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Synthesis, X-ray crystallographic and DFT studies of tow new*N*-acylsulfonamides

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Abstract

In this paper, the structural analysis of two novel derivatives of *N*-Acylsulfonamides (**1a-1b**) has been made. Packings of the two crystal structures presented herein are the results of individually weak but synergistic non covalent interactions like typical N-H ... O= (C or S) hydrogen bonds or π/π stacking effects. DFT calculation of molecular electrostatic potentials (MEP) was carried out at the basis set designed by 6-311G(d,p).

1. Introduction

N-Acylsulfonamides has attracted considerable attention in organic synthesis due to their various biological activities [1]. The molecules containing acylsulfonamides have recently described as HCV protease inhibitors [2],potent and selective EP3 receptor antagonists [3],and inhibitors of carbonic anhydrase II [4].In addition, these compounds have also been investigated as potent antiproliferative agents in three human tumor cell lines (Hep G2, PC-3 and B16-F10) [5].
There are several available procedures for the preparation of these compounds. *N*-Acylsulfonamides can be prepared by either sulfonylation of amides [6],or by direct condensation of sulfonamides with acyl chlorides or anhydrides in basic conditions [7-10].In addition, the using of different heterogeneous or homogeneous catalysts such as; $TiCl_4$, $Al(HSO_4)_3$, $Zr(HSO_4)_4$, Tin (IV) Chloride in order to increase the yield and reduce the reaction time was also reported [11-13].In our previous work, we have established that chlorosulfonyl isocyanate (CSI) and sulfuryl chloride are a suitable reagents allowing the introduction of sulfonamide moiety in diverse structures [14-19]. Two novel derivatives of *N*-Acylsulfonamides were synthesized and some appropriate quantum descriptors such as E_{HOMO}, E_{LUMO}, energy gap, dipolar moment, global hardness and molecular polarizability have been discussed.

2. Experimental details

2.1. *Materials and methods*

The purification of the compounds was performed by column chromatography using silica gel60 (35-70 µm) or Merck h60 (Art. 9385). The mass spectra (MS) were recorded in the ESI mode and the data reported in m/e (intensity to 100%). ^{1}H NMR spectra were recorded on Brûker AC 400-MHz Advance spectrophotometer in $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ (ppm) scale and coupling constants (J values) are expressed in Hertz. Multiplicity is indicated as

s(singlet), d (doublet), t (triplet), m (multiplet). All melting points were determined by open capillary tubes on an electro thermal apparatus (Barnstead/ Electrothermal) and are uncorrected.

2.2. *Synthesis of N-acylsulfonamides*

The synthetic pathway followed for the preparation of the title compounds was accomplished by a two-steps sequence (carbamoylation and sulfamoylation) as shown in Scheme **1**. Firstly, to a stirred solution of chlorosulfonyl isocyanate (CSI) (1.62 g, 11.44 mmol) in (10 mL) of anhydrous dichloromethane at 0° C was added (1.34g, 11.44.mmol) of ethyl lactate in the same solvent under nitrogen atmosphere. Secondary, after a period of 30 min, the resulting solution was slowly added into a solution containing 1 equiv of primary amine in the presence of (1.73 mL, 1.1 equiv) of triethylamine under vigorous stirring at 0 °C in the same solvent. The resulting reaction solution was allowed to warm up to room temperature for over 2 h. After the completion of the reaction, the reaction mixture was diluted with 30 mL of dichloromethane, washed with HCl 0.1 N and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified by crystallization from diethyl ether, to give the desired *N*-acylsulfonamide derivatives (**1a** and **1b**) in excellent yields.

