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# A Deep Insight into the Application of Linear Free Energy Relationships (LFER) to Five Membered Heterocyclic Ring Systems: A Chemical Education Review for Graduate Students

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**Abstract** Hammett and Taft equations are applied to the acid dissociation equilibriums of 4 and 5-substituted furan, pyrrole, thiophene, tellurophene, isoxazole, pyrazole carboxylic acids, to solvolysis data of 4 and 5-substituted-2-furylmethylcarbinyl p-nitrobenzoates and to the permanganate ion oxidation of 5-substituted-2-furfurals. Excellent correlations were observed in these studies except in the case of 1-Me-4/5-X-3-pyrazole-COOH. In the case of 5-X-2-furoic, pyrrole, thiophene carboxylic acids only the substituent -COOH deviated from these correlations for which possible explanation is given in terms of intramolecular hydrogen bonding between the -COOH and the ring heteroatom and two types of intramolecular hydrogen bonding between -COOH and ring nitrogen atom and -COOH and H of NH of pyrrole. In the case of 3,5-X-4-isoxazole carboxylic acids the -$NH_2$ group at 5 position deviated for which the explanation in terms of H-bonding between -$NH_2$ and -COOH is given. Even the possibility of the formation of zwitterion is not ruled out. 5-X-1,2,3-triazole-4-carboxylic acids did not follow any LFER. The solvolysis rate constants of both 4 and 5-substituted-2-furylmethylcarbinyl p-nitrobenzoates correlated well with para substituent constants. Further the correlation with Brown's $\sigma^+$ values is still better. It is noteworthy that $MnO_4^-$ oxidation of 5-X-2-furfural correlated well with all the para, meta and ortho substituent constants. An attempt is made for the first time by our laboratory to apply the LFER to 5 membered ring systems with one heteroatom viz. pyrroles, two heteroatoms viz. pyrazoles, imidazoles, isoxazoles, three heteroatoms viz. the triazoles and four heteroatoms viz. tetrazoles. For the first time we have shown that the p$K_a$ values of N(1)H-acidities of 3-X-pyrroles, 3-X-pyrazoles, 4-X-pyrazoles, 4-X-imidazoles, 3-X-1,2,4-triazole, 4-X-1,2,3-triazole and 5-X-1,2,3,4-tetrazoles correlated well with Hammett $\sigma$ values.

***Keywords:*** *Hammett equation, Taft equation, 5-membered heterocycles*

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## 1. Introduction

Use of Hammett equation [1,2,3,4] dealing with *meta* and *para*-substituted benzene derivatives and Taft equation [5,6] dealing with *ortho*-substituted benzene derivatives in elucidating the reaction mechanisms in organic chemistry is indubitable. Since their introduction [1,2,3,4,5,6] numerous publications have appeared in literature [3,4] and are still being published to date. Application of Hammett equation and Taft equation to five membered aromatic heterocyclic ring systems was less commonly studied. The first application of Hammett law (not as an equation) [7] to furan ring was with 5-X-2-furoic acids [8]. But this was quoted in reference [9] as it was published in 1935 [10] even before the Hammett equation came into existence. In reference [9] by Freeman, it is surprising to see even a Hammett $\rho$ value was reported for the dissociation of 5-X-2-furoic acids without knowing Hammett $\sigma$ values because evaluation of Hammett $\sigma$ values took place only in 1937 [1]. In spite of numerous works on the application of Hammett and Taft equations in organic chemistry, their application to five membered ring systems did not find much place in chemistry research [8,11] except a one-page small publication appeared 55 years ago [9] and references cited there in. In this publication [9], the information of substituents in furan and thiophene derivatives used did not find a place. In the present work we have tried a deep insight with a total of 22 heterocyclic systems.

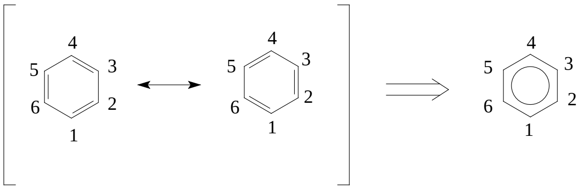
## 2. Methods

All the linear correlations were done using the KaleidaGraph software, Version 4.1, Reading, PA, USA. The chemical structures are drawn using ChemDraw software.

## 3. Results and Discussion

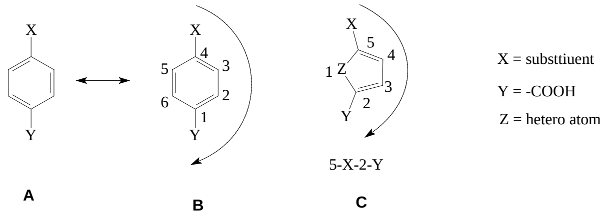
Visual observation of benzene and five membered heterocycles to look for the similarity of *para*, *meta* and *ortho*-carbons of benzene and 5th, 4th and 3rd carbons of five membered 5 or 4- or 3-(X)-2-(Y)-heterocycles:

As shown in scheme 1, it is known that all the six carbon atoms in the benzene ring are $sp^2$ hybridized and benzene is a planar hexagon molecule.



Scheme 1

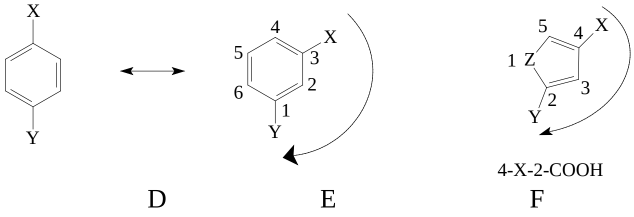
This explains an equal possibility for the formation of C1 - C2, C3 - C4, C5 - C6 π bonds or C2 - C3, C4 - C5, C6 - C1 π bonds. The hybrid structure is represented by inserting a circle in the ring as shown above in scheme 1. Hence, it explains the formation of two resonance structures proposed by Kekulé [12] and they will always be in dynamic equilibrium.



Scheme 2

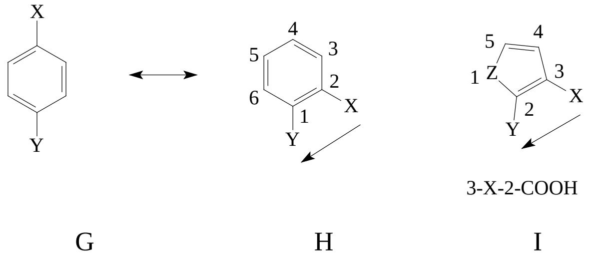
At any given point of time during the dynamic equilibrium process of benzene, the statistical percentage of existence of either **A** and **B** in scheme 2 is 50:50. Now comparing the structure **B** and the structure of the 5-X-2-Y-heterocycle **C** of scheme 2, the functional group Y and the substituent X are separated by one single bond and two double bonds or simply by two pairs of π-electrons in benzene ring **B** and the heterocycle **C**. Therefore, it can be assumed that the substituent electronic effects can be transmitted from carbon 4 bearing the substituent X to the functional group Y at carbon 1 of the **benzene**. This kind of situation of structure **C** where in the substituent electronic effects can be transmitted from carbon 5 bearing the substituent X to the functional group Y at carbon 2 of the heterocycle would be just like that of structure **B**. Therefore carbon 5 of the structure **C** of scheme 2 could best be assumed as a *para*-carbon.

Similarly, now comparing structure **E** and the structure of the 4-X-2-Y-heterocycle **F** of scheme 3, the functional group Y and the substituent X are separated by one single bond and one double bond or simply by a pair of π-electrons. It can be assumed that the substituent electronic effects can be transmitted from carbon 3 bearing the substituent X to the functional group Y at carbon 1 of the **benzene**. This kind of situation of structure **F** where in the substituent electronic effects can be transmitted from carbon 4 bearing the substituent X to the functional group Y at carbon 2 of the heterocycle would be just like that of structure **E**. Therefore, the carbon 4 of the structure **F** could best be assumed as a *meta*-carbon.



