

# Quantum-chemical study of electronic structure and transmission of substituent effects in benzothiazole derivatives

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*Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday*

Electronic structure and transmission of substituent effects from benzene ring into heterocycle and *vice versa* in benzothiazole neutral derivatives and corresponding cations have been studied by the quantum-chemical semiempirical method CNDO/2. The considerable charge delocalization occurs in the case of the cations. The transmission of the substituent effects is more pronouncing in the neutral molecule than in the corresponding cation. The available experimental data are in agreement with these findings.

С помощью квантовохимического семиэмпирического метода CNDO/2 изучена электронная структура и перенос эффекта заместителя из бензольного цикла в гетероциклический и наоборот у нейтральных производных бензотиазола и соответствующих катионов. В случае катионов наблюдается значительная делокализация заряда. Перенос эффектов заместителя более выражен у нейтральных молекул, чем у соответствующих катионов. Имеющиеся экспериментальные данные подтверждают данные заключения.

As a continuation of an experimental research of benzothiazole derivatives as substances with a significant biological activity [1—3], we performed a theoretical study of electronic structure of these compounds. The difference in electron density distribution in neutral species and corresponding cations has been investigated. Transmission of substituent effects from heterocycle to benzene moiety and *vice versa* has been studied, too. In the case of neutral molecules the theoretical results have been compared with the experimental  $^{13}\text{C}$  NMR data [4, 5].

## Computational method

The problem has been studied by the quantum-chemical semiempirical method CNDO/2 [6] suitable to describe the electronic structure of molecules.

The rigid structure of molecules under study has been used, the geometry has been constructed from the X-ray experimental data of the neutral benzothiazole skeleton [7], the benzothiazolium cation [8] and the substituted benzene derivatives [9].

## Results and discussion

### Electronic structure

Molecular diagrams of neutral benzothiazole, benzothiazolium cation originated by the protonization of nitrogen, and *N*-methylbenzothiazolium cation are presented in Fig. 1 (atomic charges, Wiberg bond indices, total charge in the benzene ring and in the heterocycle, respectively).

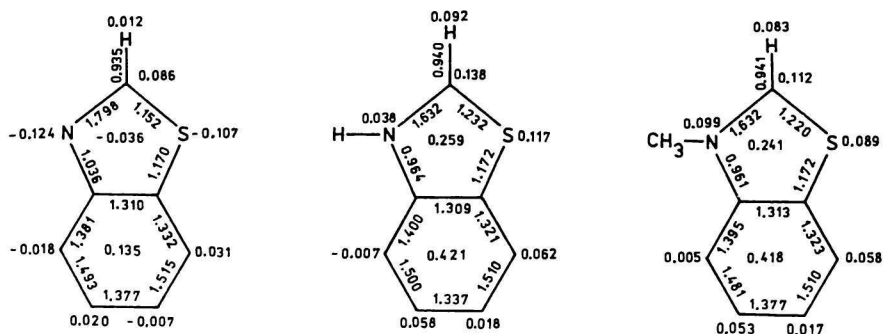


Fig. 1. Molecular diagram of benzothiazole, protonized benzothiazolium cation, and *N*-methylbenzothiazolium cation, respectively (values of atomic charge, Wiberg bond indices, total charge in the benzene ring and in the heterocycle).

The electrons in a neutral molecule are delocalized, with the highest negative charges on N and S atoms. Considerable positive charge on C-2 is in agreement with experimentally found sensitivity of this position to react as an electrophile. The values of Wiberg bond indices give evidence for C-2—N double bond character, while the bonds between N, S and carbons in the heterocycle show rather a single bond character. The total charge in the heterocycle is negative, in benzene ring positive. This fact explains the difficulty of electrophilic substitution on a six-membered ring. Just C-4 and C-6 carbons can be attacked by electrophilic agents.

The protonization of nitrogen gives rise to a cation in which the positive charge is delocalized through all the molecule. The total positive charge in benzene ring is enhanced, resulting charge in the heterocycle is positive, too. Reactivity of carbon C-2 towards nucleophiles increases, this being supported by acidic character of hydrogen attached to C-2. The enhancement of delocalization is confirmed also by decreasing of C-2—N bond index and by increasing of the C-2—S one. The same conclusions can be drawn also for the case of

*N*-methylbenzothiazolium cation. For that reason in next calculations we modeled the benzothiazolium cation with the *N*-protonized structure.

