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Crystal Structure and *Ab Initio* Studies on (*p*-Methoxyphenyl)thiosemicarbazide

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(*p*-Methoxyphenyl)thiosemicarbazide [$CH_3OC_6H_4NHNHCSNH_2$] has been prepared and characterized by elemental analysis, IR, electronic absorption spectra and X-ray single crystal diffraction. In the crystal lattice, there exist some intermolecular hydrogen bonds, π-π stacking interactions and C–H$\cdots\pi$ supramolecule interactions, which stabilize the crystal structure. *Ab initio* calculations at HF/6-31G* level of the structure, charges distribution, electronic spectra, natural population analysis and thermodynamic properties at different temperatures have been performed. The calculated results show that the sulfur atom and nitrogen atoms have bigger negative charges, which result in they are the potential sites to react with the metallic ions. The electronic transitions associated with the electronic absorption spectra are mainly derived from the contribution of bands $\pi \rightarrow \pi^*$.

Key words: (*p*-methoxyphenyl)thiosemicarbazide, crystal structure, *ab initio* calculations, electronic absorption spectra, thermodynamic properties

Recently, the discoveries of the antitumor effects of inorganic and particularly of metal complexes and their use to cure cancer diseases have received increasing attention [1]. As a ligand with potential S and N donors, thiosemicarbazide is interesting not only because of the structural chemistry of its multifunction coordination modes, but also because of the formation of metal complexes with biological activities, including the antitumor effects, which have been well documented [2–3]. On the basis of these observations, we began to synthesize and characterize polyfunctional organic molecules, belonging to the class of thiosemicarbazide derivatives, able to behave as favorable ligands towards metal centers and investigate their metal complexes. (*p*-Methoxyphenyl)thiosemicarbazide, the title compound, is one of the typical thiosemicarbazide derivatives. Although the synthesis method of it had been reported before [4], the studies of its properties have not been communicated and no structure data are available. In order to get more information of the title compound, we synthesized it and determined its crystal structure. In addition, using classical *ab initio* methods based on self-consistent field molecular orbital Hartree-Fock theory with the 6-31G* basis set (HF/6-31G*), we investigate the optimized structure,

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atomic charges distribution, electronic transition, natural population analysis and the thermodynamic properties of the title compound. Herein, we report the experimental and quantum-chemical results.

EXPERIMENTAL AND COMPUTATIONAL METHODS

Physical techniques. The C, H and N elemental analysis was performed on a Yanaco CHN FOER MT-3 element analyzer. IR spectra (FTIR) were recorded on a Perkin-Elmer 2000 FTIR spectrometer using KBr pellet. Ultraviolet (UV) spectra were recorded in a GBC UV/VIS spectrophotometer.

Experiment. The title compound was synthesized according to the literature procedures [4]. The products were collected and the orange crystals were obtained by recrystallization from EtOH; m.p. 210–211°C; anal. calcd. for $C_8H_{11}N_3OS$: C 48.70, H 5.62, N 21.30%; found: C 48.59, H 5.40, N 21.11. IR (cm^{-1}): ν(N–H) 3377, 3276, 1602; $\nu(C_{Ar}–H)$ 3187,1155, 810; $\nu(C_{methyl}–H)$ 3090, 1458; $\nu(C_{Ar}–C_{Ar})$ 1647, 1602, 1550; ν(C–S) 1240; ν(C–N) 1050; ν(N–N) 1137; $\nu(C_{methyl}–O)$ 1027. Solid electronic absorption spectra (nm, log ε): λ = 206 (2.75), λ = 287 (2.49), λ_{max} = 373~500 (2.35~1.98).

X-ray structure determination. The selected crystal of $[CH_3OC_6H_4NHNHCSNH_2]$ was mounted on a Rigaku Raxis-IV diffractometer. Reflection data were measured at 20°C using graphite monochromated Mo-K_α (λ = 0.71073 Å) radiation and a ω-2θ scan mode. A total of 1903 independent reflections were collected in the range of $1.85 < \theta < 27.47°$, of which 1390 reflections with $I > 2\sigma(I)$ were considered to be observed and used in the succeeding refinement. The correction for *Lp* factors and empirical absorption were applied to the data. The structure was solved by direct methods and refined by full-matrix least-squares method on F^2_{obs} using the SHELXTL software package [5]. All non-H atoms were anisotropically refined. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent C atoms. The final least-square cycle gave R = 0.0647, R_w = 0.1433; the weighting scheme, $w = 1/[\sigma^2(F_o^2) + (0.0884P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. Atomic scattering factors and anomalous dispersion corrections were taken from International Table for X-Ray Crystallography [6]. A summary of the key crystallographic information is given in Table 1.

Table 1. Crystal data and structure refinement for the title compound.