Scheme 3

Again, similar to the carbon 3 of the structure **I** could best be assumed as an *ortho*-carbon as shown in scheme 4.



Scheme 4

In fact, molecular orbital calculations and dipole moment data of 2-X-thiophene carboxylic acids suggested that the *para*, *meta* and *ortho* carbons of benzene correspond to 5, 4 and 3 carbons of the 5 membered heterocycle [13,14]. From the correlation of carbon-13 chemical shifts versus 1H-proton chemical shifts, in which the striking parallelism of the resonance shifts of the benzene and five membered heterocycle nuclei, implies that the resonances of both nuclei respond in a parallel way to the local π-electron density on the carbon atom [15]. And as such five membered heterocycles with one or two heteroatoms are planar pentagons. They have sp2 hybridized carbon atoms. They possess significant aromatic character resulting from the lone pair of electrons of the hetero atom/s and the two pairs of carbon π electrons.

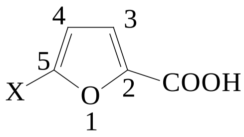
*Examples:*

To start with, tables 1-4 show the $pK_a$ and Hammett substituent constants data of 5-X-2-furoicacids, 5-X-2-pyrrole carboxylic acids, 5-X-2-thiophene carboxylic acids and 5-X-2-tellurophene carboxylic acids respectively and figures 1-12 show the corresponding Hammett and Taft plots.

*5-X-2-furoic acids:*

Below is table 1 with the data of 5-X-2-furoic acids.

**Table 1. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 5-X-2-furoicacids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H* | 3.12 | 0.00 | 0.00 | 0.49 | https://en.wikipedia.org/wiki/2-Furoic_acid |
| 2 | $NO_2$* | 2.06 | 0.80 | 0.71 | 4.00 | https://m.chemicalbook.com/ProductMSDSDetailCB0150392_EN.htm |
| 3 | Me* | 3.41 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2262105.htm |
| 4 | Et | 3.38 | -0.15 | -0.07 | -0.10 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB41117428.htm |
| 5 | Cl* | 2.84 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB51091079.htm |
| 6 | COOH | 2.28 | 0.43 | 0.36 | 2.08 | https://en.wikipedia.org/wiki/2,5-Furandicarboxylic_acid |
| 7 | $CF_3$ | 2.44 | 0.54 | 0.43 | 2.55 | https://m.chemicalbook.com/ChemicalProductProperty_EN_CB8506689.htm |
| 8 | $CH_2OH$ | 3.11 | 0.08 | 0.08 | 0.55 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB7188710.htm |

*Similar p$K_a$ values are reported in reference 10.

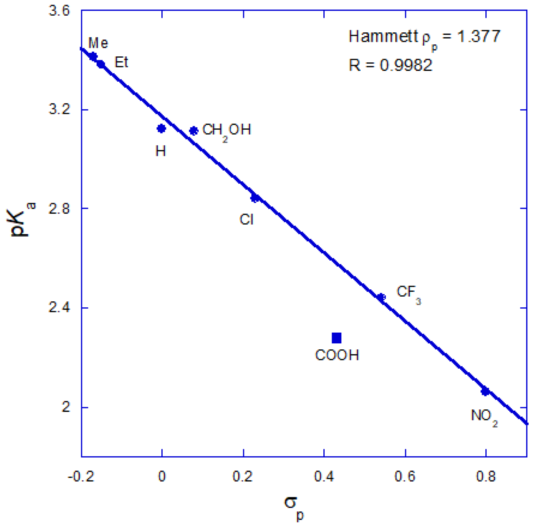


**Figure 1.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-substituted-2-furoic acids

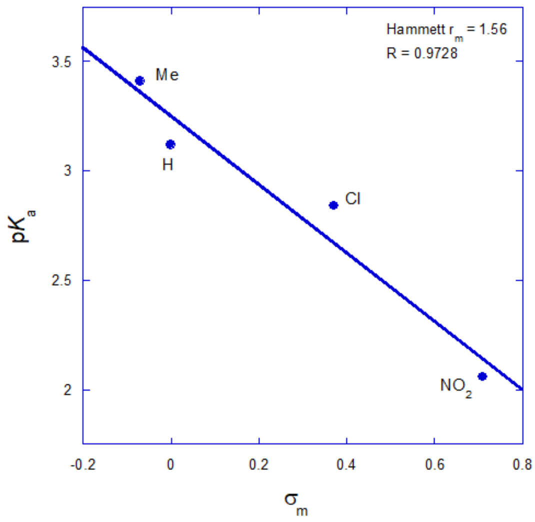


**Figure 2A.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-substituted-2-furoic acids

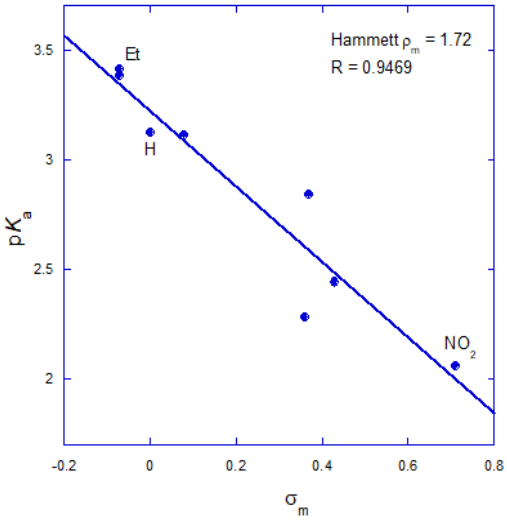


**Figure 2.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-substituted-2-furoic acids

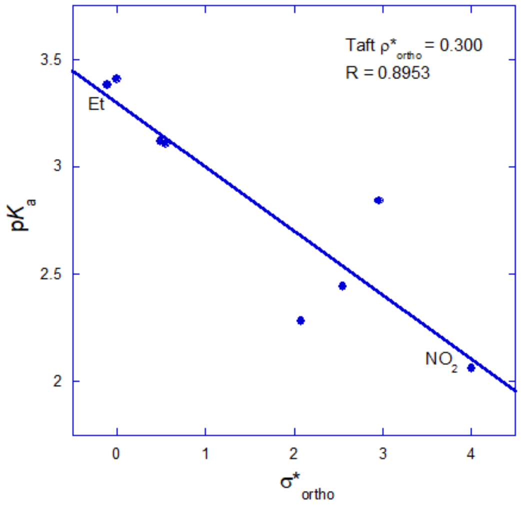
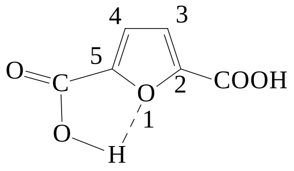


**Figure 3.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-substituted-2-furoic acids

In figures 1-3, it is clear from the correlation coefficients, the p$K_a$ data of 5-X-2-furoic acids correlated well (Hammett $\rho_p$ = 1.377, R = 0.9982) with Hammett $\sigma_p$ values with a deviation of the lone -COOH substituent. This could be due to the weak hydrogen bonding interaction as shown below in scheme 5 in one of the 2-furoic acid (trans) conformers between H of -COOH and O of the ring [16]. Therefore, good correlation of p$K_a$ data with *para*-substituent constants, the 5 position of the 2-furoic acid is best assumed as *para*-position.

Freeman reported the Hammett $\rho_m$ is for 5-X-2-furoic acids as 1.49 with a correlation coefficient of 0.943 taking the data from Catlin reference 10 [9]. There is no explanation in Freeman's paper how he has achieved these values. But we replotted here in this work (starred data from table 1, figure 2A), taking the data from the journal *Iowa State Coll. J. Sci.*, [10]. The Hammett $\rho_m$ is coming out to be 1.56 with a correlation coefficient of 0.9728 assuming 5-position as meta.

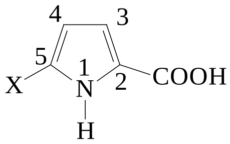


Scheme 5

*5-X-2-pyrrole carboxylic acids:*

Below is the table 2 with the data of 5-X-2-pyrrole carboxylic acids.

