

## *Short Communication*

# Investigation of the Electronic Structures of 1,4,5-Substituted Derivatives of 1*H*-Pyrimidin-2-thione

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**Summary.** Conformational analyses and quantum chemical calculations were carried out for 1,4,5-substituted derivatives of 1*H*-pyrimidin-2-thione with the common skeleton **I** by means of the methods MMP2 and SCF MO LCAO in the CNDO/2 and MNDO approximations. The analysis of the electron density distribution as a function of the nature of the substituents was performed on the basis of the data obtained.

**Keywords.** 1*H*-pyrimidin-2-thione; Electronic structure; Heterocyclic compounds.

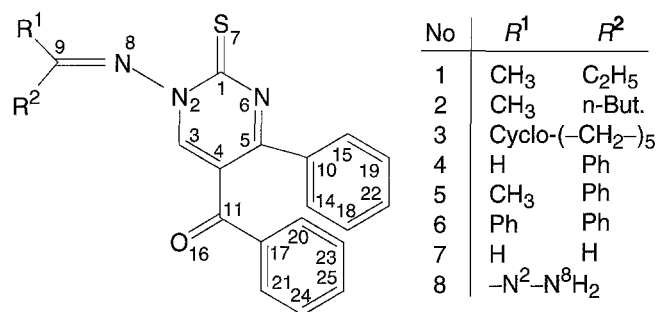
### Untersuchung der Elektronenstrukturen von 1,4,5-substituierten Derivaten des 1*H*-Pyrimidin-2-thions (Kurze Mitt.)

**Zusammenfassung.** Für eine Reihe von 1,4,5-substituierten Derivaten des 1*H*-Pyrimidin-2-thions wurden Konformationsanalysen und quantenmechanische Rechnungen durchgeführt. Als Rechenmethoden wurden das MMP2-Verfahren und die SCF-MO-LCAO-Methode in den CNDO/2- und MNDO-Näherungen benutzt. Die Elektronendichteverteilung der untersuchten Verbindungen wurde in Abhängigkeit von den Substituenten analysiert.

### Introduction

The problem of elucidating relationships between structure and biological activity of chemical compounds (in terms of their electronic features) seems to be most important for both theoretical researches and applications. Evidently, the more characteristics are taken into account, the more reliable are the predictions of biological activity.

Thiopyrimidines possess effective antibacterial, antifungal, antiviral, insecticidal, and mitocidal properties [1–4]. In this paper, the results of conformational analyses and quantum chemical investigations are discussed and used to obtain data sets needed for activity prediction. Such data sets have been applied successfully to drug design before.



Skeleton I

## Results and Discussion

Eight compounds of common skeleton I were studied. Seven of them were synthesized by us [4]. For all compounds investigated, conformational analysis was carried out by means of the MMP2 method [5, 6]. The data obtained were used in quantum chemical calculations.

The lengths of the pyrimidine skeleton bonds have been calculated and are presented in Table 1. For comparison, X-ray data compounds 6 and 8 are also given [4, 7]. The spatial structures of compounds 1–8 is shown in Fig. 1. From Table 1 it can be seen that the theoretical results and the experimental data agree. The only exception is the C=S bond. Its theoretically found value is less than the value obtained from experiments.

A comparison of the structural characteristics resulting from the two methods mentioned shows that the general tendency of changes holds for the whole series of compounds. The data for the bonds  $C_1-N_2$  and  $N_2-C_3$  differ substantially. The MNDO calculations have shown that the bond  $N_2-N_8$  is more sensitive to  $R^1$  and  $R^2$  replacement. In the limits of the accuracy admitted by the methods used, the valency and torsional angles agree satisfactorily. The values of  $\Delta H_f$  and dipole moments ( $DM$ ) calculated by means of MM2 and MNDO methods differ substantially.

Quantum chemical calculations for compounds 1–8 have been performed by the SCF MO LCAO method in the CNDO/2 and MNDO approximations [8]. The results for the pyrimidine skeleton are given in Tables 2 and 3. For the rest of atoms, the corresponding data are not given because they are relatively invariant upon variation of  $R^1$  and  $R^2$ .