Formula	$C_8H_{11}N_3OS$
Formula weight	197.26
Temperature (K)	293(2)
Wavelength (Å)	0.71073
Crystal system, space group	Monoclinic, *C*2/*c*
Unit cell dimensions (Å, °)	a = 25.071(5), b = 5.9292(12), c = 14.938(3) β = 118.40(3)
Volume ($Å^3$)	2515.19(8)
Z, Calculated density (Mg/m^3)	8, 1.342
Absorption coefficient (mm^{-1})	0.296
F (000)	832
θ range for data collection (°)	1.85 to 27.47.
Limiting indices	$-32 \le h \le 5$, $-7 \le k \le 7$, $-16 \le l \le 19$
Reflections collected/ unique	3020 / 1903 [R_{int} = 0.0658]
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.058
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0647, $wR2$ = 0.1433
R indices (all data)	R_1 = 0.1050, $wR2$ = 0.1636
Extinction coefficient	0.017(2)
Largest diff. peak and hole ($eÅ^{-3}$)	0.326 and –0.376

Computational methods. Initial molecular geometry was optimized using MM+ molecular modeling and semi-empirical AM1 methods [7] (HYPERCHEM 6.0, Hypercube, Ont., Canada). In the next step, the Hartree-Fock calculations at the 6-31G* basis set by the Berny method [8] were performed with the Gaussian 98 software package [9]. Vibrational frequencies were calculated to ascertain the structure was characterized to be the stable structure (no imaginary frequencies). Electronic absorption spectra were predicted using the CIS (configuration interaction single-excitation) method [10]. The thermodynamic properties of the title compound at different temperatures have been calculated on the basis of vibrational analyses.

All calculations were performed on a Pentium IV computer using the default convergence criteria.

RESULTS AND DISCUSSION

Crystal structure. A displacement ellipsoid plot, with the numbering scheme, is given in Fig. 1 and Fig. 2 presents a perspective view of the crystal packing in the unit cell. Atomic parameters and equivalent isotropic thermal parameters of non-H atoms for the title compound are given in Table 2. Selected bond distances and angles calculated from the X-ray data are presented in Table 3, where the corresponding HF calculated values are also shown.

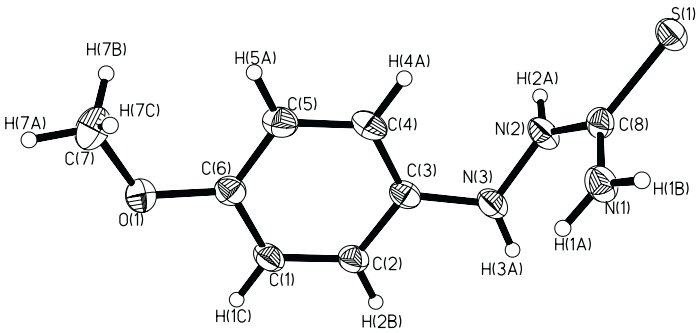


Figure 1. Molecular structure with the atomic numbering scheme for the title compound.

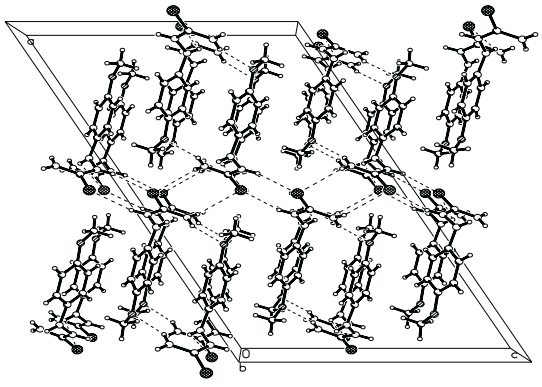


Figure 2. A view of the crystal packing down the *a* axis for the title compound.

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$).

Atom	*x*	*y*	*z*	U_{eq}	Atom	*x*	*y*	*z*	U_{eq}
S(1)	49(1)	7833(1)	–927(1)	43(1)	C(3)	1625(2)	2136(5)	306(3)	37(1)
O(1)	3480(1)	1528(4)	2290(2)	53(1)	C(4)	1921(2)	3851(5)	985(3)	46(1)
N(1)	756(1)	5989(5)	–1599(2)	47(1)	C(5)	2541(2)	3713(5)	1665(3)	46(1)
N(2)	660(1)	4018(4)	–384(2)	45(1)	C(6)	2865(2)	1830(5)	1661(3)	39(1)
N(3)	1010(1)	2279(4)	–462(2)	45(1)	C(7)	3820(2)	3368(7)	2917(4)	76(1)
C(1)	2565(2)	80(5)	1000(3)	43(1)	C(8)	516(1)	5808(5)	–979(3)	36(1)
C(2)	1955(2)	221(5)	328(3)	41(1)					

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3. Selected bond lengths, angles and torsion angles by X-ray and theoretical calculations.