**Table 2. p$K_a$, Hammett σp, σm and Taft $\sigma^*_{ortho}$ values of 5-X-2-pyrrole carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^*_{ortho}$ | |
| 1 | H | 4.50 | 0.00 | 0.00 | 0.49 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB9414565.htm |
| 2 | Me | 4.73 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2803461.htm |
| 3 | COOH | 3.47 | 0.43 | 0.36 | 2.08 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB02105716.htm |
| 4 | $CF_3$ | 3.63 | 0.54 | 0.43 | 2.55 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB03172337.htm |
| 5 | $C_6H_5$ | 4.45 | -0.01 | 0.06 | 0.60 | https://m.chemicalbook.com/ProductChemicalPropertiesCB1447413_EN.htm |
| 6 | $NO_2$ | 3.22 | 0.80 | 0.71 | 4.00 | p$K_a$ values are from F. Fringuelli, G. Marino and G. Savelli, Tetrahedron, vol. 25, page 5815, 1969 |
| 7 | Br | 4.17 | 0.23 | 0.39 | 2.84 | |
| 8 | Cl | 4.32 | 0.23 | 0.37 | 2.96 | |

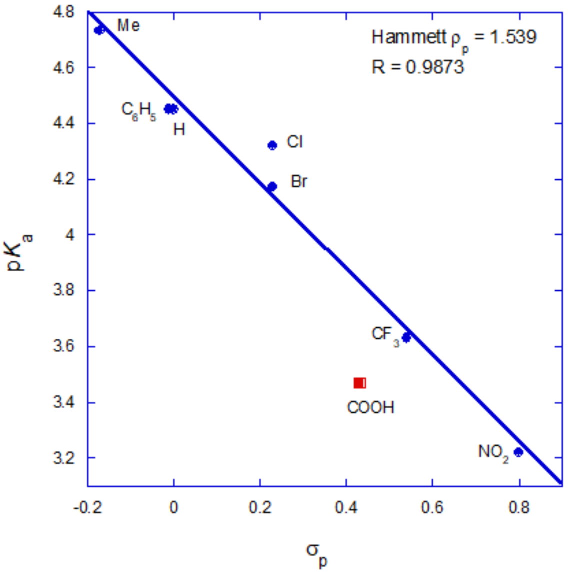


**Figure 4.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-substituted-2-pyrrole carboxylic acids

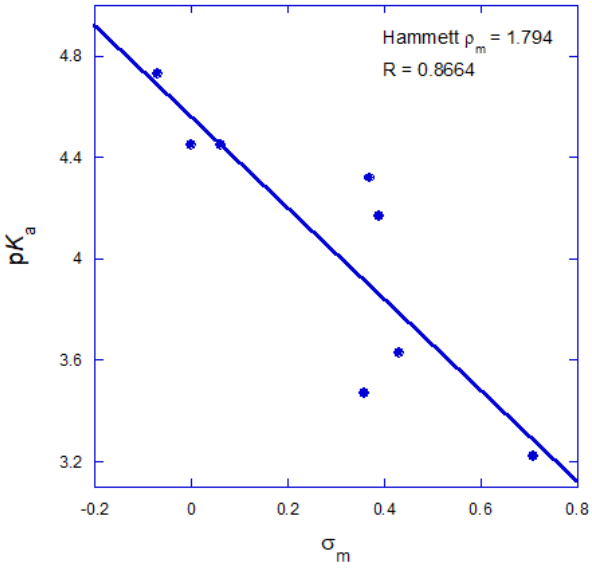


**Figure 5.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-substituted-2-pyrrole carboxylic acids

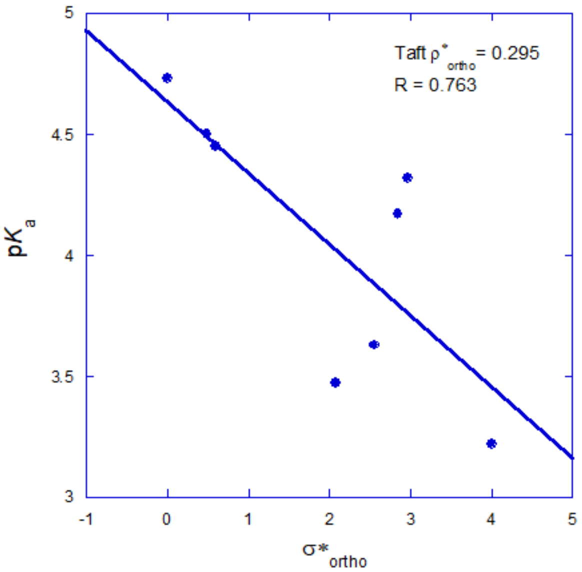
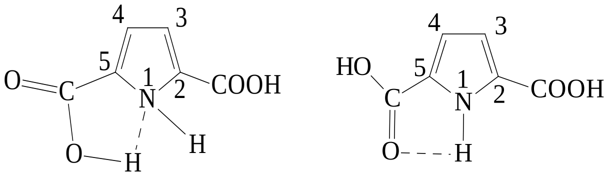


**Figure 6.** Plot of p*K*a versus Taft $\sigma^{*}_{ortho}$ for 5-substituted-2-pyrrole carboxylic acids

In the figures 4-6, it is clear from the correlation coefficients, the p$K_a$ data of 5-X-2-pyrrole carboxylic acids correlated well (Hammett $\rho_p$ = -1.539, R = 0.9873) with Hammett $\sigma_p$ values with a deviation of again the lone -COOH substituent. This could be due to two types of intramolecular hydrogen bonding interaction as shown below in scheme 6 [17]. Therefore the 5 position of the 2-pyrrole carboxylic acid is best assumed as *para*-position.

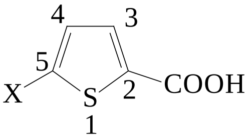


Scheme 6

*5-X-2-thiophene carboxylic acids:*

Below is table 3 with the data of 5-X-2-*thiophene* carboxylic acids.

**Table 3. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^{*}_{ortho}$ values of 5-X-2-thiophene carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^{*}_{ortho}$ | |
| 1 | H | 3.49 | 0.00 | 0.00 | 0.49 | https://www.chemicalbook.com/ProductChemicalPropertiescb1778926_EN.htm |
| 2 | $NO_2$ | 2.69 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2197443.htm |
| 3 | Me | 3.71 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB3183843.htm |
| 4 | Cl | 3.32 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB3189269.htm |
| 5 | COOH | 2.76 | 0.43 | 0.36 | 2.08 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB9224515.htm |
| 6 | MeO | 3.80 | -0.27 | 0.12 | 1.81 | p$K_a$ values are from Anthony R. Butler, *J. Chem. Soc. (B)*, page 867, 1970 |
| 7 | Et | 3.70 | -0.15 | -0.07 | -0.10 | |
| 8 | Br | 3.19 | 0.23 | 0.39 | 2.84 | |

