5. Single and Multi-Regression Analysis of 2-Hydroxy-5-(Substitutedphenylsulfonamido) Benzoic Acids by Hammett Application

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Abstract:

A series of sulfonamides have been synthesized and their purity has been tested through literature survey[1,2]. Infrared and NMR spectral data of these compounds have been correlated with Hammett substituent constant and effect of substituent have been analyzed.

Keywords:

Sulfonamide, IR, NMR, regression analysis, effect of substituent.

5.1 Introduction:

Sulfonamides are effective compounds combining (–S (=O)$_2$–NH–) group and they are generally formed by the condensation of corresponding amine and sulfonyl chlorides.

The most common method for synthesizing sulfonamides is the condensation of aromatic sulfonyl chloride with aliphatic or aromatic, primary or secondary amines in the presence of base catalysts. Numerous methods employed for the synthesis of sulfonamides. Literature survey reveals that, the study of spectral linearity on numerous organic substituents are visible. The study of effect of substituents on sulfonamide derivatives are very limited. Hence the authors have taken effort to synthesize some 2-hydroxy-5-(substituted phenylsulfonamido)benzoic acids by microwave method using Cu^{2+}/zeolite catalyst [1,2] to study the quantitative structure property relationships.

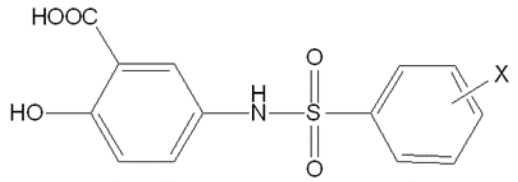
5.2 Results and Discussion:

5.3 Infrared spectral correlation:

The effects of substituent on the infrared stretching frequencies of various organic compounds have been reported in earlierliterature[3-6].In this correlation the structure parameter Hammett equation employed is as shown in **Eqn 1**.

$$\nu = \rho\sigma + \nu_0 \qquad \ldots (1)$$

Where ν_0 is the frequency for the parent number of the series. In the present study the author have synthesized a series of aryl sulfonamide derivatives as shown in **Figure 5.1.**



Where X= H, 4-Br, 2-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2

Figure 5.1: Structure of synthesized2-hydroxy-5-(substitutedphenylsulfonamido) benzoic acids

The assigned infrared frequencies (ν, cm^{-1}) such as N-H, CO and SO of synthesized aryl sulfonamide compounds are presented in Table 5.1**.** The assigned infrared stretching frequencies of all compounds in series are correlated with different substituent constants and Swain-Lupton's [7] *F* and *R* parameters according to the approach of Jaffe [8], Stewar [9]and John Shorter [10]using Hammett equations. The results of the statistical analysis are presented in Table 5.2. Table 5.1: The infrared NH, CO and SO stretches (ν, cm^{-1}), The ^1H NMR chemical shifts (δN-H, ppm), ^{13}C NMR chemical shifts (δC=O, ppm) of synthesized 2-hydroxy-5-(substituted phenylsulfonamido) benzoic acids.

Table 5.2: Results of statistical analysis of infrared frequencies ($\nu_{N\text{-}H}$, $\nu_{SO(asym)}$, $\nu_{SO(sym)}$, $\nu_{(C=O)}$ cm^{-1}), ^{1}H NMR chemical shifts ($\delta_{N\text{-}H}$, ppm), ^{13}C NMR chemical shifts ($\delta_{C=O}$, ppm) of 2-hydroxy-5-(substituted phenylsulfonamido)benzoic acid compounds with Hammett substituent constants (σ, σ^{+}, σ_{I}, σ_{R}), *F* and *R* parameters.