2.3 *Characterization of N-acylsulfonamides*

2.3.1. Ethyl (S)-2-[(N-((S)-1-phenylethyl)sulfamoyl)carbamoyloxy]propanoate 1a:

White solid, yield 89%, $\boldsymbol{R_f}$= 0.45 (CH_2Cl_2/MeOH, 9:1), m.p. = 116-118 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7,32 (s, 1H, N**H**), 7.25 (m, 5H, Ar), 5.75 (d, *J* = 7.36 Hz, 1H, N**H**), 5.00 (q, *J* = 7.00 Hz, 1H, *C**H**), 4.95 (q, *J* = 7.12 Hz, 1H, *C**H**), 4.25 (q, *J* = 7.12 Hz, 2H, C$\mathbf{H_2}$-CH_3**)**,1.60 (d, *J* = 6.88 Hz, 3H, *****CH-C$\mathbf{H_3}$**)**, 1.52 (d, *J* = 6.93 Hz, 3H, *****CH-C$\mathbf{H_3}$**)**, 1.25 (t, *J* = 6.20 Hz, 3H, CH_2-C$\mathbf{H_3}$**)**. ^{13}C NMR ($CDCl_3$, δ ppm): 170.2; 153.3; 145.0; 127.0; 126.5; 126.1; 125.5; 125.1; 69.7; 63.2; 47.0; 21.2; 18.3; 12.1. MS ESI$^+$ 30eV m/z: 367 $[M+ Na]^+$, 345 $[M+ H]^+$. HRMS calcd for $C_{14}H_{20}O_6N_2S$. **M**= 344.3834.

2.3.2 Ethyl (S)-2-[(N-cyclohexylsulfamoyl)carbamoyloxy]propanoate 1b:

White solid, yield 74%, $\boldsymbol{R_f}$= 0.66 (CH_2Cl_2/MeOH, 9:1), m.p. = 119-121 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (s,1H, NH), 5.15 (m,2H, *****C**H**-CH_3 + N**H**), 4.20 (q, *J* = 7.16 Hz, 2H, C$\mathbf{H_2}$-CH_3), 3.30 (m, 1H, C**H**NH), 1.90 (m, 2H, C$\mathbf{H_2}$-cyc), 1.60 (m ,2H, C$\mathbf{H_2}$-cyc), 1.54 (d, *J* = 6.70 Hz, 3H, *****CH-C$\mathbf{H_3}$**)**, 1.40 (m , 4H, 2CH_2-cyc), 1.31 (m, 5H, CH_2-C$\mathbf{H_3}$+ CH_2-cyc). ^{13}C NMR ($CDCl_3$, δ ppm): 171.6; 151.2; 68.3; 63.2; 54.2; 41.2; 27.1; 25.4; 25.3; 24.8; 16.2; 15.1. MS ESI+ 30eV m/z: 323 $[M+H]^+$, 345 $[M+Na]^+$. HRMS calcd for $C_{12}H_{22}O_6N_2S$. **M** = 322.3779.

2.4. *Crystallographic data*

Suitable crystals were mounted for measurements. Data collection was performed at 293K on a Nonius Kappa CCD diffractometer using Mo $K\alpha$ (λ = 0.71073Å) radiation and processed with the HKL package of programs [20]. The crystal structure was solved with direct methods using *SHELXS-97* and final refinement, based on F^2, was carried out by full matrix least squares with *SHELXL-97* software [21-22].Refinement was performed anisotropically for all non-hydrogen atoms. In the final stages of least-squares refinement, hydrogen atoms were placed in geometrically- idealized positions and were allowed to ride on the coordinates of the parent atom with thermal parameters fixed at 1.2 Ueq of the parent atom. The residual electron densities were of no chemical significance. Crystal data for the compounds **1a** and **1b** data collection procedures, structure determination methods and refinement results are summarized in Table**1**.

3. Resulats and Discussion

3.1. *Chemistry*

The synthetic route for the preparation of two *N*-acylsulfonamides derived from primary amines **1a-1b** is outlined in Scheme **1**.

The synthesis was carried out in two steps, by carbamoylation of chlorosulfonyl isocyanate with ethyl lactate in anhydrous conditions to form the *N*-chlorosulfonyl carbamate. In the second step, the carbamate reacted with primary amines in the presence of triethylamine at 0^o C. The reaction was completed within 2 hours and the remaining compounds were obtained in good yield, 89% for **1a** and 74% for **1b** after crystallization in diethyl ether.