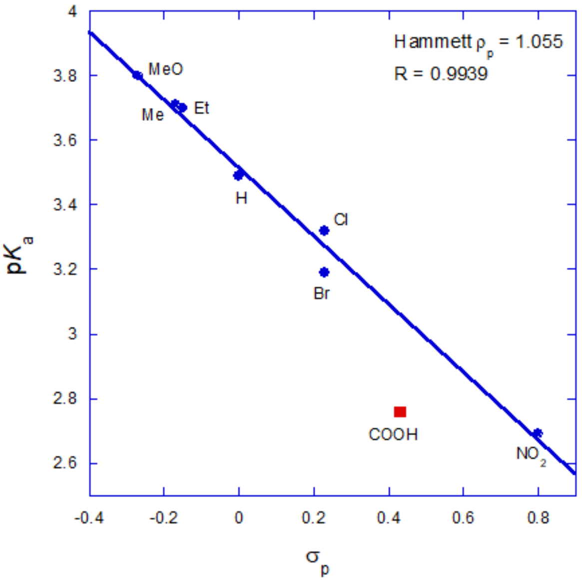


**Figure 7.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-X-2-thiophene carboxylic acids

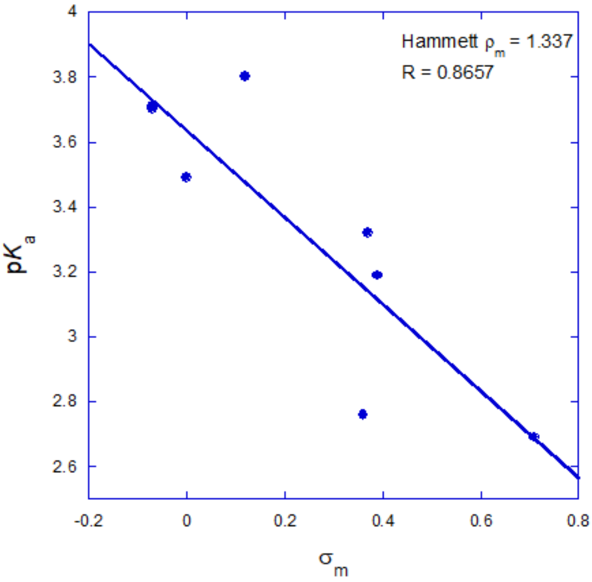


**Figure 8.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-X-2-thiophene carboxylic acids

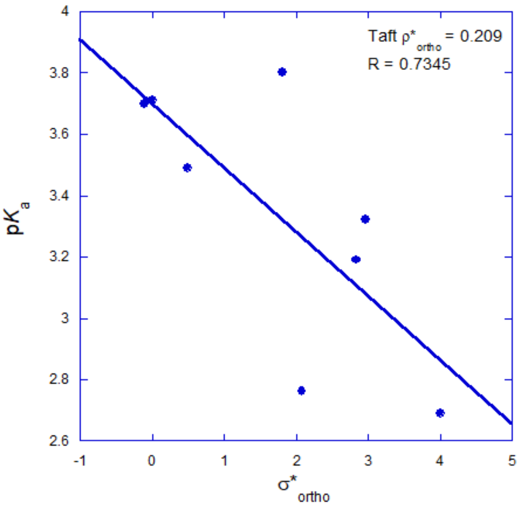
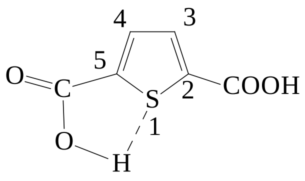


**Figure 9.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-2-thiophene carboxylic acids

In the figures 7-9, it is clear from the correlation coefficients, the p$K_a$ data of 5-X-2-thiophene carboxylic acids correlated well (Hammett $\rho_p$ = -1.055, R = 0.9939) with Hammett $\sigma_p$ values with a deviation of again the lone -COOH substituent. This could be due to the week intramolecular hydrogen bonding interaction of H of COOH with S of thiophene ring as shown below in scheme 7. It is revealed in some protein interactions that though sulfur is a moderately good H-bond donor but also a week H-bond acceptor [18]. Therefore, again the 5 position of the 2-thiophene carboxylic acid is best assumed as *para*-position.

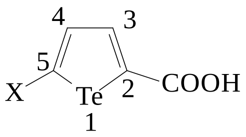


Scheme 7

*5-X-2-tellurophen carboxylic acids:*

Below is table 4 with the data of 5-X-2-tellurophene carboxylic acids.

**Table 4. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 5-X-2-tellurophene carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 3.97 | 0.00 | 0.00 | 0.49 | p$K_a$ values are from F. Fringuelli, G. Marino," and A. Taticchi, J. Chem. Soc., perkin II, page 1738, 1972 |
| 2 | Me | 4.16 | -0.17 | -0.07 | 0.00 | |
| 3 | Ac | 3.36 | 0.50 | 0.38 | 1.65 | |
| 4 | COOH | 3.11 | 0.43 | 0.36 | 2.08 | |
| 5 | $COO^-$ | 4.24 | 0.00 | -0.10 | -1.06 | |

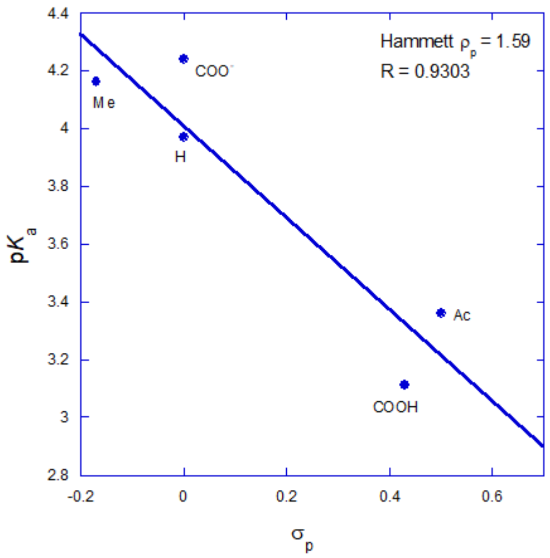


**Figure 10.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-X-2-tellurophene carboxylic acids

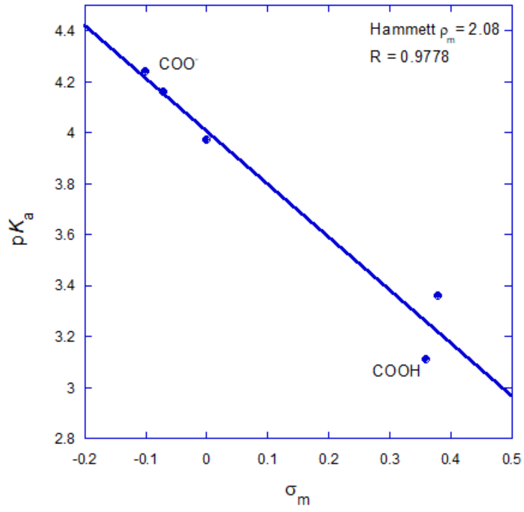


**Figure 11.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-X-2-tellurophene carboxylic acids

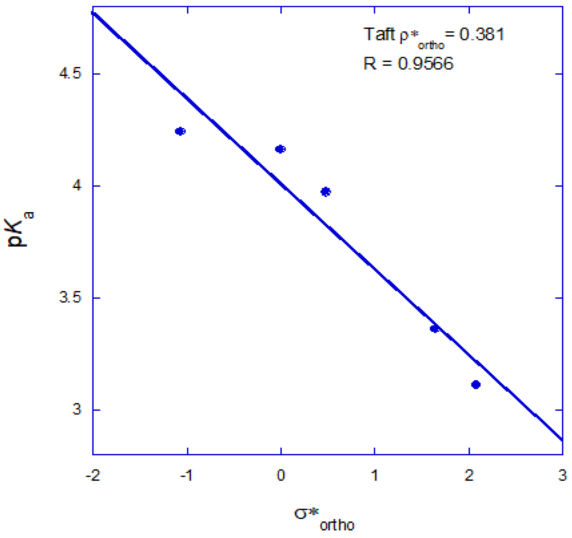
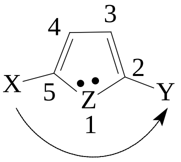


**Figure 12.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-2-tellurophene carboxylic acids

In the figures 10-12, it is clear from the correlation coefficients 0.9303, 0.9778 and 0.9566 the p$K_a$ data of 5-X-2-tellurophene carboxylic acids did not correlate well with any of the σ values. And certainly, the correlation with $\sigma_p$ values is very poor (R = 0.9303). However, though the correlation coefficient of p$K_a$ values versus $\sigma^{*}_{ortho}$ is less than that of with $\sigma_m$ the points in figure 12 are evenly distributed on either side of the line of fit. Taking this argument into confidence the correlation of p$K_a$ values with $\sigma^{*}_{ortho}$ needs a different explanation which is as follows: In benzene if we observe the substituent *ortho* to the functional group is in principle separated by a double bond again keeping in view of the statistical weight of the dynamic equilibrium of benzene or it simply needs a pair of π electrons (Scheme 4, **H**). In five membered ring system of 5-X-2-tellurophene carboxylic acid that lone π electron pair can be seen with tellurium. As tellurium has a maximum polarizability and bigger in size than either sulfur or oxygen [19] the substituent effect more easily be transmitted from the substituent to the functional group via tellurium rather than π electron pair of the five membered ring as shown below in scheme 8. And this could be the reason that the correlation with higher $\sigma_m$ is better than $\sigma_p$ and $\sigma^{*}_{ortho}$.