The greatest negative charge (see Table 2) is concentrated on  $S_7$ ,  $N_6$ , and  $C_4$ .  $C_1$ ,  $C_3$ , and  $C_5$  bear positive charges. Atom  $N_8$  aligned to atom  $N_2$  displays a small negative charge. A general tendency exists in the changes of the charges calculated by the above mentioned methods.

The situation for atoms  $C_1$ ,  $N_2$ ,  $C_4$ , and  $S_7$  is different. Comparatively high values of charges on the atoms result from the CNDO calculations. The charges on the atoms obtained by means of the MNDO method are more sensitive with respect to  $R^1$  and  $R^2$ . The greatest differences in charges resulting from  $R^1$  and  $R^2$  replacement are observed for the frontier atom  $N_8$  as suggested.

**Table 1.** Structural parameters of the compounds **1–8** (lengths in Å, angles in °).

	1		2		3		4		5		6		7		8				
	MM2	MNDO	MM2	MNDO	MM2	MNDO	MM2	MNDO	MM2	MNDO	MM2	MNDO	MM2	MNDO	MM2	MNDO	[7]		
C <sub>1</sub> -N <sub>2</sub>	1.38	1.45	1.38	1.44	1.38	1.45	1.37	1.44	1.38	1.45	1.38	1.45	1.38	1.47	1.39	1.38	1.45	1.39	
C <sub>1</sub> -N <sub>6</sub>	1.35	1.39	1.35	1.38	1.34	1.39	1.34	1.38	1.34	1.39	1.34	1.39	1.34	1.90	1.36	1.34	1.38	1.39	
C <sub>1</sub> -S <sub>7</sub>	1.58	1.57	1.62	1.57	1.58	1.56	1.60	1.57	1.60	1.56	1.57	1.58	1.58	1.56	1.66	1.58	1.57	1.66	
N <sub>2</sub> -C <sub>3</sub>	1.34	1.39	1.35	1.41	1.35	1.41	1.34	1.41	1.34	1.41	1.35	1.41	1.35	1.41	1.34	1.35	1.40	1.33	
N <sub>2</sub> -N <sub>8</sub>	1.43	1.43	1.43	1.34	1.42	1.34	1.41	1.34	1.41	1.34	1.41	1.36	1.41	1.35	1.43	1.41	1.37	1.41	
C <sub>3</sub> -C <sub>4</sub>	1.38	1.41	1.39	1.40	1.39	1.39	1.38	1.40	1.38	1.39	1.38	1.39	1.38	1.39	1.37	1.38	1.39	1.38	
C <sub>4</sub> -C <sub>5</sub>	1.42	1.43	1.42	1.46	1.42	1.44	1.42	1.46	1.42	1.44	1.42	1.46	1.42	1.46	1.42	1.42	1.47	1.42	
C <sup>5</sup> -N <sub>6</sub>	1.31	1.33	1.34	1.33	1.33	1.32	1.31	1.33	1.31	1.32	1.34	1.34	1.31	1.33	1.32	1.31	1.32	1.34	
N <sub>8</sub> -C <sub>9</sub>	1.28	1.28	1.28	1.29	1.29	1.27	1.27	1.29	1.27	1.27	1.33	1.29	1.29	1.29	1.29	—	1.30	—	
$\Delta H_f$ (kcal/mol)	238.6	151.6	239.9	129.8	309.9	220.3	338.8	142.8	322.9	192.8	555.4	322.4	—	288.8	288.8	147.5	282.4	175.9	
IP (eV)	8.68	8.57	8.61	8.80	8.45	8.46	8.01	8.80	8.24	8.45	7.90	8.46	—	8.68	8.68	8.78	8.48	8.69	
DM (Debye)	3.68	4.25	3.74	2.30	1.44	5.64	3.19	2.30	2.91	4.19	4.20	4.30	—	4.23	4.23	3.50	2.22	3.39	
C <sub>1</sub> -N <sub>2</sub> -C <sub>3</sub>	122	120	120	117.5	119	119.5	120	117.5	119	118.6	116	113.8	122.3	121	122.3	121	119.5	119	121.8
C <sub>1</sub> -N <sub>6</sub> -C <sub>5</sub>	121	124.1	121	124.2	122	124.8	121	124.2	121	123.1	121	119.9	122.2	119	122.2	119	123.4	120	123.1
C <sub>3</sub> -N <sub>2</sub> -N <sub>8</sub>	125	127.8	119	108.9	115	125.4	123	108.9	119	115.9	127	138.7	117.6	118	118.7	118	115.9	121	118.7
N <sub>2</sub> -C <sub>1</sub> -S <sub>7</sub>	123	124.5	122	126.6	124	124.9	120	126.6	121	124.2	121	124.7	120.9	121	120.9	121	122.2	123	122.6
S <sub>7</sub> -N <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub>	164	156.9	165	146.8	161	156.9	163	146.8	165	155.7	159	136.6	164.5	167	164.5	167	159.1	169	158.3

