Synthesis, Characterization and DFT Studies of 2-[(2-substitutedphenyl) carbamoyl] benzoic acids

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Abstract: 2-[(2-substitutedphenyl) carbamoyl] benzoic acids are synthesized by using phthalic anhydride with o-aminophenol, o-anisidine and o-chloroaniline. The synthesized compounds were characterized by spectral analysis. For the synthesized compounds the density functional theory at the B3LYP levels was performed using Gaussian 03(W). The frontier molecular energies, electronic chemical potential, chemical hardness, chemical softness and global electrophilicity indices have been calculated at DFT/B3LYP/6-31G (d,p) level of theory. In our present study the theoretical FT-IR spectra and GIAO/SCF ^{1}H NMR calculations of the title molecules were carried out and compared with the experimental data.

Keywords: Carbamoylbenzoic acid, DFT, HOMO, LUMO.

INTRODUCTION

The carbonyl group is a part of several biologically important molecules such as proteins, lipids and hormones. This group can interact with basic group like –OH/NH$_2$ to form a complex and influence the properties of such compounds[1]. Intramoleculer and intermolecular hydrogen bonding have been found to

exert a crucial and highly effective influence of structural features on non-biomolecules and biomolecules as well as on the rate of various biological and non-biological reactions[2,3].

Experimental results have been frequently supported with theoretical calculations, which have been quite helpful in explaining the comparative relativities and many other properties of organic molecules and complexes. Extensive calculations are carried out to determine the optimized geometries, electronic structure and theoretical data.

EXPERIMENTAL

Phthalic anhydride, o-amino phenol, o-chloroaniline, o-anisidine were provided by Sigma Aldrich having purity greater than 99.5%. All other chemicals used were also of Analytical Reagent grade. An effective combination route to substituted carbamoylbenzoic acids is achieved by mixing phthalic anhydride and ortho substituted aniline.
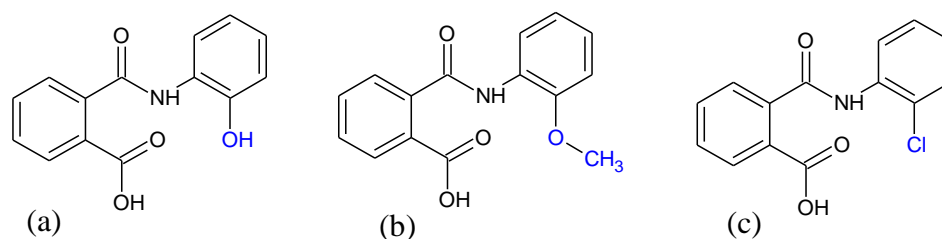
Synthesis of 2-[(2-hydroxyphenyl) carbamoyl] benzoic acid (a): Phthalic anhydride 0.5g. (3.38 mmol) and 2-amino phenol 0.369 g. (3.38 mmol) were dissolved in 2 ml dichloromethane in a separate flask, then they were mixed in a 50 ml round bottom flask containing 20 ml of dichloromethane. The reaction mixture was stirred vigorously at room temperature for an hour. The resulting product was filtered and recrystallized by using equal amount of acetone and diethyl ether and then washed with cold diethyl ether and very faint yellow colored crystals were formed. The melting point of recrystallized product is 223°C (the literature[4] value 224-225°C) and the yield is 0.770 g (88%). ^{1}H NMR (300 MHz, DMSO) δ : 6.81-6.84 (1H, m), 6.90 (1H, dt, J 8.0), 7.0-7.05 (1H, m), 7.56-7.61 (2H, m), 7.64-7.66 (1H, m), 7.67-7.69 (1H, m), 7.88 (1H, dt, J 8.0), 9.58 (1H, s), 9.66 (1H, s), 13-14 (1H, s) and IR (KBr) ν (cm^{-1}): 3473.91 (OH), 3178.79 (NH) 1718.63 and 1641.48 (C=O).