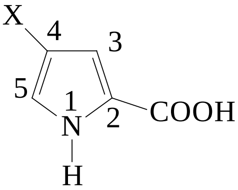
5-X-2-COOH

Scheme 8

*4-X-2-pyrrole carboxylic acids:*

Below is theTable 5 with p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^{*}_{ortho}$ values of 4-X-2-pyrrole carboxylic acids

**Table 5. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^{*}_{ortho}$ values of 4-X-2-pyrrole carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^{*}_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 4.50 | 0.00 | 0.00 | 0.49 | p$K_a$ values are from F. Fringuelli, G. Marino and G. Savelli, Tetrahedron, vol. 25, page 5815 |
| 2 | Me | 4.60 | -0.17 | -0.07 | 0.00 | |
| 3 | $NO_2$ | 3.37 | 0.80 | 0.71 | 4.00 | |
| 4 | Br | 4.06 | 0.23 | 0.39 | 2.84 | |
| 5 | Cl | 4.07 | 0.23 | 0.37 | 2.96 | |

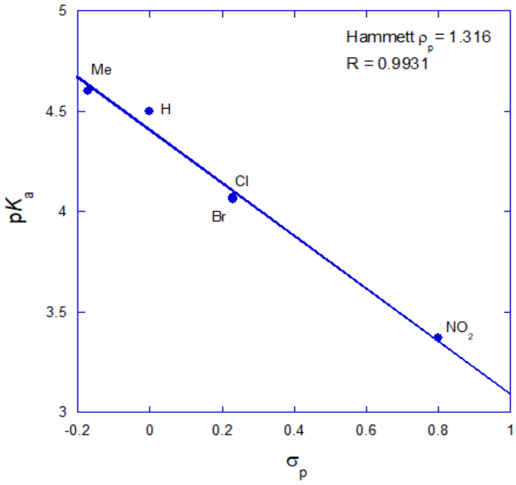


**Figure 13.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 4-X-2-pyrrole carboxylic acids

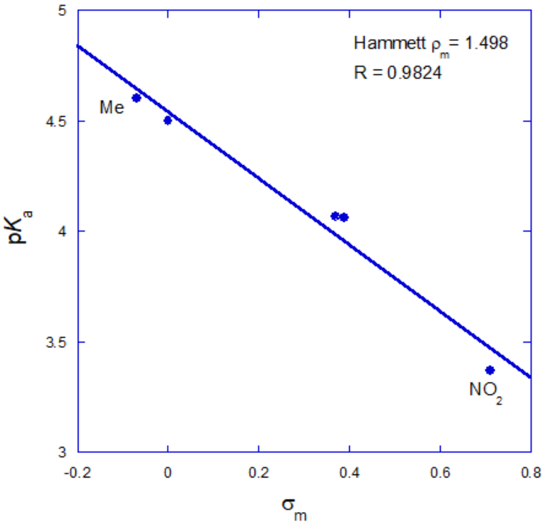


**Figure 14.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 4-X-2-pyrrole carboxylic acids

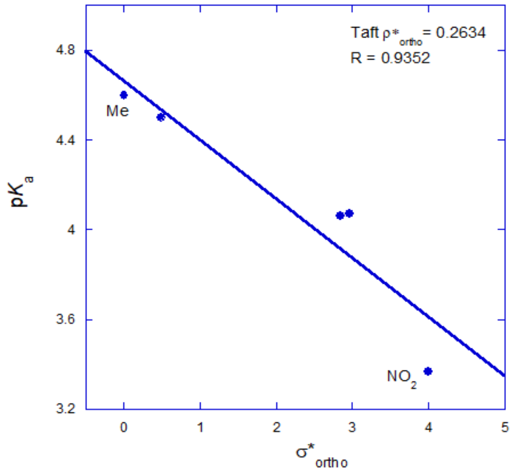
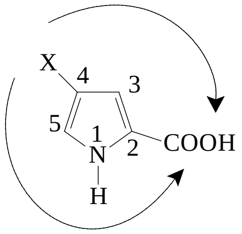


**Figure 15.** Plot of p$K_a$ versus Taft $\sigma^{*}_{ortho}$ for 4-X-2-pyrrole carboxylic acids

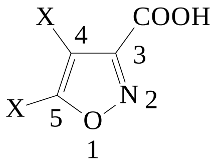
In figures 13-15 it is noteworthy to see that p$K_a$ values of 4-X-2-pyrrole carboxylic acids correlate well with both $\sigma_p$ and $\sigma_m$ substituent constants. This is best visualized in scheme 9. The transmission of substituent effect from X to COOH can take place in two directions one via carbon 5 and ring nitrogen and the other via carbon 3 as shown in scheme 9. If X behaves as a *para*-substituent, what it needs is a pair of two double bonds (see structure **B** of scheme 2) or a double bond and a pair of π electrons or a pair of non-bonded electrons. A pair of non-bonded electrons is from nitrogen. Therefore, the correlation with both $\sigma_m$ and $\sigma_p$ are good (figures 13 and 14).



Scheme 9

### *4,5-X-3-isoxazole carboxylic acids*

**Table 6. p$K_a$, Hammett $\sigma_m$ + Taft $\sigma^*_{ortho}$values of 4,5-X-3-isoxazole carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett $\sigma_m$ + Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|
| 1 | H | 3.39 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2311713.htm |
| 2 | 5-Me | 3.46 | -0.07 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2156853 |
| 3 | 4-$NO_2$-5-Me | 1.02 | 4.0 + (-0.07) = 3.93 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB62457633.htm |
| 4 | 4,5-diMe | 3.14 | -0.07 + 0.00 = -0.07 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB71119463.htm |
| 5 | 5-($C_6H_4$-4-$CH_3$) | 3.33 | 0.06 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4505376.htm |

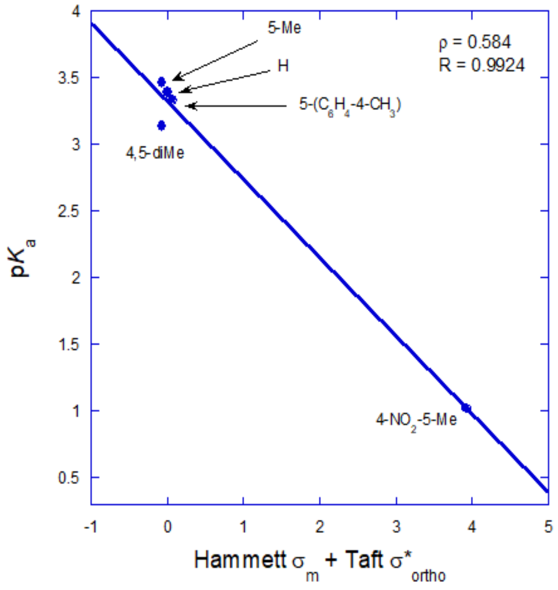
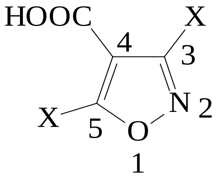


**Figure 16.** Plot of p$K_a$ versus Hammett $\sigma_m$ + Taft $\sigma^*_{ortho}$ for 4,5-X-3-isoxazole carboxylic acids

p$K_a$ values of 4,5-substituted-3-isoxazole carboxylic acids correlated well with (Hammett $\sigma_m$ + Taft $\sigma^*_{ortho}$) (Table 6, figure 16) which indicates that the carbon 4 and carbon 5 of 3-isoxazole carboxylic acid just resemble as *ortho* and *meta* substituents respectively to COOH.