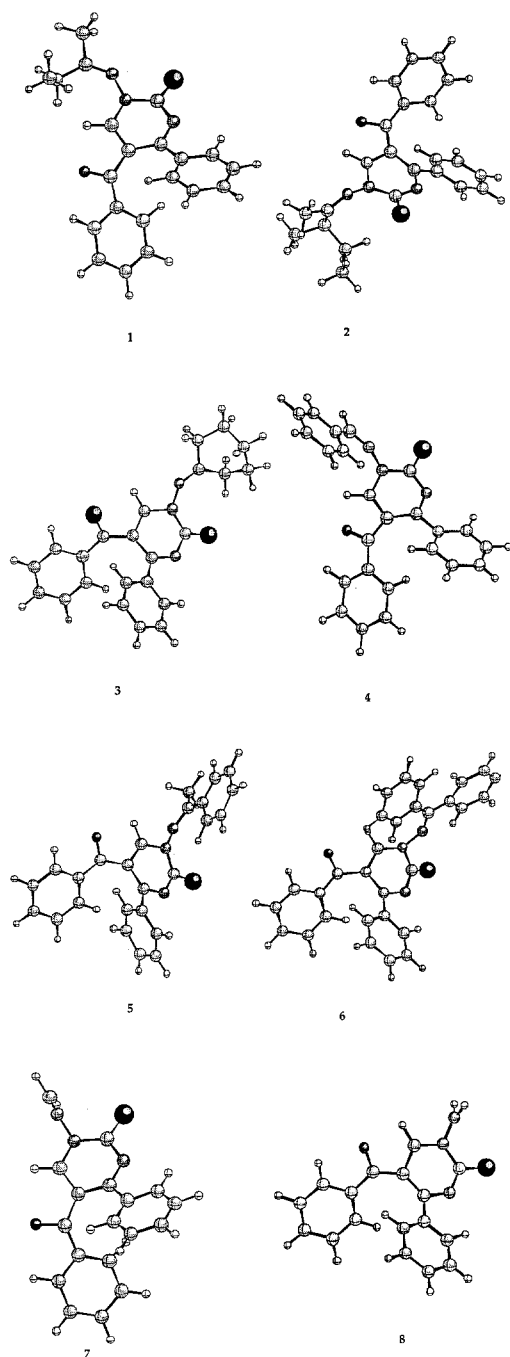


Fig. 1. Spatial structures of compounds 1–8

The analysis of the electron density distribution at the bonds (see *Wiberg's* indices in Table 3) shows that in the pyrimidine ring,  $\pi$ -bonds are delocalized into a unique  $\pi$ -electron system overlapping with the neighbouring  $\pi$ -electron substituents  $R^1$  and  $R^2$ . Replacement of  $R^1$  and/or  $R^2$  influences the electronic density distribution at the atoms  $N_2$ ,  $N_8$ , and  $C_9$  and the bonds formed by them. For example, the presence of two  $\pi$ -acceptors at  $C_9$  (compound **6**) causes  $\alpha$  delocalization and