Entry	**Substituent**	**IR**				**^{1}H NMR**	**^{13}C NMR**
		$V_{N\text{-}H}$ (cm^{-1})	**$V_{(c=o)}$ (cm^{-1})**	**$V_{(SO)\ sym}$ (cm^{-1})**	**$V_{(SO)\ asym}$ (CM^{-1})**	**δ N-H(ppm)**	**δ c=o(ppm)**
1	H	3262.4	16959	1311.9	1158	10.832	172.40
2	4-Br	3263.2	1670.8	1332.8	1156	10.832	172.36
3	4-Cl	3262.5	1670.8	1332.8	1157.3	10.077	171.06
4	2F	3264.4	1694.1	1321.2	1168.7	10.364	171.58
5	4-F	3264.5	1670.8	1325.7	1161.5	10.290	171.53
6	4-OCH_3	3250.1	1677.3	1333.9	1158.0	9.893	171.67
7	4-CH_3	3262.8	1669.9	1333.3	1157.3	10.330	171.65
8	2-NO_2	3293.2	1665.6	1322.8	1175.9	10.446	171.53
9	4-NO_2	3263.6	1670.8	1311.9	1159.5	10.399	171.50

Fre. (cm^{-1}	**Const.**	**r**	**I**	**P**	**S**	**N**	**Correlated Derivatives**
N-H	σ	0.917	3260.66	21.552	8.55	8	H, 4-Br, 4-Cl, 2-F, 4-F,4-OCH_3, 4-CH_3, 2-NO_2
	σ^{+}	0.906	3262.89	14.419	9.23	8	H, 4-Br, 4-Cl, 2-F, 4-F,4-OCH_3, 4-CH_3, 4-NO_2
	σ_{I}	0.814	3257.69	19.264	10.97	9	H, 4-Br, 4-Cl, 2-F, 4-F,4-OCH_3, 4-CH_3, 2-NO_2,4-NO_2
	σ_{R}	0.851	3269.32	24.477	10.31	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	F	0.838	3269.89	10.379	11.38	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	R	0.852	3269.89	20.244	10.37	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
(SO)asym	σ	0.850	1327.77	-11.992	8.32	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ^{+}	0.853	1326.73	-9.299	8.14	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_{I}	0.813	1327.13	-4.838	9.53	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_{R}	0.812	1161.93	3.446	7.04	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	F	0.857	1155.64	12.883	5.82	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2

Fre. (cm^{-1}	**Const.**	**r**	**I**	**P**	**S**	N	**Correlated Derivatives**
	R	0.819	1161.92	2.452	7.05	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
(C=O)	σ	0.831	1678.15	-9.219	11.22	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ^+	0.808	1676.51	-1.822	11.77	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_I	0.839	1682.73	-16.745	10.88	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_R	0.828	1674.04	-12.9	11.31	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	F	0.819	1679.38	-7.141	11.60	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	R	0.826	1673.96	-9.731	11.41	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
N-H	σ	0.825	10.34	0.204	0.32	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3,4-CH_3, 2-NO_2, 4-NO_2
	σ^+	0.847	10.34	0.283	0.29		
	σ_I	0.811	10.44	-0.136	0.32		
	σ_R	0.843	10.47	0.544	0.29		
	F	0.814	10.45	-0.155	0.32		
	R	0.844	10.49	0.464	0.29		
C=O	σ	0.823	171.75	-0.264	0.44	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ^+	0.805	171.7	-0.046	0.45	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_I	0.842	171.97	-0.703	0.41	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	σ_R	0.813	171.73	0.232	0.45	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	F	0.843	171.97	-0.621	0.41	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
	R	0.812	171.73	0.176	0.45	9	H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2
r = correlation coefficient; I = intercept; ρ = slope; s = standard deviation; n = number of substituents.							

From the Table 5.2, it is observed that the infrared frequency ($\nu_{N\text{-}H}$, cm^{-1}) values of all 2-hydroxy-5-(substituted phenylsulfonamido)benzoic acid compounds in series, have shown satisfactory correlation with Hammett substituent constant σ(r = 0.917)except those with 4-NO_2 substituent and shown satisfactory correlation with σ^+(r=0.906) except those with 2-NO_2.