### *3,5-X-4-isoxazole carboxylic acids:*

**Table 7. p$K_a$, Taft $\sigma^*_{ortho}$ values of 3,5-X-4-isoxazole carboxylic acids**



| Sl. No. | X | p$K_a$ | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|
| 1 | 3-Me | 2.90 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB5332030.htm |
| 2 | 5-Me | 2.85 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB8342928.htm |
| 3 | 5-Et | 2.81 | -0.10 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4320960.htm |
| 4 | 3-Br-5-Me | 1.53 | 2.84 + 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB51275509.htm |
| 5 | 5-$NH_2$-3-Me | 3.57 | 0.62 + 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB0511575.htm |

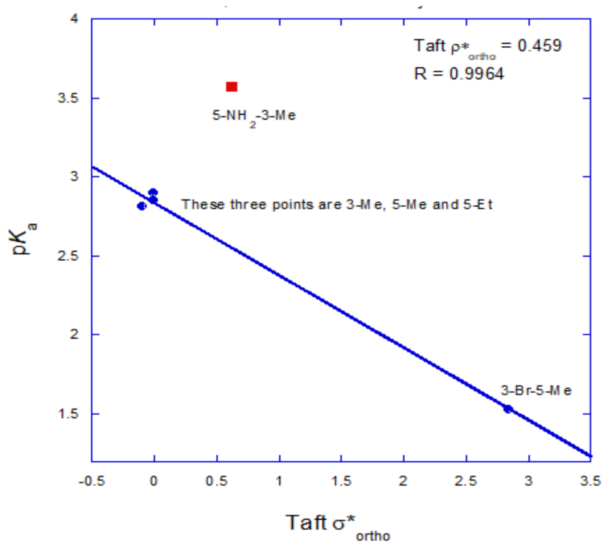
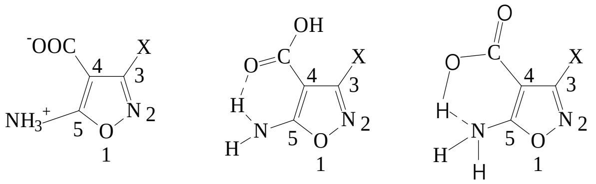


**Figure 17.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 3,5-X-4-isoxazole carboxylic acids

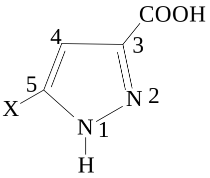
In 3,5-X-4-isoxazole carboxylic acids, the substituent X on either side of the functional group –COOH may just act as it is on ortho position. The deviation of the point of 5-$NH_2$-3-Me in the correlation of p$K_a$ values with Taft $\sigma^*_{ortho}$ of 3,5-X-4-isoxazole carboxylic acid may be due to the formation of a zwitterion or two types of intramolecular H-bonding as shown in scheme 10 below.



Scheme 10

### 5-X-3-pyrazole carboxylic acids

**Table 8. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and $\sigma^*_{ortho}$ values of 5-X-3-pyrazole carboxylic acids**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 3.98 | 0.00 | 0.00 | 0.49 | https://www.chemicalbook.com/ProductList_en.aspx?kwd=3-pyrazolecarboxylic%20acid |
| 2 | Me | 4.04 | -0.17 | -0.07 | 0.00 | D. D. Perrin, B. Dempsey and E. P. Serjeant, p*Ka* prediction of organic acids and bases, Springer Science & Business media, 1981, page 85 |
| 3 | $NO_2$ | 3.22 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB0223469.htm |
| 4 | Br | 3.59 | 0.23 | 0.39 | 2.84 | https://m.chemicalbook.com/ChemicalProductProperty_EN_CB82594026.htm |
| 5 | Cl | 3.61 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB91501525.htm |

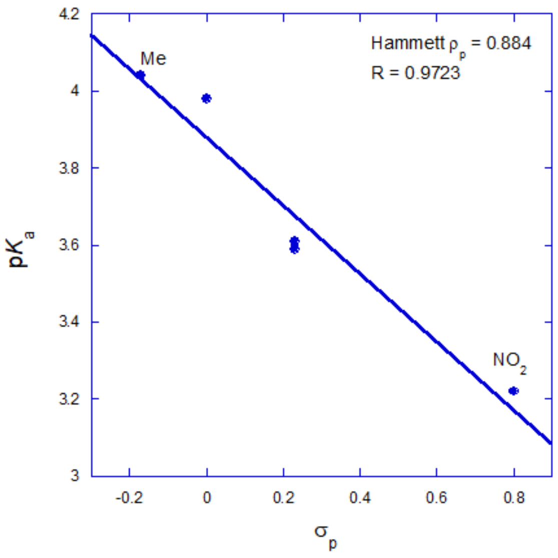


**Figure 18.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-X-3-pyrazole carboxylic acids

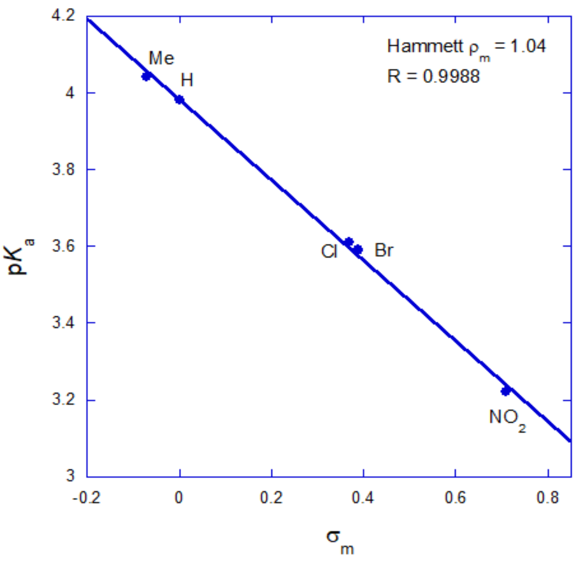


**Figure 19.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-X-3-pyrazole carboxylic acids

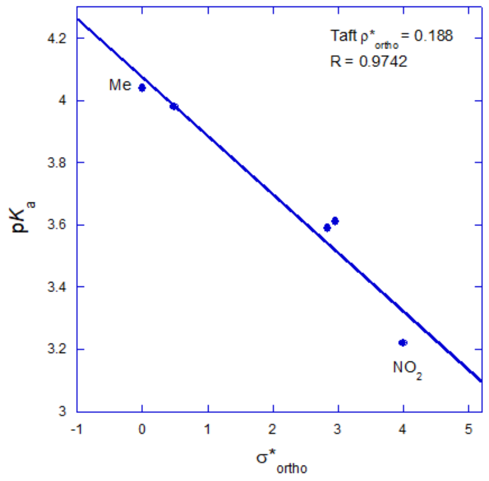
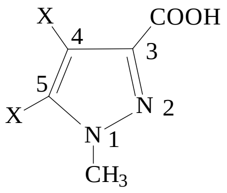


**Figure 20.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-3-pyrazole carboxylic acids

In figures 18-20, it is clear from the correlation coefficients, the p$K_a$ data of 5-X-3-pyrazole carboxylic acids correlated well (Hammett $\rho_m$ = -1.04, R = 0.9988) with Hammett $\sigma_m$ values. Therefore the 5 position of the 3-pyrazole carboxylic acid is best assumed as *meta*-position.