**Table 2.** Effective atomic charges ( $Q_i$ ) calculated (electron charge units)

	Method	C <sub>1</sub>	N <sub>2</sub>	C <sub>3</sub>	C <sub>4</sub>	C <sub>5</sub>	N <sub>6</sub>	S <sub>7</sub>	N <sub>8</sub>	C <sub>9</sub>
<b>1</b>	CNDO	0.31	-0.13	0.16	-0.11	0.21	-0.29	-0.48	-0.11	0.02
	MNDO	0.14	-0.22	0.22	-0.31	0.25	-0.31	-0.04	-0.09	0.05
<b>2</b>	CNDO	0.30	-0.14	0.16	-0.11	0.21	-0.29	-0.50	-0.10	0.12
	MNDO	0.12	-0.24	0.23	-0.30	0.25	-0.31	-0.07	-0.12	0.09
<b>3</b>	CNDO	0.31	-0.25	0.19	-0.12	0.16	-0.31	-0.55	-0.07	0.09
	MNDO	0.12	-0.19	0.27	-0.30	0.26	-0.31	-0.09	-0.17	0.10
<b>4</b>	CNDO	0.37	-0.19	0.21	-0.13	0.20	-0.30	-0.56	-0.05	0.09
	MNDO	0.13	-0.18	0.21	-0.29	0.25	-0.30	-0.03	-0.20	0.16
<b>5</b>	CNDO	0.31	-0.18	0.18	-0.11	0.20	-0.30	-0.52	-0.10	0.12
	MNDO	0.11	-0.21	0.22	-0.29	0.23	-0.31	-0.08	-0.18	0.11
<b>6</b>	CNDO	0.35	-0.16	0.20	-0.12	0.22	-0.31	-0.55	-0.11	0.14
	MNDO	0.11	-0.23	0.22	-0.28	0.21	-0.30	-0.02	-0.13	0.10
<b>7</b>	CNDO	0.35	-0.17	0.19	-0.12	0.22	-0.30	-0.53	-0.01	0.02
	MNDO	0.13	-0.31	0.24	-0.30	0.34	-0.31	-0.10	-0.15	0.11
<b>8</b>	CNDO	0.34	-0.17	0.19	-0.11	0.22	-0.30	-0.53	-0.19	-
	MNDO	0.12	-0.32	0.26	-0.15	0.34	-0.32	-0.08	-0.42	-

weakening of bond N<sub>8</sub>-C<sub>9</sub> ( $W_{ij} = 1.67$ ). The absence of conjugation (compound **7**) results in a bond order close to two ( $W_{ij} = 1.99$ ). Aliphatic substituents yield a  $W_{ij}$  value close to 1.85. Mixed  $\sigma$ - and  $\pi$ -substituents decrease  $W_{ij}$  because of the non-symmetric electron distribution at this bond. The bond between C<sub>1</sub> and S<sub>7</sub> is substantially polarized and resembles nearly a one-and-a-half-bond as follows from  $W_{ij} = 1.37$  found by CNDO calculations. From MNDO calculations, this bond is more covalent ( $W_{ij} = 1.74$ ). A comparison of all  $W_{ij}$  values obtained by the different methods shows that the CNDO method results in greater  $\pi$ -delocalization.

As a result of quantum chemical calculations, values of the energy levels and LCAO coefficients are obtained. In Fig. 2, some of the MO levels are shown for "the active zone" (a few of the last occupied and of the first free molecular orbitals) of compounds **1–8**.