The poor correlation is attributed to the weak inductive, field and resonance effects of the substituents for predicting the reactivity on the infrared stretching frequency of ($\nu_{N\text{-}H}$, cm^{-1}) values through resonance as per the conjugative structure as shown in **Figure 5.2.**

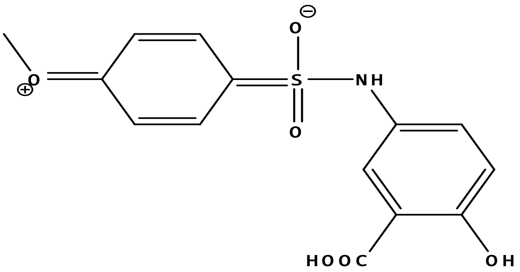


Figure 5.2: Resonance-conjugative structure

All the correlations with ($\nu_{N\text{-}H}$, cm-1) values shown positive ρ values. This indicates the operation of normal substituent effect. Since most of the single regression analyses, have shown poor correlations, it is decided to go for multi regression analysis.

The multi regression analysis of the stretching frequency (νN-H, cm-1) values of all aryl sulfonamide compounds with inductive, resonance and Swain-Lupton's7 parameters produce satisfactory correlations as shown in Eqns 2&3.

$$\nu_{N\text{-}H}\ (\text{cm}^{-1}) = 3262.10(\pm 6.655) + 18.174(\pm 13.372)\sigma_I + 23.569(\pm 13.905)\sigma_R$$

$$(R = 0.967,\ n = 9,\ P > 95\%) \qquad \ldots (2)$$

$$\nu_{N\text{-}H}\ (\text{cm}^{-1}) = 3262.27(\pm 5.933) + 19.508(\pm 11.284)F + 24.694(\pm 11.254)R$$

$$(R = 0.971,\ n = 9,\ P > 95\%) \qquad \ldots (3)$$

From the Table 5.2, it is evident that the infrared frequency ($\nu_{SO(asym)}$, cm^{-1}) values have shown poor correlations (r<0.900) and negative ρ valueswith all Hammett substituent constants(σ, σ^+, σ_I, σ_R), F and R parameter. This is attributed to the weak polar, inductive, field and resonance effects of the substituents for predicting the reactivity on the infrared stretching frequency of νSO(asym)cm-1 values through resonance as per the conjugative structure as shown in **Figure 5.1** and the operation of reverse substituent effect.

Since most of the single regression analyses, have shown poor correlations it is decided to go for multi regression analysis. The multi regression analysis with inductive, resonance and Swain-Lupton's[7] parameters produce satisfactory correlations as shown in **Eqns 4&5.**

$$\nu_{SO(asym)}(\text{cm}^{-1}) = 1324.20(\pm 6.328) + 4.113(\pm 2.717)\sigma_I - 15.680(\pm 3.223)\sigma_R$$

$$(R = 0.945,\ n = 9,\ P > 90\%) \qquad \ldots (4)$$

$$\nu_{SO(asym)}(\text{cm}^{-1}) = 1325.48(\pm 5.741) - 8.649(\pm 1.920)F - 15.508(\pm 1.891)R$$

$$(R = 0.952,\ n = 9,\ P > 95\%) \qquad \ldots (5)$$

From the **Table 5.2**, it is evident that the infrared stretching frequencies ($\nu_{SO(sym)}$, cm^{-1}) values in series have shown satisfactory correlation with Hammett substituent constants σ($r = 0.957$) and σ_I($r = 0.905$) except those with 2-F, 2-NO_2 substituent.

However they have shown poor correlations ($r < 0.900$) with the remaining Hammett substituent constant σ^+, σ_R, F and R parameter. The reason is as stated earlier in this section. All the correlations produce positive ρ values. The multi regression analysis produce satisfactory correlations as shown in **Eqns 6&7.**

$$\nu_{SO(sym)}(cm^{-1}) = 1156.86(\pm 4.498) + 12.774(\pm 4.040)\sigma_I + 2.808(\pm 1.399)\sigma_R$$

$$(R = 0.951, n = 9, P > 95\%) \qquad \ldots (6)$$

$$\nu_{SO(sym)}(cm^{-1}) = 1156.38(\pm 3.888) + 14.187(\pm 7.395)F + 5.688(\pm 3.375)R$$

$$(R = 0.962, n = 9, P > 95\%) \qquad \ldots (7)$$

From the **Table 5.2**, it is evident that the infrared stretching frequencies ($\nu_{(C=O)}$, cm^{-1}) of all the 2-hydroxy-5-(substituted phenylsulfonamido)benzoic acid compounds have shown poor correlations ($r < 0.900$) with Hammett substituent constants (σ, σ^+, σ_I, σ_R), F and R parameters and negative ρ values. The reason is same as stated earlier. The multi regression analysis produce satisfactory correlations as shown in **Eqns 8 & 9**.