*1-Me-4/5-X-3-pyrazole carboxylic acids:*

**Table 9.** p$K_a$, Hammett $\sigma_m$ values of 1-Me-4/5-X-3-pyrazole carboxylic acids



| Sl. No. | X | p$K_a$ | Hammett $\sigma_m$ | Literature for p$K_a$ values |
|---|---|---|---|---|
| 1 | 4-Me | 3.82 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB42510213.htm |
| 2 | 5-Me | 5.12 | -0.07 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB1410011.htm |
| 3 | 5-Et | 4.12 | -0.07 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB0160148.htm |

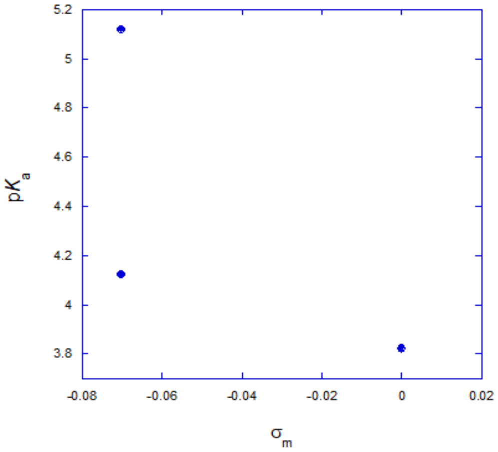
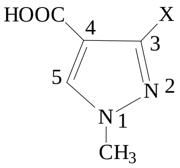


**Figure 21.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 1-Me-4/5-X-3-pyrazole carboxylic acids

*1-Me-3-X-4-pyrazole carboxylic acids:*

**Table 10. p$K_a$, Taft $\sigma^*_{ortho}$ values of 1-Me-3-X-4-pyrazole carboxylic acids**



| Sl. No. | X | p$K_a$ | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|
| 1 | H | 4.02 | 0.49 | Robert G. Franz, *AAPS Pharmsci.*, 2001; 3 (2) article 10 (http://www.pharmsci.org/) |
| 2 | $CF_3$ | 3.79 | 2.61 | |
| 3 | $CH_3$ | 4.52 | 0.00 | |

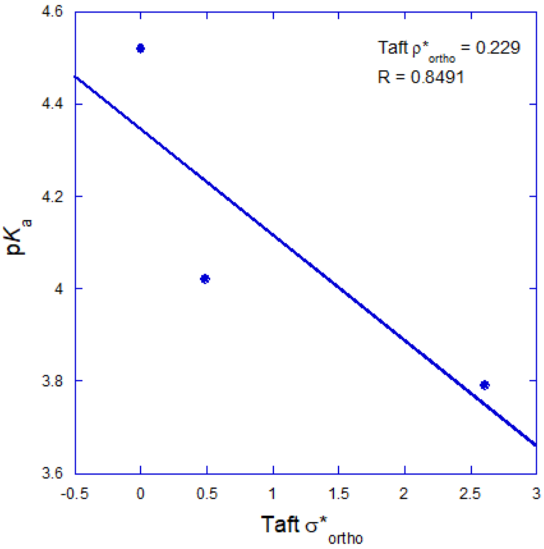
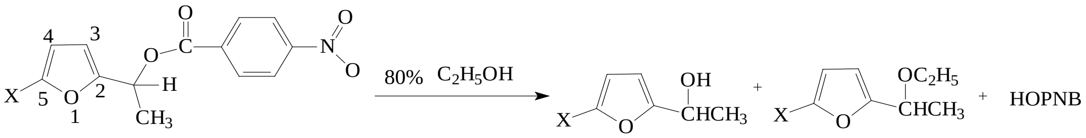


**Figure 22.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 1-Me-3-X-4-pyrazole carboxylic acids

From the figures 21 and 22 with limited data it is hard to draw any conclusion.

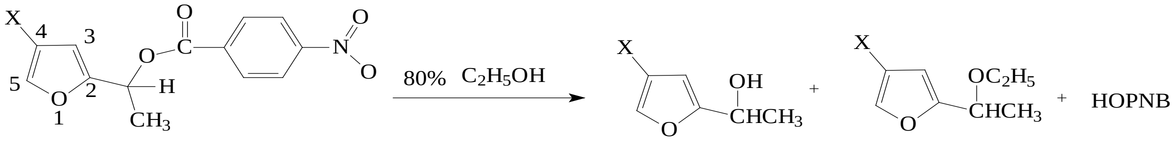
*Solvolysis data for 5-X-2-furylmethylcarbinyl p-nitrobenzoates:*

**Table 11. Solvolysis data for 5-X-2-furylmethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C**



| Sl. No. | X | $k_{relative}$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for $k_{relative}$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | Me | 212 | -0.17 | -0.07 | 0.00 | $k_{relative}$ values are from Donald S. Noyce and Gary V. Kaiser, *J. Org. Chem.*, vol. 34, page 1008, 1969 |
| 2 | H | 1.00 | 0.00 | 0.00 | 0.49 | |
| 3 | Br | 0.271 | 0.23 | 0.39 | 2.84 | |
| 4 | $COOC_2H_5$ | 3.70 X $10^{-4}$ | 0.45 | 0.37 | 2.12 | |
| 5 | $NO_2$ | 1.45 X $10^{-6}$ | 0.80 | 0.71 | 4.00 | |

**Table 12. Solvolysis data for 4-X-2-furylmethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C**



| Sl. No. | X | $k_{relative}$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for $k_{relative}$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 1.00 | 0.00 | 0.00 | 0.49 | $k_{relative}$ values are from Donald S. Noyce and Gary V. Kaiser, J. Org. Chem., vol. 34, page 1008, 1969 |
| 2 | Br | 4.76 X $10^{-3}$ | 0.23 | 0.39 | 2.84 | |
| 3 | $COOC_2H_5$ | 7.67 X $10^{-4}$ | 0.45 | 0.37 | 2.12 | |

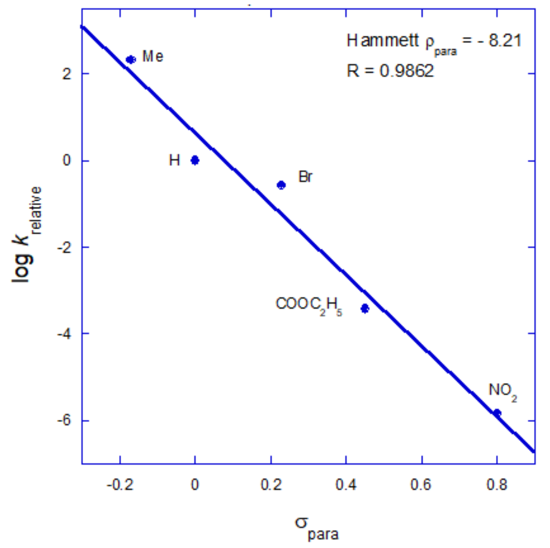


**Figure 23.** Plot of log $k_{relative}$ versus Hammett $\sigma_p$ for 5-X-2-furylmethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

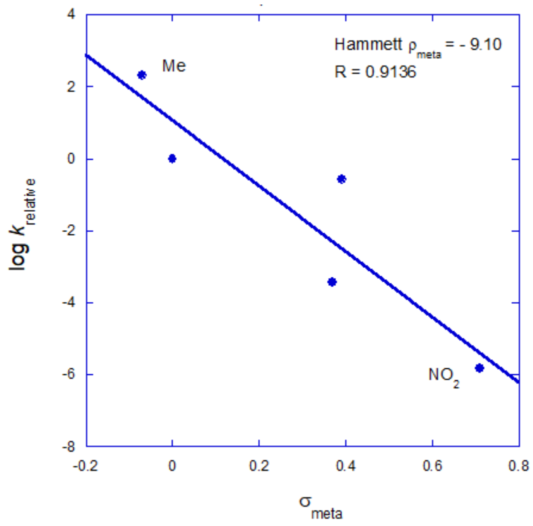


**Figure 24.** Plot of log $k_{relative}$ versus Hammett $\sigma_m$ for 5-X-2-furymethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

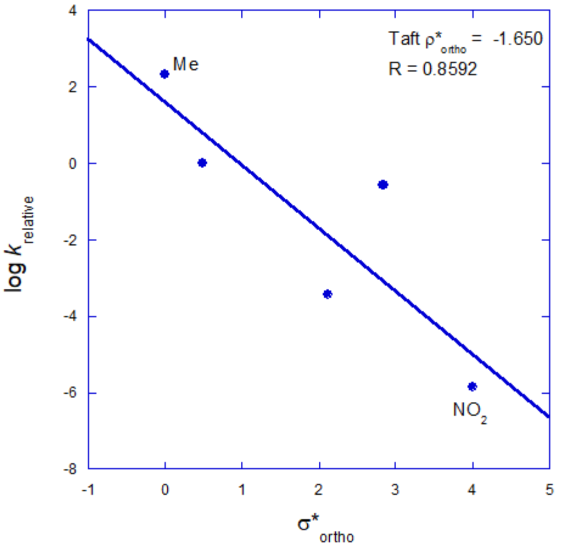


**Figure 25.** Plot of log $k_{relative}$ versus Taft $\sigma^*_{ortho}$ for 5-X-2-furylmethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