From Fig. 2 we can see that the energy levels change smoothly and keep their nature. Some differences in the values of the MO energies are observed for  $\sigma$ - and  $\pi$ -substituents. For example, the values of the energy levels for the HOMO (the highest occupied MO) vary for the  $\sigma$ - and  $\pi$ -substituents in the interval of 8.45–8.65 eV (compounds **1, 2, 3, 7, 8**) and 7.89–8.24 eV (compounds **4–6**). The reverse dependence concerning the energy levels for  $\sigma$ - and  $\pi$ -substituents is observed for the LUMO (lowest occupied MO). The structures of the HOMOs and LUMOs are given in Table 4. The LCAO coefficient analysis has shown that the nature of these MOs is determined by the  $\pi$ -orbitals of the atoms belonging to the pyrimidine ring. They are mainly 2p<sub>z</sub>-orbitals (N<sub>2</sub>, C<sub>4</sub>, N<sub>6</sub>, and S<sub>7</sub> for the HOMO and C<sub>1</sub>, C<sub>3</sub>, N<sub>2</sub>, N<sub>6</sub> etc. for the LUMO). The nearest orbital to the HOMO belongs to a free electron pair of sulfur.

**Table 3.** Calculated Wiberg's indices ( $W_{ij}$ )

	1		2		3		4		5		6		7		8	
	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO	CNDO	MNDO
C <sub>1</sub> -N <sub>2</sub>	1.15	0.92	1.16	0.92	1.22	0.98	1.14	0.92	1.17	0.95	1.15	0.93	1.13	0.92	1.14	1.00
C <sub>1</sub> -N <sub>6</sub>	1.28	1.11	1.29	1.14	1.28	1.13	1.25	1.10	1.29	1.12	1.25	1.09	1.26	1.14	1.26	1.14
C <sub>1</sub> -S <sub>7</sub>	1.34	1.69	1.30	1.63	1.29	1.62	1.35	1.70	1.31	1.64	1.35	1.74	1.37	1.64	1.37	1.66
N <sub>2</sub> -C <sub>3</sub>	1.31	1.15	1.30	1.12	1.28	1.11	1.27	1.12	1.30	1.12	1.27	1.06	1.27	1.15	1.27	1.17
N <sub>2</sub> -N <sub>8</sub>	0.98	1.02	0.98	1.01	0.99	1.02	0.99	1.02	0.99	1.00	1.01	1.01	1.00	0.94	1.00	0.98
C <sub>3</sub> -C <sub>4</sub>	1.49	1.55	1.50	1.56	1.52	1.59	1.47	1.57	1.48	1.60	1.47	1.62	1.50	1.58	1.50	1.51
C <sub>4</sub> -C <sub>5</sub>	1.20	1.06	1.20	1.05	1.20	1.05	1.20	1.06	1.21	1.09	1.19	1.04	1.19	1.06	1.19	1.08
C <sub>5</sub> -N <sub>6</sub>	1.48	1.64	1.48	1.63	1.48	1.63	1.46	1.67	1.47	1.64	1.46	1.67	1.47	1.63	1.47	1.59
N <sub>8</sub> -C <sub>9</sub>	1.85	1.89	1.85	1.84	1.86	1.84	1.83	1.81	1.76	1.75	1.67	1.72	1.99	1.92	-	-

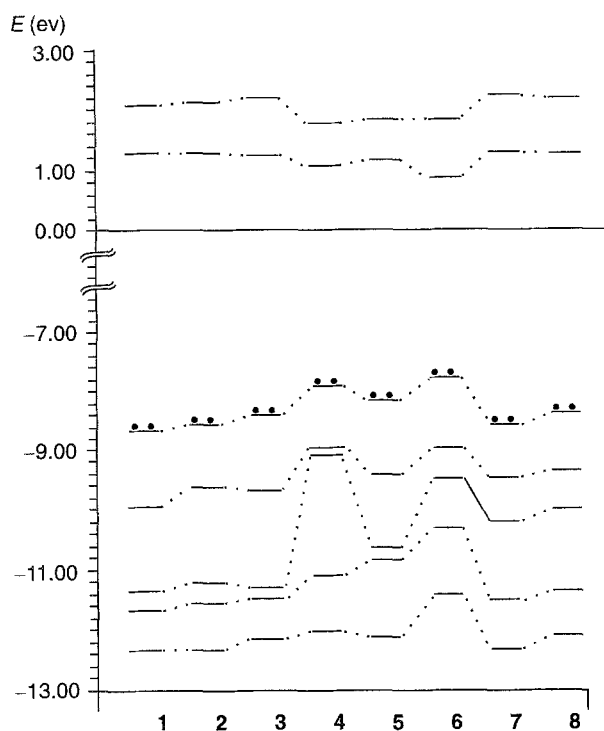


Fig. 2. Energy levels of "active zero"