Synthesis of 2-[(2-methoxyphenyl) carbamoyl] benzoic acid (b): Phthalic anhydride 1.1990 g. (13.3 mmol) and 2-methoxyaniline 1.5 ml. (13.3 mmol) were dissolved in 5 ml tetrahydrofuran (THF) in a separate flask, and then they were mixed in a 50 ml round bottom flask containing 15 ml of THF. The reaction mixture was stirred vigorously at room temperature for an hour. Resulting product was filtered and purified by using diethyl ether, a white colored product is formed. The melting point of product is 190-192°C (the literature[4] value 187-188°C) and the yield is 2.59 g (71%). ^{1}H NMR (300 MHz, DMSO) δ : 3.80 (3H, s), 6.96-6.98 (1H, m), 7.06 (1H, dt, J 8.0), 7.11-7.14 (1H, m), 7.54-7.57 (2H, m), 7.61-7.64 (1H, m), 7.87 (1H, dt, J 8.0), 8.02 (1H, dt, J 8.0), 9.40 (1H, s), 13.05 (1H, s), and IR (KBr) ν (cm^{-1}): 3404.47 (OH), 3120.93 (NH) 1712.85 and 1640.00 (C=O).

Synthesis of 2-[(2-chlorophenyl) carbamoyl] benzoic acid (c): Phthalic anhydride 2.00 g. (13.51 mmol) and 2-chloroaniline 1.43 ml. (13.51 mmol) were dissolved in 5 ml tetrahydrofuran (THF) in a separate flask, and then they were mixed in a 50 ml round bottom flask containing 20 ml of THF. The reaction mixture was refluxed in water bath for an hour, cooled and then poured in 10 ml cold water. Resulting product was filtered and purified by using diethyl ether, a very faint brown colored product was formed. The melting point of product is 140°C and the yield is 2.59 g (71%). ^{1}H NMR (300 MHz, DMSO) δ 7.22-7.24 (1H, m), 7.38 (1H, dt, J 8.0), 7.41-7.51 (1H, m), 7.56-7.59 (2H, m), 7.67-7.71 (1H, m), 7.88 (1H, dt, J 8.0), 10.02(1H, S) 13.13(1H, S). and IR (KBr) ν (cm^{-1}): 3302 (OH), 1707 and 1674 (C=O).

(A = OH, OCH$_3$ and Cl)
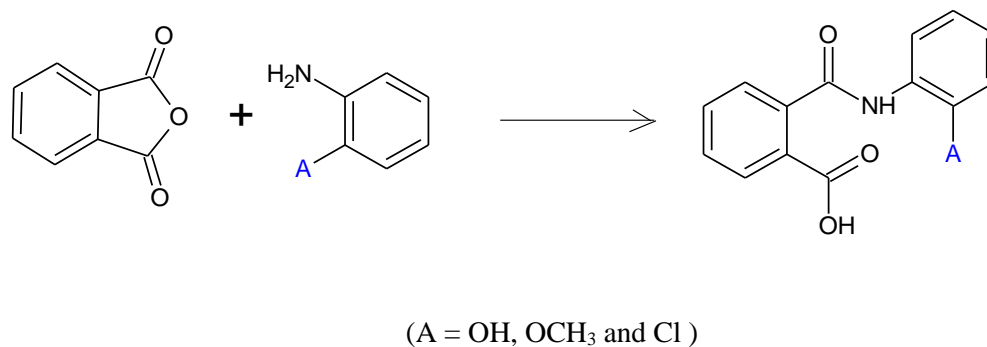
Fig. 1: General route of synthesis of 2-[(2-substitutedphenyl) carbamoyl] benzoic acids.

Figure 2: (a) 2-[(2-hydroxyphenyl)carbamoyl]benzoic acid; (b) 2-[(2-methoxyphenyl)carbamoyl]benzoic acid; (c) 2-[(2-chlorophenyl)carbamoyl]benzoic acid

In ^{1}H-NMR study, protons that can show hydrogen bonding exhibit extremely variable absorption positions over a wide range. The more hydrogen bonding takes place, the more deshielded a proton. The amount of hydrogen bonding is often a function of concentration and temperature. The more concentrated the solution, the more molecules can come into contact with each other and hydrogen bond.