Bond lengths (Å)	Exp.	Calc.	Bond angles (°)	Exp.	Calc.
S(1)–C(8)	1.704(3)	1.6802	C(6)–O(1)–C(7)	118.1(3)	119.52
O(1)–C(6)	1.384(4)	1.351	C(8)–N(2)–N(3)	121.3(3)	125.13
O(1)–C(7)	1.427(4)	1.3987	N(2)–N(3)–C(3)	117.4(3)	118.78
N(1)–C(8)	1.329(4)	1.3371	C(2)–C(1)–C(6)	120.9(3)	120.58
N(2)–C(8)	1.320(4)	1.3476	C(1)–C(2)–C(3)	120.5(3)	120.67
N(2)–N(3)	1.395(3)	1.374	C(4)–C(3)–N(3)	123.3(3)	122.44
N(3)–C(3)	1.422(4)	1.4152	C(2)–C(3)–N(3)	118.1(3)	118.75
C(1)–C(2)	1.376(5)	1.376	C(1)–C(6)–C(5)	119.2(3)	118.91
C(3)–C(4)	1.377(5)	1.3806	C(1)–C(6)–O(1)	116.1(3)	115.99
C(5)–C(6)	1.383(4)	1.3824	C(5)–C(6)–O(1)	124.7(3)	125.10
			N(2)–C(8)–N(1)	117.7(3)	116.52
			N(2)–C(8)–S(1)	120.6(3)	120.64
			N(1)–C(8)–S(1)	121.6(3)	122.83
Torsion angles (°)					
C(8)–N(2)–N(3)–C(3)	105.06	80.86	C(2)–C(3)–N(3)–N(2)	170.42	158.96
C(2)–C(1)–C(6)–O(1)	–178.75	–179.76	C(4)–C(3)–N(3)–N(2)	–14.00	23.40
C(4)–C(5)–C(6)–O(1)	179.05	179.86	N(3)–C(3)–C(4)–C(5)	–174.09	177.66
C(1)–C(6)–O(1)–C(7)	174.17	178.89	S(1)–C(8)–N(2)–N(3)	175.86	168.80
C(5)–C(6)–O(1)–C(7)	–6.60	–1.34	N(1)–C(8)–N(2)–N(3)	–5.46	–10.45

The crystal structure consists of eight discrete (*p*-methoxyphenyl)thiosemicarbazide molecules. Bond lengths and angles in the phenyl ring are generally normal. The bond lengths of C(7)–O(1) and O(1)–C(6) [1.427(4) and 1.384(4) Å]

agree with the corresponding distances in the compounds of *p*-methoxybenzoic [1.438 and 1.362 Å] [11] and 2-(4′-methoxyphenyl)-2,4-dithia-1,3,2-diazaphospholidine-5,1′-spircyclohexane [1.426(5) and 1.363(5) Å] [12], respectively. All the bonds and angles observed in the part of thiosemicarbazide are also normal and consistent with those of the related structures reported earlier [1,13]. The C(3)–N(3) bond length 1.422(4) Å compared with the normal $C(_{sp}{}^2)$–N (1.426 Å) bond shows the delocalization between the N(3) with phenyl ring group. The phenyl-ring and conjunctive N(3), O(1) atoms define a plane: $-15.2782\,X - 2.5223\,Y + 13.1215\,Z = -2.6488$, with the largest deviation –0.075 Å. The non-H atoms involving the part of thiosemicarbazide defined another plane: $13.0059\,X + 2.7535\,Y + 5.7462\,Z = 1.7052$, the largest atom deviation from the least squares plane is 0.039 Å for N(3) atom. The dihedral angle between above two planes is 88.08°, indicating they are almost perpendicular.

In the crystal lattice, there exist some intermolecular hydrogen bonds, π-π stacking interactions and C–H$\cdots\pi$ supramolecule interactions [14–16]. There are three types intermolecular hydrogen bonds. The donor and acceptor distances are 2.9725 Å for N(1)–H(1A)···O(1) (symmetry code: 1/2-*x*,1/2-*y*,-*z*), 3.4389 Å for N(1)–H(1B)···S(1) (symmetry code: -*x*, *y*,-1/2-*z*) and 3.3910 Å for N(2)– H(2A)···S(1) (symmetry code: -*x*,1-*y*,-*z*), respectively. The π-π stacking interactions exist in the phenyl ring (*X, Y, Z*)-phenyl ring (1/2-*X*,1/2-*Y*,-*Z*), with the center-to-center distance 3.791 Å and the shortest interplanar distance 3.641 Å. There is one type of C–H$\cdots\pi$ supramolecule interactions between C–H and aromatic ring in the crystal lattice. The distance between C(5)–H(5A) and phenyl ring is 3.062 Å. In the solid state, all above intermolecular interactions in the title compound stabilized the crystal structure.