Table 4. Main Orbital Components and HOMO-LUMO energies of compounds 1-8

$\Psi$	Main Orbital Components	$E$ (eV)	
1	HOMO	$0.23p_zC_4 - 0.23p_zN_6 - 0.43p_xS_7 - 0.24p_yS_7 + 0.60p_zS_7$	-8.68
	LUMO	$-0.21p_yC_1 - 0.28p_xC_5 + 0.29p_zC_5 - 0.22p_xC_{10} + 0.20p_zO_{16} + 0.25p_xC_{22}$	1.30
2	HOMO	$0.20p_xN_2 - 0.27p_zN_2 - 0.51p_xS_7 + 0.25p_yS_7 + 0.55p_zS_7$	-8.61
	LUMO	$-0.33p_xC_5 + 0.24p_zC_5 - 0.24p_xC_{10} - 0.28p_xC_{22}$	1.29
3	HOMO	$-0.32p_yN_2 - 0.21p_zN_2 - 0.24p_zC_4 + 0.56p_yS_7 + 0.53p_zS_7$	-8.45
	LUMO	$-0.20p_yN_2 - 0.27p_yC_5 - 0.30p_zC_5 + 0.21p_zN_6 - 0.22p_yC_{18}$	1.20
4	HOMO	$0.33p_zN_2 - 0.26p_zC_4 - 0.64p_zS_7$	-8.01
	LUMO	$-0.27p_zC_5 + 0.21p_zN_6 - 0.23p_zN_8$	1.03
5	HOMO	$0.33p_zN_2 - 0.28p_zC_4 + 0.26p_zN_6 - 0.69p_zS_7$	-8.24
	LUMO	$-0.21p_zC_1 + 0.20p_zN_2 + 0.37p_zC_5 - 0.27p_zN_6 + 0.20p_zS_7$	1.11
6	HOMO	$-0.36p_yN_2 + 0.27p_zC_4 - 0.21p_zN_6 - 0.31p_xS_7 + 0.64p_zS_7 - 0.21p_yO_{16}$	-7.90
	LUMO	$0.21p_zC_5 + 0.35p_zN_8 - 0.28p_zC_9 - 0.21p_xN_8$	0.78
7	HOMO	$0.33p_zN_2 - 0.28p_zC_4 + 0.26p_zN_6 + 0.33p_xS_7 - 0.69p_zS_7$	-8.68
	LUMO	$0.20p_zN_2 + 0.37p_zC_5 - 0.27p_zN_6 + 0.26p_zC_{19} - 0.21p_zC_{12}(R2)$	1.15
8	HOMO	$0.33p_zN_2 - 0.27p_zC_4 + 0.25p_zN_6 - 0.67p_zS_7 + 0.35p_xS_7$	-8.48
	LUMO	$0.36p_zC_5 - 0.26p_zN_6 - 0.24p_xC_{20} + 0.25p_zC_{20}$	1.16

Summarizing, we can say that the investigation of the electronic structure of 1,4,5-substituted derivatives of 1*H*-pyrimidin-2-thione sheds light on the peculiarities of the electron density distribution in the system and the character of the density variations depending on the nature of the substituents.

## Experimental

We used standard parameters and programs [8,9] for the MNDO and CNDO calculations. All geometries were optimized at the SCF level employing the *Davidon-Fletcher-Powell* algorithm [10, 11] for minima and gradient norm minimization [12] for transition states. A force constant analysis was performed for all MNDO SCF stationary points.

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