Computational Details: All the synthesized and non-synthesized molecules are optimized and submitted to density functional theory (DFT) calculations at B3LYP levels with 6-31G (d, P) basis set by the use of G03 W series of program. For the synthesized compounds the DFT at the B3LYP levels was performed using Gaussian 03(W)[5-9].The frontier molecular energies, electronic chemical potential, chemical hardness, chemical softness and global electrophilicity indices have been calculated at DFT / B3LYP/ 6-31G(d,p) level of theory. In our present study the theoretical FT-IR spectra and GIAO/SCF ^{1}H NMR calculations of the title molecules were carried out and compared with the experimental data.

RESULTS AND DISCUSSION

The values of dipole moment and energies for molecule were calculated as shown in **Table 1**. According to DFT (B3LYP) calculations, the compound (b) has large dipole and large energy.

The HOMO-LUMO energy gap of 2-[(2-substitutedphenyl) carbamoyl] benzoic acids given in **Table 2**, reflects the chemical activity of the molecule. LUMO as an electron acceptor represents the ability to obtain an electron, and HOMO represents the ability to donate an electron.

Table-1: Total Energy, Dipole Moment (D), Thermal Energy (E), Heat Capacity (CV) and
Entropy (S) of 2-[(2-substitutedphenyl) carbamoyl] benzoic acids.

Compounds	D (Debye)	E (kcal mol^{-1})	CV (cal mol^{-1} K^{-1})	S (cal mol^{-1} K^{-1})
(a)	3.0039	153.133	61.674	132.141
(b)	3.2288	171.946	66.319	138.915
(c)	1.0774	144.405	61.035	133.469

Table-2: The DFT/B3LYP/6-31G (d,p) compound optimized energies, electronic chemical
Potential (μ), chemical hardness (η) and global electrophilicity indices (ω) of 2-[(2-
Substituted phenyl) carbamoyl] benzoic acids.

Compound	Optimized energy (au)	HOMO energy (eV)	LUMO energy (eV)	μ (eV)	η (eV)	ω (eV)
(a)	-895.81	-0.20998	-0.05731	-0.134	0.076	0.117
(b)	-935.12	-0.20704	-0.05696	-0.132	0.075	0.116
(c)	-1280.18	-0.22864	-0.06326	-0.146	0.083	0.129

**Table-3:** Vibrational assignments of 2-[(2-substitutedphenyl) carbamoyl] benzoic acids.

Compound	-OH stretching		N-H stretching		C=O stretching of Acid		C=O stretching of Amide	
	Exp.	Theo.	Exp.	Theo.	Exp.	Theo.	Exp.	Theo.
(a)	3637,	3620	3179	3471	1719	1728	1642	1685
(b)	3405	3614	3121	3483	1713	1743	1640	1697
(c)	3302	3613	3152	3471	1707	1745	1674	1704

Table-4: GIAO nuclear magnetic shielding tensor of phthalamic acids.

Molecule	δ in ppm	Protons
2-[(2-hydroxyphenyl)carbamoyl]benzoic acid **(a)**	3.43	Phenolic - proton
	6.13	Acidic proton
	7.43	N-H proton
2-[(2-methoxyphenyl)carbamoyl]benzoic acid **(b)**	3.74 & 4.05	-OCH$_3$ protons
	6.11	Acidic proton
	7.62	N-H proton
2-[(2-chlorophenyl)carbamoyl]benzoic acid **(c)**	6.15	Acidic proton
	7.37	N-H proton

The shapes of HOMO and LUMO of all the compounds obtained by the population analysis were shown in **Figure 3 to 6** for compound (a), (b) and (c) respectively. In the case of HOMO high electron density is on carbamoyl group and on substituted benzene while LUMO shows it is on benzoic acid moiety, i.e. HOMO to LUMO transition implies an electron density transfer to benzoic acid moiety from the rest part of the molecule.