### *Transmission of substituent effects*

To investigate the influence of the substituent on the electronic structure of basic skeleton and the transmission of substituent effects through the skeleton we chose four substituents: NH<sub>2</sub>, CH<sub>3</sub>, Cl, NO<sub>2</sub>. The NH<sub>2</sub> and NO<sub>2</sub> represent strong electron-donating and -withdrawing groups. In some cases the calculated values can be compared with the experimental values. The transmission of the substituent effects from the heterocycle to the benzene ring was studied in such a way that a substituent was attached to C-2 and the change of electron density on carbons of benzene ring in comparison with the unsubstituted molecule was investigated. The transmission in the opposite direction has been studied too, the substituent was bound step-by-step to all positions of benzene ring and the change of C-2 charge density has been examined. The study was carried out for a neutral molecule and for its protonized form. Totally 42 calculations were performed, the results of which are in Tables 1 and 2 (neutral molecule) and in Tables 3 and 4 (*N*-protonized cation). In Tables 1—4 the values were calculated as a difference between electron density on the corresponding position of substituted molecule and the unsubstituted one.

Table 1

The change of the electron density ( $\Delta Q \cdot 10^3$ ) caused by the substituents in neutral benzothiazole derivatives (the transmission from C-2 to the benzene ring)

Atom	2-NH <sub>2</sub>	2-CH <sub>3</sub>	2-Cl	2-NO <sub>2</sub>
C-4	+103	+61	-30	-95
C-5	-60	-14	-26	-30
C-6	+98	+32	-36	-94
C-7	-57	-14	-29	-28

The presence of a substituent on C-2 in the neutral molecule results in the greatest variation of electron density on carbons C-4 and C-6, the variation of C-5 and C-7 density is smaller. This fact is in agreement with experimental finding that the primary path of transmission is through nitrogen, while trans-

Table 2

The change of the electron density ( $\Delta Q \cdot 10^3$ ) caused by the substituents in neutral benzothiazole derivatives (the transmission to the heterocycle)

Atom	4-NH <sub>2</sub>	4-CH <sub>3</sub>	4-Cl	4-NO <sub>2</sub>	5-NH <sub>2</sub>	5-CH <sub>3</sub>	5-Cl	5-NO <sub>2</sub>
S	+1	+15	-124	-238	+77	+19	-140	-278
C-2	+70	+23	-21	-66	-40	-20	-23	-33
N	-74	-8	-114	-218	+64	+44	-27	-74
Atom	6-NH <sub>2</sub>	6-CH <sub>3</sub>	6-Cl	6-NO <sub>2</sub>	7-NH <sub>2</sub>	7-CH <sub>3</sub>	7-Cl	7-NO <sub>2</sub>
S	+30	+7	-154	-274	+51	+35	-286	-523
C-2	+74	+17	-40	-77	-37	-20	-1	+16
N	-55	+2	-1	-28	+36	+33	-17	-43

Table 3

The change of the electron density ( $\Delta Q \cdot 10^3$ ) caused by the substituents in *N*-protonized benzothiazole cation derivatives (the transmission from C-2 to the benzene ring)

Atom	2-NH <sub>2</sub>	2-CH <sub>3</sub>	2-Cl	2-NO <sub>2</sub>
C-4	+75	+43	+6	-52
C-5	-11	+9	-15	-30
C-6	+88	+56	+10	-32
C-7	-21	+14	-7	-3

Table 4

The change of the electron density ( $\Delta Q \cdot 10^3$ ) caused by the substituents in *N*-protonized benzothiazole cation derivatives (the transmission to the heterocycle)

Atom	4-NH <sub>2</sub>	4-CH <sub>3</sub>	4-Cl	4-NO <sub>2</sub>	5-NH <sub>2</sub>	5-CH <sub>3</sub>	5-Cl	5-NO <sub>2</sub>
S	+39	+60	-77	-137	+108	+74	-48	-180
C-2	+62	+29	-8	-54	-16	-1	-14	-31
N	-111	-11	-24	+47	+60	+29	-18	-35
Atom	6-NH <sub>2</sub>	6-CH <sub>3</sub>	6-Cl	6-NO <sub>2</sub>	7-NH <sub>2</sub>	7-CH <sub>3</sub>	7-Cl	7-NO <sub>2</sub>
S	+87	+82	-68	-218	+119	+137	-149	-386
C-2	+79	+37	-8	-47	-32	-12	+4	+21
N	-96	-47	-21	+13	+35	-1	-20	-23

mission *via* sulfur atom is limited [4]. Carbons C-4 and C-6 are in *ortho* and *para* position with respect to carbon carrying nitrogen. NH<sub>2</sub> and CH<sub>3</sub> substituents produce increasing of a negative charge in positions C-4 and C-6, Cl and NO<sub>2</sub> substituents decrease this charge. All four substituents increase the positive charge on carbons C-5 and C-7 (Table 1).