Synthesized compounds were characterized by FT-IR; the characteristic band at 3255.22-3298.18 cm^{-1} of (N-H) amide and two bands 1184.96-1118.15, 1384.18-1355.55 cm^{-1} of (SO_2) presented all compounds reveal the formation of sulfonamides. $[M+1]^+$ Peaks obtained by ESI-MS represented the

molecular peaks in two synthesized compounds. The structures of compounds **1a** and **1b** were also confirmed by ^{1}H, ^{13}C and ^{31}P NMR by dissolving in $CDCl_3$. ^{1}H NMR spectra of both compounds showed a signal at δ 7.30-7.70 ppm corresponding to NH group of sulfonamide.

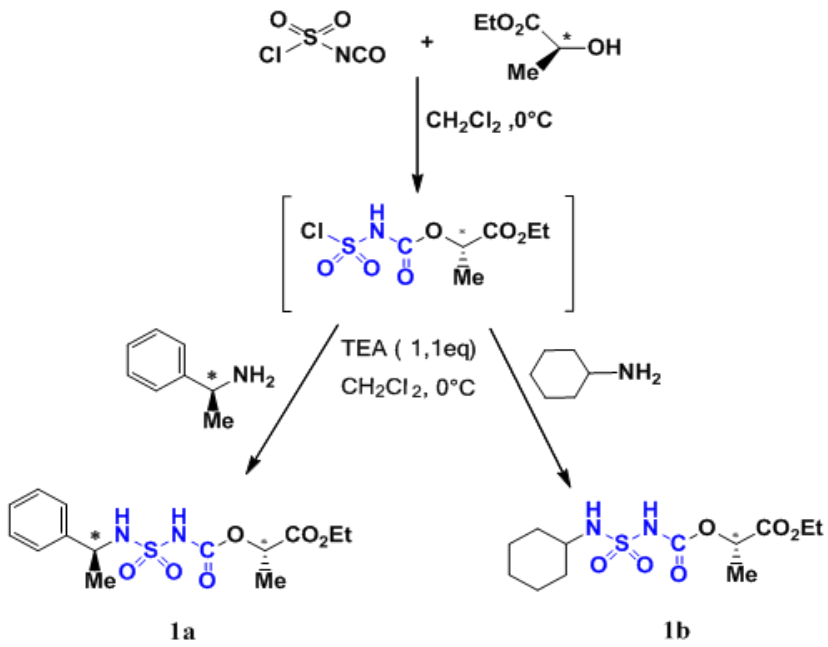
Table 1. Crystallographic data for compound **1a** and **1b** and refinement data

Compound reference	Compound **1a**	Compound **1b**
Chemical formula	$C_{14}H_{20}N_2O_6S$	$C_{12}H_{22}N_2O_6S$
Formula Mass	344.39 g.mol^{-1}	322.39 g.mol^{-1}
Crystal System	orthorhombic	monoclinic
a (Å)	5.184 (1)	9.115 (1)
b (Å)	10.548 (1)	9.258 (1)
c (Å)	31.415 (2)	10.017 (2)
α (°)	90	90
β (°)	90	111.217 (4)
γ (°)	90	90
Unit cell volume (Å^3)	1717.8 (4)	788.0 (2)
Temperature (K)	293 (2)	293 (2)
Space group	P 2_1 2_1 2_1	P 2_1
Z	4	2
Radiation :	Mo K_α (λ = 0.71073 Å)	Mo K_α (λ = 0.71073 Å)
θ range for data collection :	0.978° to 25.35°	0.977° to 25.67°
Reflections collected /unique / with [I > 2σ(I)] :	11438/2912 / 1887	8 436/ 2796/ 2547
Data/restraints/parameters :	2912/ 0/ 208	2796/1/190
Goodness of fit on F^2 :	1.151	1.152
Final R indices [I > 2σ(I)] :	R1 = 0.0686, wR2 = 0.1620	R1 = 0.0394, wR2 = 0.1023
R indices (all data) :	R1 = 0.1032, wR2 = 0.2159	R1 = 0.0489, wR2 = 0.1214
$(\Delta\rho)_{max}$:	0.36 e. Å^{-3}	0.46 e. Å^{-3}
$(\Delta\rho)_{min}$:	-0.67 e. Å^{-3}	-0.56 e. Å^{-3}
CCDC deposition number	XXX	XXX

3.2.*X-ray structural analyses*

The compounds **1a** and **1b** crystallize respectively in the $P2_12_12_1$ and $P2_1$ space groups (n°19 and 4) (table**1**). The asymmetric units are only composed of one molecule; an ORTEP view with numbering scheme of the asymmetric entities for the two crystal structures is given on figure **1**. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii [23].

