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Syntheses, spectroscopic investigation and electronic properties of two sulfonamide derivatives: A combined experimental and quantum chemical approach

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ABSTRACT

Two sulfonamides derivatives, *N*-phenethyl-4-methylbenzenesulfonamide (**1**) and *N*-(4-hydroxyphenethyl)-4-methylbenzenesulfonamide (**2**), were successfully synthesized and fully characterized using ^{1}H NMR, ^{13}C NMR, FT–IR spectroscopies and elemental analysis. The molecular and electronic structures of the compounds were further investigated using density functional theory calculation at B3LYP and B3PW91 functionals using 6–311++G(d,p) basis set to provide structural and spectroscopic information and guide spectral assignments. The experimental and simulated ^{1}H NMR, ^{13}C NMR and FT–IR spectra were compared and the accuracy was discussed. The conformational analysis was performed in order to find the most stable molecular structure of the compounds. Molecular quantities such as ionization potential, electron affinity, electronegativity, electrophilicity index and chemical hardness and softness were calculated and used as an additional molecular characteristic to predict the stability of the molecules. Electronic properties such Mullikan atomic charges, HOMO, LUMO and HOMO–LUMO energy gaps and molecular electrostatic potential maps predict the large intramolecular charge transfer within the molecules and significant substitution effects.

1. Introduction

The relationship between chemical structure of the medicinal agents and their biological activity i.e. structure–activity relationship (SAR) is one of the long standing problems in medicinal and structural chemistry. Based on the assumption that the similar compounds have similar physical and biological properties, the biological effects of a new chemical compound can be predicted without the cost of performing the traditional toxicology studies and/or in vitro/in vivo assays. As a result, many efforts have been made to elucidate this relationship and along with the experimental determination of the bioactivity of the compounds with different structural characters, several computations based techniques such as quantum chemical approaches have been employed to predict the chemical structure and electronic properties [1–8] The sulfonamides have played a leading role in the determination and our current understanding of this relationship. Numerous studies on the bioactivity and the structure activity relationship of sulfonamides have been published [9–17].

Sulfonamides are of great chemical interest as they show distinct physical, chemical and pharmaceutical properties. They are the first antibacterial drugs [18] commonly known as sulfa drugs which were introduced clinically in 1934. Sulfonamides are active against gram-positive and gram-negative bacteria and are used in the treatment of diseases like tonsillitis, urinary tract infections etc. Aromatic sulfonamides were reported to inhibit the growth of tumor cells [19]. The heterocyclic sulfonamide derivatives have been reported to show substantial in vitro and in vivo, anticancer, antitumor, anti-HIV, antimicrobial, antimalarial, anticonvulsant, analgesic and anti-inflammatory activities [18–29]. Because of the wide variety of the biological importance of the sulfonamides, the synthesis of several substituted sulfonamides, the study of their molecular structure and physical, chemical, biochemical and electronic properties has become interesting field in research. The studied compounds are such organic compound that belongs to the sulfonamide family.

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Density functional theory (DFT) [30,31] is a dominating method for the investigation of electronic structures and properties of medium-to large-size molecules. It is among the well-known and versatile methods available in computational chemistry and computational physics to study the electronic structures and microscopic properties of the wide variety of compounds [32–41]. DFT have been used to study the electronic structures and molecular properties of sulfonamide derivatives, including their molecular, electronic (HOMO–LUMO, natural bond orbital (NBO) analysis, dipole moment and electrostatic potential, etc.), and spectroscopic properties (NMR, mass fragmentation, electronic, vibrational, etc.) [42–55]. The study of microscopic properties of energetic materials such as electronic structure and interatomic forces remains to be a challenging task for the theoretical researchers. Theoretical calculations play an important role in investigating the physical and chemical properties of energetic materials at atomic level and to establish the structure-property relationship. Most of these studies involved the comparison of DFT (mainly B3LYP, B3PW91, and PBE1PBE) calculated results with those calculated experimentally. Thus, one of the goals of the presents study is to determine the reliability of these functionals to predict the molecular structure as well as the spectroscopic properties of the studied and other systems relevant to medicinal chemistry.