According to Koopman's theorem, a correlation is expected between the HOMO energy level and the oxidation potential, because the negatives of the orbital energies in the ground state are equal to the ionization potentials[10]. The electron affinity of the electrolyte is also correlated to the LUMO energy level; therefore, the electrical potential window can be estimated from the energy gap (Eg) between HOMO and LUMO energy level.
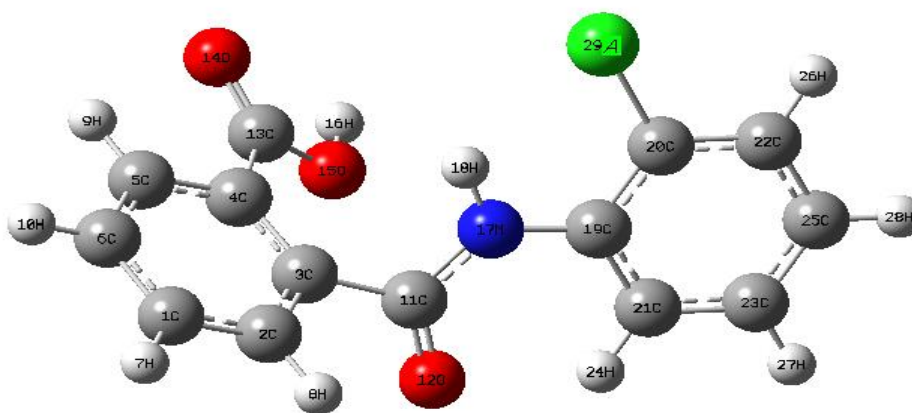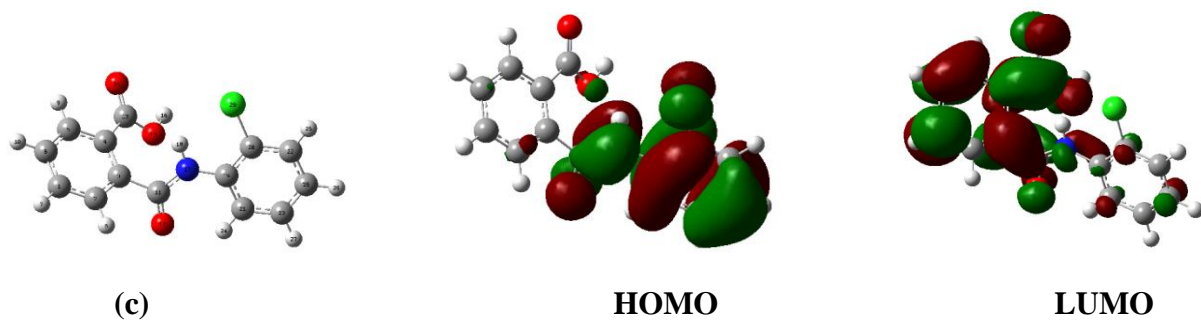

Figure 3: Numbering system used in the DFT study of 2-[(2-substitutedphenyl) Carbamoyl] benzoic acid. (A = OH, OCH$_3$ and Cl).

| **(a)** | **HOMO** | **LUMO** |
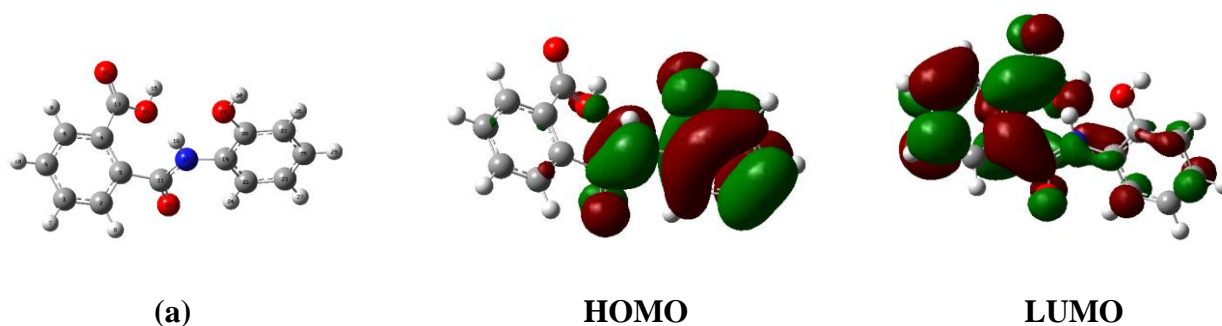
Figure 4: 2-[(2-hydroxyphenyl) carbamoyl] benzoic acid **(a)**; and the shapes of HOMO and LUMO of **(a)**