All H atoms attached to C atoms were fixed geometrically and treated as riding with C–H = 0.93 Å (aromatic) or 0.97 and 0.96 Å (secondary CH_2 group and tertiary CH_3 group respectively) with U_{iso}(H) = 1.2 U_{eq}(C) or 1.5 U_{eq}(C), respectively. H atoms of amino group were located in a difference Fourier map and included in subsequent refinement restraints (N--H= 0.90 (1) Å andH...H = 1.66 (2) Å with U_{iso}(H) = 1.2 U_{eq}(N). In the last stage of refinement, they were treated as riding on their parent N atom.



Scheme1. Synthesis of *N*-Acylsulfonamide derivatives

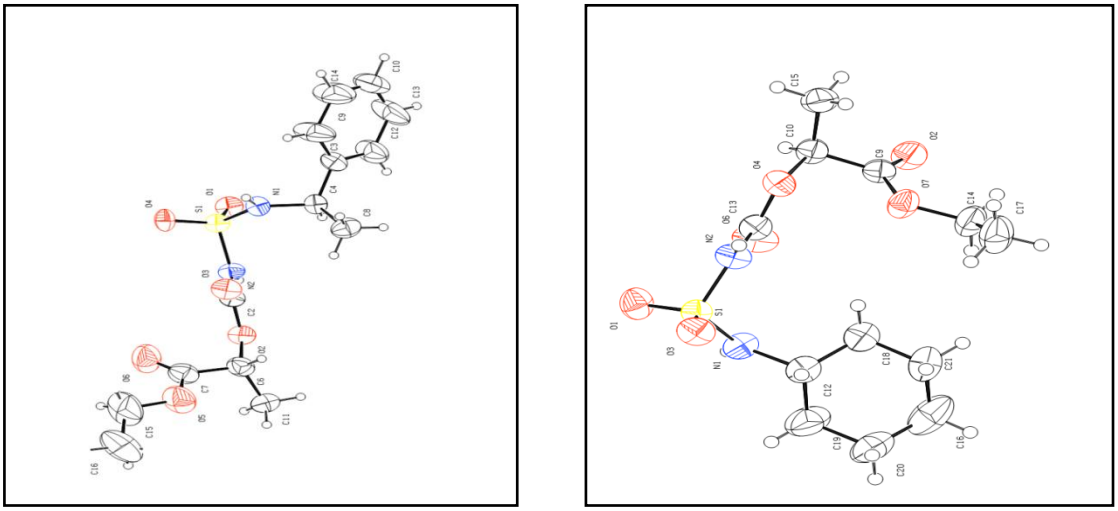


Figure 1.ORTEP diagram of the asymmetric unit content of **1a** and **1b**.

Table 2. Intermolecular NH …O=(C,S) hydrogen bond parameters (distances in Å and angles in °)
For compound **1a**

D-H	d (D-H)	d (H ... A)	DHA	d (D ..A)	A
N1 - H1	0.860	2.173	152.66	2.963	O1 [x+1, y, z]
N2 - H2	0.860	2.232	158.74	3.049	O3 [x-1, y, z]

For compound **1b**

D-H	d (D-H)	d (H ..A)	DHA	d (D ..A)	A
N1 - H1	0.860	2.136	166.79	2.980	O3 [-x+1, y-1/2, -z]
N2 - H2	0.860	2.028	169.44	2.878	O2 [-x-1, y+1/2, z+1]

3.3. Optimized geometric parameters

The molecular structure of titled compounds **1a**, **1b** was optimized by DFT using Beck's three parameters hybrid method and the Lee–Yang–Parr correlation functional (B3LYP)[24] combined with 6-31G(d) basis set [25].All the calculations were performed without specifying using Gauss view molecular visualization program[26] and Gaussian 09[27] in both gas and solvent (DMSO) media.