In our previous study, we published the crystal structure of several sulfonamide derivatives and performed a DFT computational study of the structural, spectroscopic and electronic properties [32,33,56,57]. Thus, in continuation to this contribution, we here describe our results on *N*-phenethyl-4-methylbenzenesulfonamide (**1**) and *N*-(4-hydroxyphenethyl)-4-methylbenzene-sulfonamide (**2**) concerning the synthesis, electronic structure, ^{1}H NMR, ^{13}C NMR, vibrational and charge transfer analysis. The two compounds were previously synthesized [58,59], however, no further studies were performed on molecular and electronic structure and spectroscopic properties. We followed the procedure used in Ref. [59] with some modifications to synthesize the compounds. To the best of our knowledge, no computational study has yet been performed on the compounds presented in this article. We believe that the potential sulfonamide derivatives deserve more detailed and systematic theoretical study of the molecular and electronic structure and spectroscopic and charge transfer properties using the advance computational methods for understanding its chemical and biological properties. The purpose of this study is thus to investigate the molecular and electronic structure, NMR and vibrational spectroscopy (experimentally and theoretically) and electronic properties (reactivity and stability through the calculations of HOMO, LUMO and HOMO–LUMO energy gap, ionization potential, electron affinity, electronegativity, electrophilicity index and chemical hardness and softness) of **1** and **2** and the effect of presence of hydroxyl group on these properties. This study can be regarded as an effort towards understanding and predicting molecular structure and electronic and spectroscopic properties of this class of molecules that are relevant to medicinal chemistry.

The structures of the synthesized compounds were characterized using spectroscopic techniques and were further optimized using DFT functionals at two different theoretical levels. A conformational stability study was performed to find the most stable structures. The proton– and ^{13}C NMR and Infrared (IR) spectra were calculated and compared with those obtained experimentally. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), and HOMO–LUMO energy gaps were computed to predict the charge transfer within the molecules and other related electronic properties. Molecular electrostatic potential (MEP) analysis was performed to predict the reactive sites of the studied molecules.

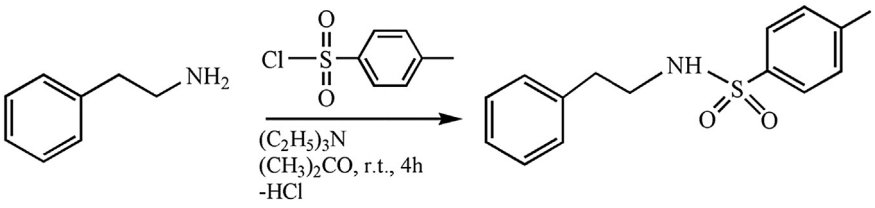
2. Experimental

2.1. Material and measurements

2-Phenethylamine (CAS No.: 64-04-0), 2-(4-Hydroxyphenyl) ethylamine (CAS NO.: 51-67-2) and p-Toluenesulfonyl chloride (CAS No.: 98-59-9) were purchased from Sigma–Aldrich. All other reagents and solvents were obtained from common commercial sources and used without further purification. FT–IR spectra over the range 4000–400 cm^{-1} were obtained with a Thermo Nicolet FT–IR–200 (USA) spectrometer using KBr pellets. Melting points were determined in open capillary tubes on Gallenkamp melting point apparatus. Elemental analysis for N, C and H were performed on Vario Micro Cube, Elementar, Germany. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 300 MHz spectrometer at room temperature. Chemical shifts values are reported in parts per million (ppm) from tetramethylsilane (TMS).

2.2. Synthesis of N-phenethyl-4-methylbenzenesulfonamide (*1*)

2-Phenylethanamine (0.232 g, 1 mmol) was dissolved in anhydrous acetone (10 mL) and triethyamine (10 mL) was added. Subsequently, p-Toluenesulfonyl chloride in the stoichiometric ratio (0.227 g, 1 mmol) was added drop-wise with continuous stirring. The resulting reaction mixture was stirred for 4 h under nitrogen atmosphere at room temperature (Scheme 1). By means of TLC, the consumption of p-Toluenesulfonyl chloride was monitored. When the reaction was completed, the reaction mixture was washed using 3M HCl and further with distilled water. The solvent was evaporated under reduced pressure. The obtained product was further purified by crystallization from methanol solution by slow evaporation. Yield of the reaction was 79% (0.54 g); m.p.165–172 °C. ^{1}H NMR (Chloroform, 300 MHz) δ: 2.42 (s, 3H, CH_3), 2.75 (t, 2H, CH_2), 3.21 (t, 2H, CH_2), 4.46 (br. s, 1H, NH), 7.07 (d, 2H, Ar–H), 7.26 (m, 5H, Ar–H), 7.70 (d, 2H, Ar–H). FT–IR (KBr, cm^{-1}): 3262.6 (N–H str.), 3020.0 (C–$H_{aromatic}$ asymm. str.), 2910.0 (C–$H_{(CH2/CH3)}$ asymm. str.), 2810.0 (C–$H_{(CH2/CH3)}$ symm. str.), 1598.1 (C–C=C symm. str.), 1380.0 (N–H out-of-plane bending), 1155.6 (S=O asymm. str.), 1095.6 (S–C str.). Elemental analysis: calculated (%) for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; O, 11.62; S, 11.64; found (%): C, 64.57; H, 6.04; N, 4.96; O, 10.84; S, 11.12.



Scheme 1. Synthetic pathway to *N*-phenethyl-4-methylbenzenesulfonamide.