 7, 8, 4, and 3 by the methyl group never resulted in the inversion of the initial stability series, but made it possible to evaluate the blocking effect of the methyl group. This effect stipulates the decrease in the relative stability of the corresponding cationic σ-complex by 5—7 kcal mol^{-1} (see Table 7). When the methyl groups are simultaneously inserted into two positions (5 and 3), the C_5-protonated form remains most preferential, but it already competes strongly with both the C_3- and C_4-protonated structures, and the highest difference in the formation enthalpies decreases to ΔE = 8.6 kcal mol^{-1}. For simultaneous blocking of the C_5-, C_4-, and C_3-carbon centers, the former sequence of stability remains unchanged, and the similar energy difference ΔE = 9.9 kcal mol^{-1} indicates that the C_7-protonated structure cannot become competitive by methyl screening.

Table 7. Enthalpies of formation (kcal mol^{-1}) of the cationic σ-complexes with methyl substituents

R = Me	Protonation center			
	C_3	C_4	C_5	C_7
R_7	202.3	211.2	201.0	222.3
R_8	203.7	211.7	202.3	215.8
R_5	203.7	210.0	207.7	216.7
R_4	203.9	217.1	202.1	217.1
R_3	209.9	211.1	202.5	216.9
$R_5 = R_3$	198.8	198.6	196.9	205.5
$R_5 = R_4 = R_3$	190.3	195.4	188.1	198.0

New derivatives of compound **1**, pyrrolo[2,1-*b*]selenium- and telluriumazoles, have previously been synthesized.[1] Naturally, it is necessary to compare the potential abilities of protonating the most promising carbon centers. As shown above (see Table 1), for **1** the relative stability of the cationic σ-complexes decreases in the series $C_5 > C_3 > C_4 > C_7$. The interval of the stability change is 14.8 kcal mol^{-1}. On going to pyrrolo[2,1-*b*]seleniumazole, this series remains almost unchanged ($C_5 \approx C_3 > C_4 > C_7$). Against the background of the alignment of the relative stabilities of the C_5- and C_3-protonated forms, the competing ability of the C_4- and C_7-centers increases substantially (the maximum difference in the energies of these σ-complexes is ΔE = 7.6 kcal mol^{-1}). The probabilities of the protonation of these centers are still more aligned for pyrrolo[2,1-*b*]telluriumazole ($C_5 \approx C_3 > C_4 \approx C_7$, ΔE = 2.6 kcal mol^{-1}). Therefore, the equilibrium can be purposefully shifted, most likely, by the insertion of methyl substituents into the corresponding positions of the derivative, taking into account their blocking factor.

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