$$\nu_{(C=O)}(cm^{-1}) = 1680.47(\pm 7.670) - 16.186(\pm 5.413)\sigma_I - 12.091(\pm 1.026)\sigma_R$$

$$R = 0.947, n = 9, P > 90\%) \qquad \ldots (8)$$

$$\nu_{(C=O)}(cm^{-1}) = 1677.82(\pm 7.699) - 9.890(\pm 4.644)F - 11.987(\pm 4.605)R$$

$$R = 0.936, n = 9, P > 90\%) \qquad \ldots (9)$$

5.4 NMR Spectral Study:

^{1}H NMR spectral study:

The ^{1}H NMR spectra of all the synthesized aryl sulfonamide compounds in the present investigation are recorded in DMSO and$CDCl_3$ using tetramethylsilane (TMS) as internal standard. The signal of the sulfonamide proton has been assigned and their chemical shift values are presented in **Table 5.1**.

The chemical shifts (δ_{N-H}, ppm) of aryl sulfonamide compounds have been correlated with Hammett substituent constants (σ, σ^+, σ_I, σ_R), F and R parameters using single and multi-regression analysis. While seeking Hammett correlation involving the chemical shift (δ, ppm) values, the form of the Hammett equation employed is as shown in **Eqn. 10**.

$$\delta = \rho\sigma + \delta_0 \qquad \ldots (10)$$

Whereδ_0 is the ^{1}H NMR chemical shift (δ, ppm) of the corresponding parent compound.

The assigned ^{1}H NMR chemical shifts (δ_{N-H}, ppm) of 2-hydroxy-5-(substitutedphenylsulfonamido) benzoic acid compounds are correlated with different Hammett substituent constants (σ, σ^+, σ_I, σ_R), *F* and *R*parameters[11,12,13]. The results of statistical analysis are presented in **Table 5.2**. From **Table 5.2**, it is observed that the ^{1}H NMR chemical shifts (δ_{N-H}, ppm) of compounds have shown poor correlation ($r < 0.900$) and positive ρ values with Hammett substituent constants (σ, σ^+, σ_I, σ_R), *F* and *R* parameters. The multi-regression analysis shown in **Eqns11 & 12.**

$$\delta_{N-H}(\text{ppm}) = 10.54(\pm 0.218) - 0.162(\pm 0.038)\sigma_I + 0.552(\pm 0.255)\sigma_R$$

$$(R = 0.945,\ n = 9,\ P > 90\%) \qquad \ldots (11)$$

$$\delta_{N-H}\ (\text{ppm}) = 10.51(\pm 0.208) - 1.052(\pm 0.395)F + 0.452(\pm 0.094)R$$

$$(R = 0.944,\ n = 9,\ P > 90\%) \qquad \ldots (12)$$

^{13}C NMR spectral study:

The ^{13}C NMR spectral correlations of numerous compounds will be reported in the literature. The same study with sulfonamides are limited[13]. In the present investigation, the assigned chemical shifts ($\delta_{C=O}$, ppm) of synthesized aryl sulfonamides are presented in **Table 5.1.**