Optimized structure. The calculated skeletal bond lengths and angles show an agreement with the experimental X-ray values (see Table 3). The largest differences of the bond lengths, bond angles and torsion angles mainly occur in the thiosemicarbazide group [*i.e*. N(2)–C(8), C(8)–N(2)–N(3) and C(8)–N(2)–N(3)–C(3)], which can be easily understood taking into account the intermolecular hydrogen-bond interactions present in the crystal. In the crystal state, the close packing of all the molecules and the existence of the crystal fields make the title compound have to have some twists so as to adapt to the highly selective and directional nature of intermolecular hydrogen bonds, thus leading to longer C(7)–O(1), C(6)–O(1) and shorter N(1)–C(8), N(2)–C(8) distances in the crystal than in the isolated molecule, and the difference of torsion angles between the calculated values and the X-ray data (see Table 3).

Atomic charges. The non-H atomic charges of the title compound calculated at HF/6-31G* level are presented in Table 4. Although the existence of the methoxyphenyl group, sulfur and nitrogen atoms in the part of thiosemicarbazide still have bigger negative atomic charges, suggesting that they are potential sites to react with metallic ions. This phenomenon not only consists with many experimental facts reported early, but also supports the original idea of our synthesis.

Table 4. Atomic charges (*e*) of the title compound at HF/6-31G* level.

atom	the title compound	atom	the title compound
S(1)	–0.3620	C(1)	–0.2326
N(1)	–0.8681	C(2)	–0.2446
N(2)	–0.5517	C(3)	0.2460
N(3)	–0.5745	C(4)	–0.2262
C(8)	0.4601	C(5)	–0.2705
O(1)	–0.6550	C(6)	0.4193
C(7)	–0.1876		

Electronic absorption spectra. Electronic absorption spectra calculation shows that the maximum absorption wavenumber corresponding to the electronic transitions from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) is at 211.23 nm, with oscillator strength f = 0.0941. This wavenumber is smaller than the experimental value. Natural population analyses indicate that the frontier molecular orbitals are mainly composed of *p* atomic orbitals, so above electronic transitions are mainly derived from the contribution of bands $\pi \rightarrow \pi^*$. Fig. 3 shows the surfaces the HOMO and LUMO. As observed from Fig. 3, the HOMO of the title compound is delocalized among all the atoms and the LUMO is principally delocalized among the atoms of methoxy-phenyl group.

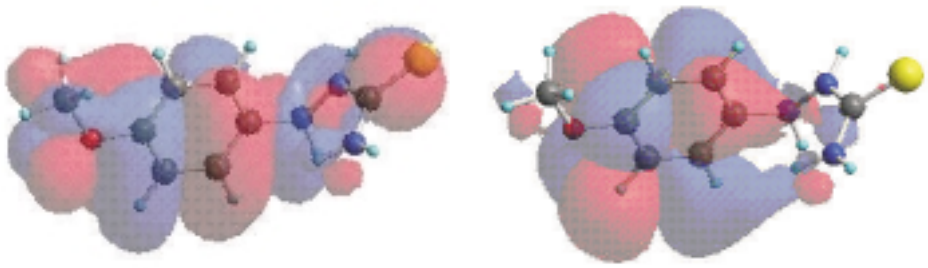
Thermodynamic properties. On the basis of vibrational analysis and statistical thermodynamics, the standard thermodynamic functions – heat capacity ($C^0_{p,m}$), entropy (S^0_m) and enthalpy (H^0_m) – were obtained and listed in Table 5. The scale factor for frequencies is also 0.89, which is typical scaled factor for HF/6-31G* method.

As observed from Table 5, the standard heat capacities, entropies and enthalpies increase at any temperature from 200.00 K to 800.00 K, due to that the intensities of molecular vibration increase while the temperature increases. The correlation equations between these thermodynamic properties and temperature *T* are as follows:

$C^0_{p,m} = 8.90971 + 0.81062\ T - 3.87577\times10^{-4}\ T^2$,

$S^0_m = 167.68765 + 1.48406\ T$, $H^0_m = -54.42592 + 0.30864\ T$

These equations will be helpful for the further studies of the title compound.



HOMO LUMO

Figure 3. HOMO and LUMO of the title compound.

Table 5. Thermodynamic properties of the title compound at different temperatures.

T(K)	$C^0_{p,m}$ (J/mol·K)	S^0_m (J/mol·K)	H^0_m (kJ/mol)
200.0	155.51	413.76	18.83
298.1	215.79	487.20	37.08
400.0	272.04	558.69	62.00
500.0	318.02	624.50	91.58
600.0	355.18	685.89	125.31
700.0	385.31	742.98	162.38
800.0	410.13	796.10	202.19

Supplementary materials. CCDC-236305 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1222-336033; email: deposit@ccdc.cam.ac.uk].

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