(b)   **HOMO**   **LUMO**
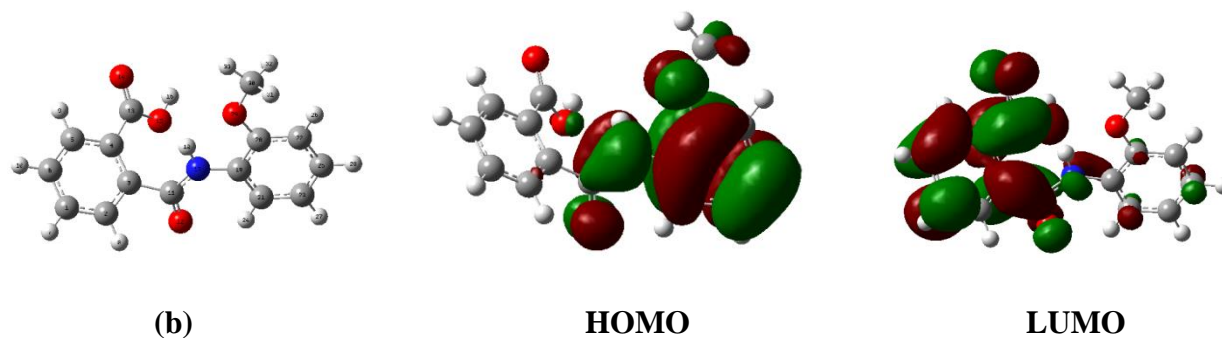
Figure 5: 2-[(2-methoxyphenyl) carbamoyl] benzoic acid **(b)**; and the shapes of HOMO and LUMO of **(b)**

(c)   **HOMO**   **LUMO**

Figure 6: 2-[(2-chlorophenyl) carbamoyl] benzoic acid **(c)**; and the shapes of HOMO and LUMO of **(c)**

The optimized geometric parameters of 2-[(2-substitutedphenyl)carbamoyl]benzoic acids bond length and bond angle, were calculated by the B3LYP method with 6-31G(d,p) as basis set. The literature survey reveals that H-bond and pKa value studies of phthalamic acids have been reported[11] and in our present study we have reported the DFT study of the phthalamic acids. The bond angles in degree between carbonyl carbon, amido nitrogen and hydrogen attached to nitrogen (C_{11}-N_{17}-H_{18}) is 117.34, 117.51 and 116.32 for the compounds (a), (b) and (c) respectively. This clearly indicates that compound (b) has a highest bond angle and the bond angle between carbonyl carbon-amido nitrogen and ring carbon (C_{18}-N_{17}-C_{19}) is 114.24, 113.85 and 114.96 of structure (a), (b) and (c) respectively. This clearly indicates that (b) has lowest. The bond length in case of N-H and C=O of amido has comparatively very small difference.

Chemical hardness is associated with the stability and reactivity of chemical systems. In molecule, it measures the resistance to change in the electron distribution or charge transfer. Chemical hardness is approximated using equation-1.

$$\eta = (\varepsilon \, LUMO - \varepsilon \, HOMO) / 2 \qquad\qquad\qquad (1)$$

The chemical hardness is considered to be a measure of the stability of the molecule. The larger the HOMO-LUMO energy gap the harder and more stable or less reactive the molecule.[12,13] From the Table-2, the result indicates that η values of the compounds (a) and (b) are less, and may be less stable, the structural (c) is harder and less reactive form.