The assigned ^{13}C NMR chemical shifts ($\delta_{C=O}$, ppm) of compounds are correlated with different Hammett substituent constants (σ, σ^+, σ_I, σ_R), *F* and *R*parameters[11,12,13]. The results of statistical analysis are shown in **Table 5.2**.From **Table 5.2** it is observed that the ^{13}C NMR chemical shifts ($\delta_{C=O}$, ppm) values have shown poor correlation ($r < 0.900$) with Hammett substituent constants (σ, σ^+, σ_I, σ_R), *F* and *R* parameters. All the correlations have shown negative ρ values. The correlation of $\delta_{C=O}$ (ppm) modes of 2-hydroxy-5-(substituted phenylsulfonamido) benzoic acid compounds were fail with Hammett substituent constants (σ, σ^+, σ_I, σ_R), *F* and *R* parameters. All the correlations with Hammett substituent constants viz., σ_R and *R* parameters have shown positive ρ values. They show satisfactory correlations in multi-regression analysis with Swain-Lupton's parameters[7]. The generated multi-regression equations are given in **Eqns 13 & 14**.

$$\delta_{C=O}\ (\text{ppm}) = 172.02(\pm 0.299) - 0.716(\pm 0.001)\ \sigma_I + 0.268(\pm 0.024)\ \sigma_R$$

$$(R = 0.945,\ n = 9,\ P > 90\%) \qquad \ldots (13)$$

$$\delta_{C=O}\ (\text{ppm}) = 171.97(\pm 0.287) - 0.613(\pm 0.046)F + 0.036(\pm 0.046)R$$

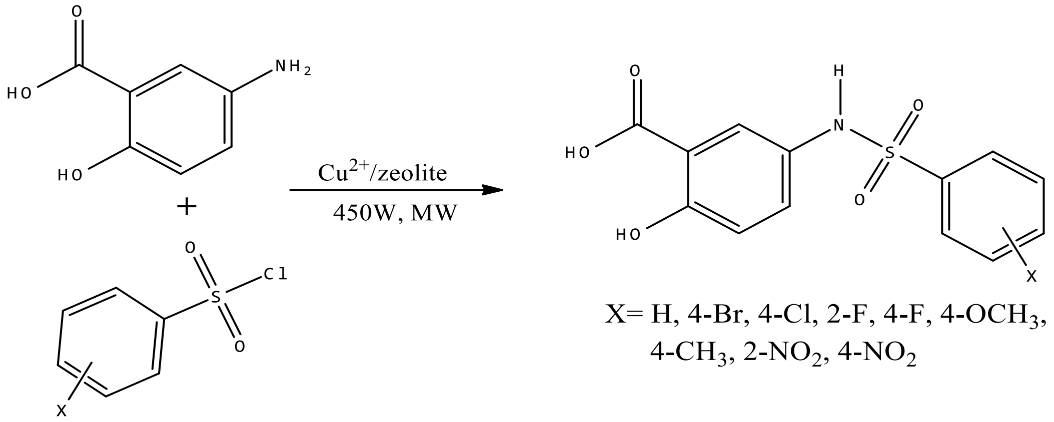
$$(R = 0.943,\ n = 9,\ P > 90\%) \qquad \ldots (14)$$

5.5 Experimental:

The compound 5-aminosalicylic acid has been procured along with various substituted benzenesulfonylchlorides from Sigma-Aldrich, Alfa Aesar and E. Merck chemical companies.

Preparation of 2-hydroxy-5-(substituted phenylsulfonamido) benzoic acids:

An equimolar quantity of substituted benzenesulfonylchlorides (1 mmol), 5-aminosalicylicacid (1 mmol) and Cu^{2+}/zeolite[1] (80mg) clay catalyst were taken in 100mL beaker and mixed thoroughly. This mixture was subjected to microwave irradiation for 5-8 min in a microwave oven (**Scheme 5.1,** X=H) at 450W (Samsung Grill, GW73BD Microwave oven, 230V A/c, 50 Hz, 2450 Hz, 100–750 W(ICE–705)). During the reaction 0.1 mL of triethylamine was added to neutralize the formation of hydrochloride. The completion of the reaction was monitored by TLC. The resulting product was washed with *n*-hexane and separated the catalyst using methanol by filtration and dried to obtain the solid. These data were well agreed with the earlier literature report[1]



X= H, 4-Br, 4-Cl, 2-F, 4-F, 4-OCH_3, 4-CH_3, 2-NO_2, 4-NO_2

Scheme 5.1: Preparation of 2-hydroxy-5-(substituted phenylsulfonamido) benzoic acids

5.6 References:

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