The computed quantum chemical descriptors based upon DFT calculations in both gas and solvent (DMSO) media are presented in table **3**.

Table 3. Quantum chemical descriptors based upon DFT calculations used for compounds **1a** and **1b.**

Quantum descriptors	***Gas phase***		***Solvent phase (DMSO)***	
	1a	*1b*	*1a*	*1b*
E_{LUMO} *(eV)*	*-0.07774*	*-0.07503*	*-0.08816*	*-0.05759*
E_{HOMO} *(eV)*	*-0.22061*	*-0.27439*	*-0.25343*	*-0.26854*
ΔE_{gap} *(eV)*	*0.14287*	*0.19936*	*0.16527*	*0.21095*
Average linear polarizability α_{Tot} *(Bohr*^{3}*)*	*111.959*	*228.303*	*135.785*	*259.101*
Total dipole moment μ *(Δ)*	*3.9273*	*2.8345*	*4.3215*	*3.2136*

Figure**2** shows the optimized structures obtained by B3LYP/6-31G(d) level in solvent phase (DMSO). Carbon atoms are represented with gray spheres, oxygen with red, nitrogen with blue, sulfur with yellow, hydrogen with white spheres.

Frontier molecular orbitals were carried out with the same level of theory. The highest occupied molecular orbitals HOMO and the lowest unoccupied molecular orbitals LUMO are commonly known as Frontier molecular Orbitals (FMOs) and were found to be extremely useful in explaining chemical reactivity and pharmacological processes [28] both HOMO and LUMO are the main orbitals occur in chemical reactions. The value of HOMO energy describes the ability of electron donating and of LUMO energy describes the ability of electron accepting. Electrophilic attacks were shown to correlate very well with atomic sites having high density of the HOMO orbital, where as nucleophilic attacks correlated very well with atomic sites having high density of the LUMO orbital. Substituents have a stronger effect on the energy of the HOMO than of the LUMO. In **1a**, the aromatic group has an important effect that higher the HOMO and lower the LUMO energies compared to **1b**. Generally, higher values of E_{HOMO} is an indication of the greater ease of donating electrons to the unoccupied orbital of the receptor, the E_{LUMO} is, the smaller the resistance to accept electron.

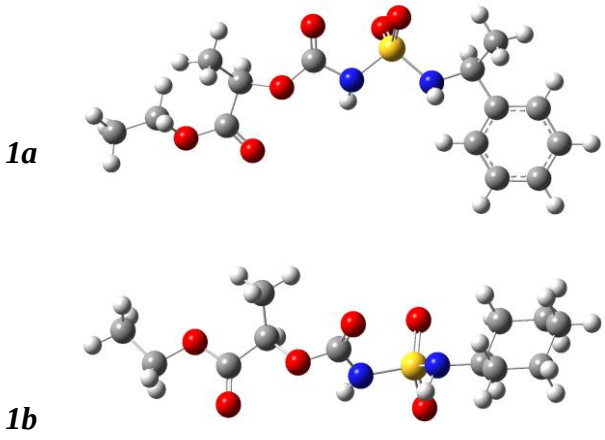


Figure 2. Optimized structures of **1a** and **1b** obtained at B3LYP/6-31G (d,p) level in DMSO.

Figure **3** shows HOMO and LUMO frontier orbitals obtained at the same level using a contour threshold of 0.02 a.u. for the studied compounds.

The gap energy between HOMO and LUMO determine the stability and the chemical reactivity of structures [29].The energy gap is basically responsible for spectroscopic properties of the molecules [30]. Generally, a large gap implies high stability and low chemical reactivity, small gap implies low stability and high chemical reactivity. In our calculation, the energy gap between HOMO and LUMO is found to be 0.14287 eV, 0.19936 eV in gaz phase, respectively for **1a** and **1b**.

