Tautomeric properties, conformations and structure of 2-hydroxyacetophenone methanesulfonylhydrazone

S. Alyar a, Ü. Özdemir Özmen a, N. Karacan a,*, O.Ş. Şentürk b, K.A. Udachin c

a Department of Chemistry, Faculty of Science and Art, Gazi University, Teknikokullar, 06500 Ankara, Turkey
b Department of Chemistry, Faculty of Science and Art, Technical University of Istanbul, TR-34469 Maslak, Istanbul, Turkey
 c Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ont., Canada K1A 0R6

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Abstract

The compound, 2-hydroxyacetophenone methanesulfonylhydrazone (apmsh) has been synthesized and its crystal structure has been investigated by X-ray analysis. The compound crystallizes in the monoclinic space group $P2_1/c$ and the following unit cell parameters: $a = 20.9496(15)$ Å, $b = 4.9849(4)$ Å, $c = 10.2300(8)$ Å; $\alpha = 90^\circ$, $\beta = 98.2750(10)^\circ$, $\gamma = 90^\circ$; $V = 1057.21(14)$ Å$^3$ and $Z = 1$. The molecular geometry of the apmsh in the ground state has been calculated using the restricted Hartree–Fock with HF/6-31G** and density functional method with B3LYP/6-31G** basis set. The optimized bond lengths and bond angles obtained by using B3LYP/6-31G** are in better agreement with the experimental values than those by using RHF/6-31G**. The conformers located at minima by PM3 semi-empirical calculation were re-optimized by using B3LYP/6-31G** method. Quantum-chemical calculations indicate that enol-imine tautomeric form is favored and the most stable conformer in gas phase is approximately 6 kcal/mol stable than next conformer.

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1. Introduction

N-substituted sulfonamides are well known for their diuretic, antidiabetic, antibacterial and antifungal, anticancer activities are widely used in the therapy of patients [1,2]. These important bioactive properties are strongly affected by the special features of $-\mathrm{CH}_2-\mathrm{SO}_2-\mathrm{NR}$-linker and intramolecular motion. Thus, the studies of energetic and spatial properties on N-substituted sulfonamides are of great importance to improve our understanding of their biological activities and enhance abilities to predict new drugs [3–6].

Sulfonyl hydrazones, derivative of sulfonamide, were also found to exhibit medicinal applications. Benzaldehyde arylsulfonylhydrazones possess antineoplastic activity against human stomach cancer SGC 7901 [7]. 4-Substituted benzenesulfonylhydrazone has been studied for antibacterial activity [8]. N-Arylsulfonyl hydrazones have been identified as novel inhibitors of IMP-1 a metallo-\beta-lactamase enzyme [9].

In our previous studies, experimental and theoretical studies of methanesulfonic acid hydrazide were reported [10]. Aliphatic sulfonamides and methanesulfonyl hydrazone derivatives were synthesized and used for antimicrobial and cytotoxic activity screening [10,11], as well as their transition metal complexes [12–16]. As part of our ongoing studies, the crystal structure of 2-hydroxyacetophenone methanesulfonylhydrazone was determined by X-ray analysis. Conformational analysis and tautomerism were also studied by quantum chemical methods.

2. Experimental

2.1. Preparation of 2-hydroxyacetophenone methanesulfonylhydrazone

Synthesis of 2-hydroxyacetophenone methanesulfonylhydrazone (apmsh): Solution of 1.10 g (10 mmol)
methanesulfonylhydrazine in 5 ml of water was mixed with hot solution of 2-hydroxyacetophenone in 10 ml of ethanol and the reaction mixture was acidified with 2–3 drops of acetic acid and stirred for 1 h. Upon cooling, the obtained crystalline precipitates were filtered, washed with ethanol–ether, recrystallized from benzene–ethanol and dried in vacuo over P2O5. Yield: 55–65%, mp 160–161 °C. (Found: C, 47.13; H, 5.13; N, 12.17; S, 13.53 Calcd for C9H13N2S O3(%): C, 47.36; H, 5.30; N, 12.27; S, 14.05).

2.2. Crystal structure determination

A single crystal of apmsh was mounted on a glass fibre. Diffraction measurements were made on a Siemens SMART CCD automatic diffractometer using graphite-monochromated Mo–Kα radiation. The unit cell was determined from randomly selected reflections obtained using the SMART [V 4.043] CCD automatic search, center index and least-squares routines. Crystal data and collection parameters are listed in Table 1. Integration was carried out using the program SAINT [17] and an absorption correction was performed using SADABS [18]. Structure solution was carried out using the SHELXTL [19] programs. The space group P 21/c was chosen based upon systematic absences. The initial solution was obtained by direct methods and refined by successive least-squares cycles.

2.3. Method of calculation

Initial estimate of the geometry of the structure was obtained by crystal structure data, then 1D potential energy scans were carried out by PM3 semiempirical method. All the stationary points on PES diagrams were optimized with no symmetry constraint at the RHF/6-31G** and B3LYP/6-31G** levels and verified to be either minima or transition states by calculating harmonic vibrational frequencies at the same levels. Calculations were carried out with the package of Gaussian 03 [20] on Intel Pentium IV computer. Surface area (approx) and molecular volume of apmsh were calculated by using the HyperChem [21] (release 7.5) package software [21].
3. Results and discussion

3.1. Crystal structure analysis

Molecular structure with the atom-numbering scheme of apmsh was given in Fig. 1. Crystal data and structure refinement parameters of apmsh were given in Table 1. Atomic coordinates and equivalent isotropic displacement parameters were listed in Table 2. Anisotropic displacement parameters were tabulated in Table 3.