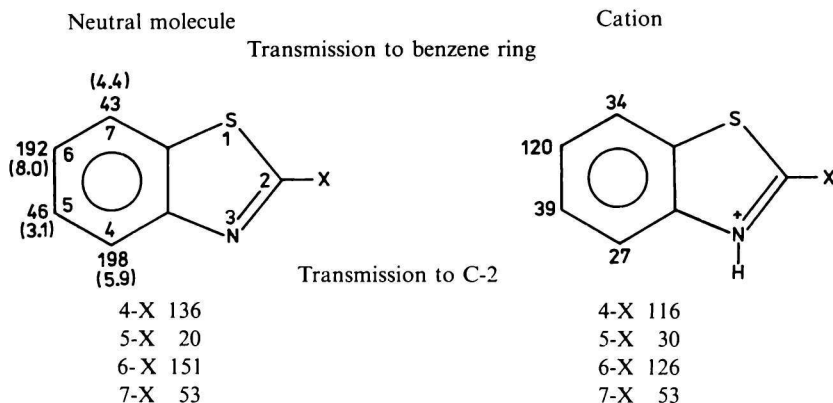


Fig. 2. Values of charge variation ( $\Delta Q \cdot 10^3$ ) obtained as a difference between the highest and the lowest values of charge density in the corresponding position (in parentheses there are the differences between the highest and the lowest values of  $^{13}\text{C}$  chemical shifts).

In the case of cations (Table 3) the negative charge is just in position C-4 of benzene ring, the other carbons have the positive charge. Better transmission is again from C-2 to C-4 and C-6. In these positions  $\text{NH}_2$ ,  $\text{CH}_3$ , and  $\text{Cl}$  substituents enhance the charge density,  $\text{NO}_2$  diminishes it.

The quantitative value of the transmission of the substituent effects can be expressed by the charge variation in dependence on substituents, which is calculated as a difference between the highest and the lowest value of the charge density in the corresponding position. These values originate mostly from substituents with the strongest electron-donating ( $\text{NH}_2$ ) and electron-withdrawing ( $\text{NO}_2$ ) effect (Fig. 2). For the sake of comparison the analogical differences between the highest and the lowest value of  $^{13}\text{C}$  chemical shift of substituted benzothiazoles calculated from the data of Ref. [4] are given in parentheses. If the substituent is in position C-2, this difference is much greater for the neutral molecule than for the cation.

In the opposite direction, *i.e.* from benzene ring to heterocycle, the substituent effects are best transmitted from positions C-4 and C-6. Attached to position C-5 all four substituents increase positive charge on C-2, from C-4 and C-6 positions  $\text{NH}_2$  and  $\text{CH}_3$  reduce positive charge on C-2,  $\text{Cl}$  and  $\text{NO}_2$  increase it.  $\text{NH}_2$  and  $\text{CH}_3$  bound to C-7 increase positive charge on C-2,  $\text{NO}_2$  decreases it, while 7- $\text{Cl}$  has almost no effect on it. That holds for a neutral molecule and also for its cation (Tables 2 and 4).

The range of charge variation in Fig. 2 shows also much better transmission from the position C-4 and C-6 to C-2. It follows that transmission of the substituent effects from the benzene part to the heterocycle is also realized predominantly *via* nitrogen. From the mentioned positions the transmission is

better in the neutral molecule than in the cation, for C-5 and C-7 carbons it cannot be stated. The transmission from the positions C-5 and C-6 has been experimentally studied in a neutral molecule [4]. In agreement with our results better transmission from carbon C-6 has been determined.

Comparing the range of charge variation in a neutral molecule one can see that the transmission of substituent effects is more pronouncing from C-2 to C-4, C-5 or C-6 than the transmission in the opposite direction, which does not hold for transmission from C-2 to C-7. On the basis of the experimental data [4], the range of  $^{13}\text{C}$  NMR shift of C-2 is 13.6 ppm, which is greater than the value determined for the transmission from C-2 to C-6 (8 ppm). This result does not agree with our findings. The explanation can lie in the fact that our calculated values are not fully comparable with the  $^{13}\text{C}$  NMR data.

Analogical study in the case of cations results in conclusion that transmission of the substituent effects from the heterocycle to the benzene ring is approximately as great as transmission in the opposite direction.

### Conclusion

The benzothiazole molecule represents a delocalized system with the negative charge in a heterocyclic part and with the positive charge in a benzene part of the molecule. After protonization or alkylation of the nitrogen the compound gains a positive charge, which is delocalized throughout the molecule. The transmission of the substituent effect is better from the heterocycle to the benzene part than in the opposite direction in the case of a neutral molecule. The most effective transmission occurs between positions C-4, C-6, and C-2 in both directions. The transmission in the neutral molecule is better than in the cation.

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