Polarizability (α) measures the ability of electrons in a molecule to move easily as a result of stimulus. The softer a molecule is the higher is its average polarizability. With the smallest gap value, **1a** have a low stability and high chemical reactivity compared to **1b**, hardest compound and is associated with the lowest polarizability value.

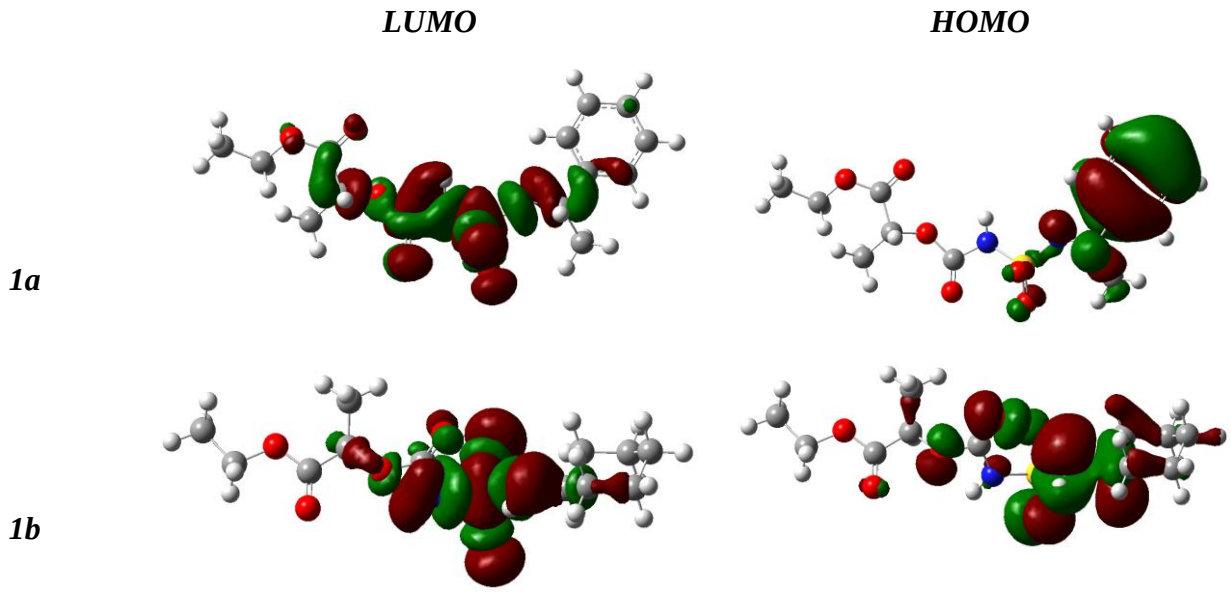


Figure 3. Frontier orbitals for **1a** and **1b** obtained at the B3LYP/6-31G (d,p) level using a contour threshold of 0.02 a.u.

The calculated dipole moment for all the molecules is given in table**2**. The dipole moment in a molecule is an important property that is mainly used to study the intermolecular interactions involving the non-bonded type dipole-dipole interactions, because higher the dipole moment, stronger will be intermolecular interactions, which agrees with the experimental results.

Some chemical descriptors, such as HOMO and LUMO energy values, frontier orbital energy gap, polarizability (α) and molecular dipole moment (μ) were calculated and have been used to understand the properties and reactivity of the newly prepared compounds.

Lower value in the HOMO and LUMO energy gap explains the ultimate charge transfer interactions happen within the molecule, which influences its chemical and biological activities.

Conclusion

The present paper reports the structure of two novel *N*-acylsulfonamides derivatives **1a** and **1b.**The X-ray structural analysis showed that the synthesis compounds **1a** and **1b** crystallized respectively in orthorhombic, space group $P2_12_12_1$and monoclinic, space group $P2_1$. The geometry of these compounds was optimized with DFT/B3LYP methods using 6-31G (d,p) basis. The value of the smallest energy gap between HOMO and LUMO showed **1a** have a low stability and high chemical reactivity compared to **1b.**

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