The phenyl ring of the salicylidene part of the molecule is, of course, planar. The average phenyl C—C bond length of 1.393 Å is normal [22]. The C1—C7 [1.479 (e.s.d.) Å] bond shows the influence of conjugation between the C1—C6 phenyl ring and the C7—N1 [1.295 (e.s.d.) Å] dou-

![Fig. 2. The energy profile for the rotation about τ₁ C1—C7—N1—N2 and τ₂ C7—N1—N2—S.](image)

![Fig. 3. The energy profile for the rotation about τ₃ N1—N2—S—C9 and τ₄ H—N2—S—O3.](image)
ble bond. The torsion angle $C_2-C_1-C_7-N_1$ is $-3.60$ (e.s.d.) Å. The observed nitrogen–hydrogen bond length in sulfonyl hydrazone group $N_2-H_2$ is $0.845$ (e.s.d.) Å which is shorter than that in ordinary amines ($\sim 1.01$ Å) [23]. This fact suggests that there is no intramolecular hydrogen bonding between the amino hydrogen and sulfonyl oxygen. (Furthermore, the acidity of the hydrazone hydrogen decreases so that $apmsh$ coordinates to the metals through imino N).

The crystal structure contains intramolecular hydrogen bonds which play an important role in stabilization. The conformation of the sulfonylhydrazone fragment orients the imino N atom in such a way that an intramolecular hydrogen bond is formed from N1 to O1—H1 hydroxyl group of the salicylidene part of the molecule, resulting in the formation of a planar six membered ring; (C1/C2/O1/H1/N1/C7). The presence of an O1—H1---N1 intramolecular hydrogen bond [O1—N1 2.572 (e.s.d.) Å, H1...N1 1.841 (e.s.d.) Å, O1—H1...N1 144 (e.s.d) Å] has been found to be a general feature in the molecular structures of sulfonylhydrazones, thiocarbazides and thiocarbazones [22–25].

![Fig. 4. Optimized (HF/6-31G**) geometries of conformation.](image-url)
3.2. Computational study

To determine the most stable structure, all the possible conformations of apmsh were obtained by potential energy scan. One-dimensional potential energy scans were performed for four torsion angles—$\tau_1$ C1—C7—N1—N2, $\tau_2$ C7—N1—N2—S, $\tau_3$ N1—N2—S—C9 and $\tau_4$ H—N2—S—O3—in the full range of 0°—360°, starting with the eclipsed conformation and increasing of 30° at PM3 method (Figs. 2 and 3). The experimental and optimized geometric parameters by RHF/6-31G** and B3LYP/6-31G** are listed in Table 4. The optimized geometric bond lengths and angles obtained by using RHF/6-31G** are in better agreement with the experimental values than using B3LYP/6-31G**.

As seen in Figs. 2 and 3, the energy profiles of $\tau_1$ shows two local minima at about 30° and 240°, global minima at 120°, local maxima at 60° and global maxima at 180°. Second scan for $\tau_2$ shows local minima at 360°, global minima at 180°, local maxima at 270° and global maxima at 90°. Third scan for $\tau_3$ shows two local minima at about 270° and 360°, global minima at 30°, local maxima at 300° and the global maxima at about 180°. Final scan for $\tau_4$ shows local minima at 240°, the global minima at 30°, local maxima at 300° and the global maxima at 150°.

The structure of optimized geometries of conformations are illustrated in Fig. 4. Total and relative energies of the conformers are listed in Table 5. Salicylaldehyde group exists in synperiplanar conformation in (1) and (3) with C=N—N moiety, due to hydrogen bonding between N1...H1 atoms.

As seen in Figs. 2 and 3, the most stable conformer is (1) in the vacuo, but (3) in the crystal system. The most different angle between (1) and (3) is N1—N2—S—C9 torsion angle. It changes form +84.61° to 54.68° when conformers goes from (1) to (3), which is accompanied by changing surface area and molecular volume. Surface area (approx) and molecular volume of these conformers are 380.73 Å² and 647.42 Å³ in the (1) form but 377.04 Å² and 644.70 Å³ in the (3) form, respectively. The data indicate that decreasing of molecular volume leads to more strong intermolecular interaction or crystal packing effect, which makes conformer (3) more stable in crystal system. Clearly, the effect of intermolecular interaction in the solid phase must be considered, as their effect on the conformation is not negligible.

The geometries and energies of six tautomers were computed. These tautomers were optimized with HF/3-21G** level and their total energies were calculated with HF/3-21G** and HF/6-31G** levels. Possible tautomers of apmsh presented in Fig. 5. Calculated total energies of tautomers were given in Table 6. Among the six tautomeric states, the phenol-imine (a) is the most stable form. The
Table 6

<table>
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<tr>
<th>Tautomer</th>
<th>HF/3-21G** // HF/6-31G**</th>
<th>ΔE (kcal/mol)</th>
<th>HF/3-21G** // HF/6-31G**</th>
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<tbody>
<tr>
<td>a</td>
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<td>1078.694</td>
<td>b</td>
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<tr>
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<td>1078.669</td>
<td>27.61</td>
<td>15.37</td>
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</tbody>
</table>

* a.u = 627.51 kcal/mol.

Keto-amine tautomer (b) is less stable (~2.1 kcal/mol) than the (a) form. The similar results are shown for the same tautomerism in the literature [21,22]. Azo form (c) is less stable than imine and amine forms. Tautomers (d)–(f) are about 20 kcal/mol less stable than (a) form. The far lower stability of these tautomers arises from loss of resonance energy in phenyl ring.

4. Conclusion

Conformational analyses were carried out using ab initio and DFT methods to investigate the experimentally observed conformational preference of apmsn. The RHF/6-31G** level calculations are in good agreement with the observed X-ray diffraction geometry. The result shows that apmsn crystallizes in phenol-imine form, which is also the energetically favored form in gas phase.

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References