Electronic chemical potential is the negative of all molecules and determined[14] using equation-2

$$\mu = (\epsilon\ LUMO + \epsilon\ HOMO) / 2 \tag{2}$$

The values μ for compound (a) to (c) are presented in **Table 2**. The electronic chemical potential for the compounds is in the order (b) > (a) > (c). The greater the electronic potential, the less stable or more reactive is the compound. Therefore (b) and (a) are more reactive and (c) is the least reactive. The global electrophilicity indices (ω) is calculated[15] using the electronic chemical potential and chemical hardness as shown in equatuion-3

$$\omega = \mu^2 / 2\ \eta \tag{3}$$

The 'ω' includes the property of the electrophile to acquire an additional electronic charge as well as the resistance to exchange the electronic charge with the environment simultaneously. The values ω (**Table 6),** among the compounds (b) is the strongest nucleophile while (c) is the strongest electrophile.

The spectral assignments have been made on recorded FTIR in solid phase. FTIR gas phase based on the theoretically predicted wave number by density functional B3LYP/6-31G1(d.p) method. The determination and vibrational frequencies by computational method is increasing in many areas of chemistry. It is customary to scale down the calculated harmonic frequencies in order to improve the agreement with experimental data. Vibrational frequencies calculated at B3LYP/6-31G(d.p) were scalel[16,17] by 0.9614.

A strong FT-IR band observed at 1719 and 1642 cm^{-1} is assigned to carbonyl (C=O) group of acid and amide respectively, stretchers and 3474, 3179 (wide) assigned to –OH and N-H stretching frequencies in 2-[(2-hydroxyphenyl) carbamoyl] benzoic acid **(a)** coincide with theoretical 1728 and 1685 cm^{-1} of carbonyl group of acid and amide, and band at 3620 and 3471 of- OH and N-H stretching frequencies. Similar trends in the case of another synthesized compounds (b) and (c) are as shown in Table-3. Small difference between experimental and calculated vibrational modes were observed, it may be due to the fact that hydrogen bond vibrations present in the crystal lead to strong perturbation of the Infrared wave number. The experimental results reported here are for the solid phase while theoretical calculations pertain to the isolated molecule in the gas phase.

Theoretical calculations of NMR typically benefit from an accurate geometry and large basis set. Cheeseman[18] and coworkers had suggested that B3LYP/6-31G (d) optimized structures are minimum recommended modes for predicting NMR properties. In our present study, GIAO/SCF" ^{1}HNMR calculations[19] of the pthalamic acid, geometry optimized at DEF/ B3 LYP level with a higher basic set 6-31+G(d,p) were carried out at B3LYP level using 6-311+G(d,p) basic set.

The acidic proton shows a small difference of chemical shift in ppm in all molecules as shown in the Table-4, maximum in 2-[(2-chlorophenyl) carbamoyl] benzoic acid **(c)**. The amino proton shows a predictable chemical shift, maximum (7.62) in 2-[(2-methoxyphenyl) carbamoyl] benzoic acid **(b)** and minimum (7.37) in compound **(c).**

CONCLUSION

2-[(2-substitutedphenyl) carbamoyl] benzoic acids were synthesized and characterized by spectral analysis. The same compounds were used for computational study, the theoretical FT-IR spectra and GIAO/SCF ^{1}H NMR calculations of the title molecules were carried out and compared with the experimental data. Small difference between experimental and calculated vibrational modes were observed it may be due to the fact that hydrogen bond vibrations were present in the crystal, the experimental result reported here are for the solid phase while theoretical calculations pertain to the isolated molecule in the gas phase. The frontier molecular energies, HOMO and LUMO energies, electronic chemical potential, chemical hardness, chemical softness and global electrophilicity indices have been calculated at DFT/B3LYP/6-31G(d,p) level of theory and concludes that (b) and (a) are more reactive and (c) is the least reactive.

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