*4-X-2-furylmethylcarbinyl p-nitrobenzoates:*

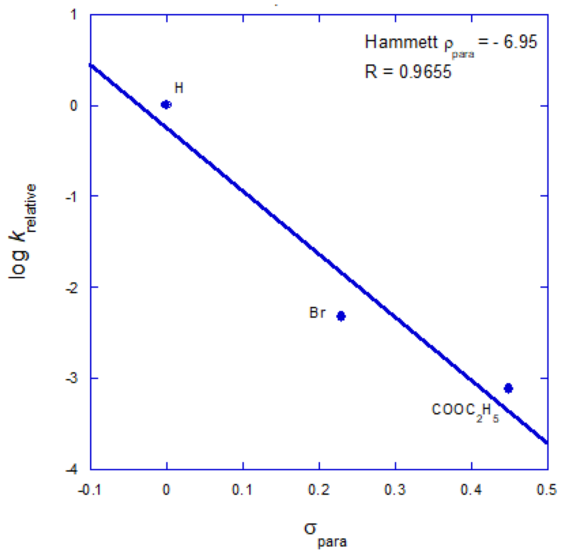


**Figure 26.** Plot of log $k_{relative}$ Versus Hammett $\sigma_p$ for 4-X-2-furymethycarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

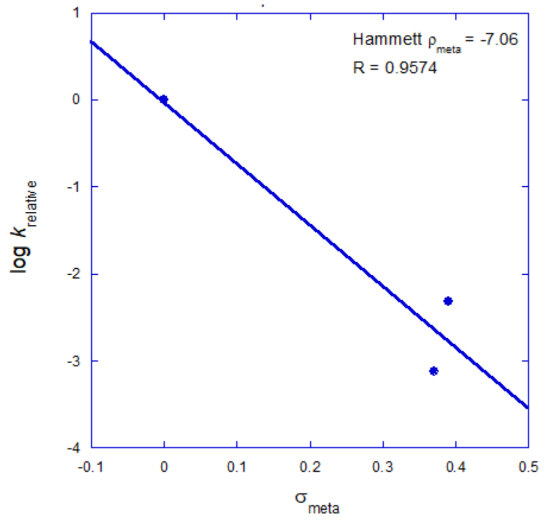


**Figure 27.** Plot of log $k_{relative}$ versus Hammett $\sigma_m$ for 4-X-2-furylmethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25 °C

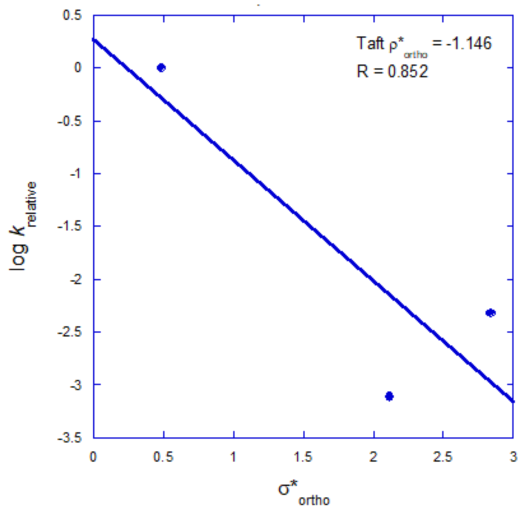


**Figure 28.** Plot of log $k_{relative}$ versus Taft $\sigma^*_{ortho}$ for 4-X-2-furymethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

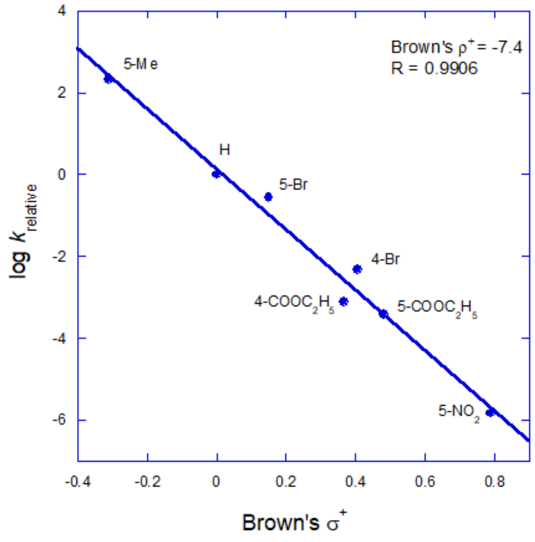
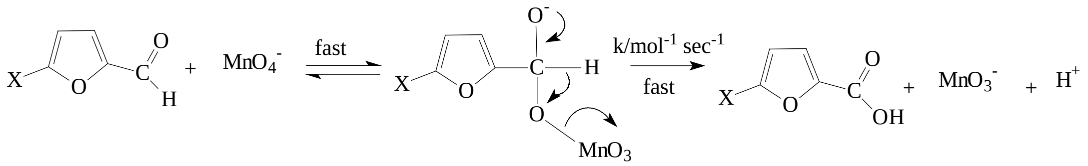


**Figure 29.** Plot of log $k_{relative}$ versus Brown's $\sigma^+$ for 4-X-2-furymethylcarbinyl p-nitrobenzoates in 80% aqueous ethanol at 25°C

Brown's $\sigma^+$ values are from Y. Okamoto and H. C. Brown *J. Am. Chem. Soc.*,80, 4979 (1958)

The rate constants $k_{relative}$ of the solvolysis of 5-X-2-furylmethylcarbinyl p-nitrobenzoates and 4-X-2-furylmethylcarbinyl p-nitrobenzoates were originally treated with Brown's $\sigma^+$ values [20]. As the $\sigma^+$ values are free from the mesomeric effects, the correlation was good irrespective of the position of the substituent [20]. In the insight of the present work, we have tried the correlation of the rate data of the solvolysis of 5-X-2-furylmethylcarbinyl p-nitrobenzoates and 4-X-2-furylmethylcarbinyl p-nitrobenzoates separately assuming 5-X substituted derivatives as *para*-substituents and 4-X substituted derivatives as *meta*-substituents because it was shown that the 5 and 4 positions of 5-membered heterocycles just correspond to the *para* and *meta* positions of benzene ring [13,14]. Consequently, the rates of solvolysis of 5-X-2-furylmethylcarbinyl p-nitrobenzoates correlated well with $\sigma_{para}$ (figure 23) with a correlation coefficient of 0.9862 and the rates of solvolysis of 4-X-2-furylmethylcarbinyl p-nitrobenzoates correlated well with $\sigma_{meta}$ (figure 27) with a correlation coefficient of 0.9574.

**Table 13. Rate data of $MnO_4^-$ oxidation of 5-X-furfurals in aqueous neutral medium**



| Sl. No. | X | Hammett | | Taft $\sigma^*_{ortho}$ | $k$/mol$^{-1}$ sec$^{-1}$ | log $k$ | Literature for $k$ values |
|---|---|---|---|---|---|---|---|
| | | $\sigma_p$ | $\sigma_m$ | | | | |
| 1 | Me | -0.17 | -0.07 | 0.00 | 2.60 | 0.415 | F. Freeman, J. B. Brant, N. B. Hester, A. A. Kamego, M. Kasner, T. G. Mclaughlin, and E. W. Paull, *The Journal of Organic Chemistry*, vol. 35, page 985, 1970 |
| 2 | H | 0.00 | 0.00 | 0.49 | 2.70 | 0.431 | |
| 3 | $NO_2$ | 0.81 | 0.71 | 4.00 | 47.8 | 1.679 | |

$MnO_4^-$ oxidation of 5-X-furfurals:

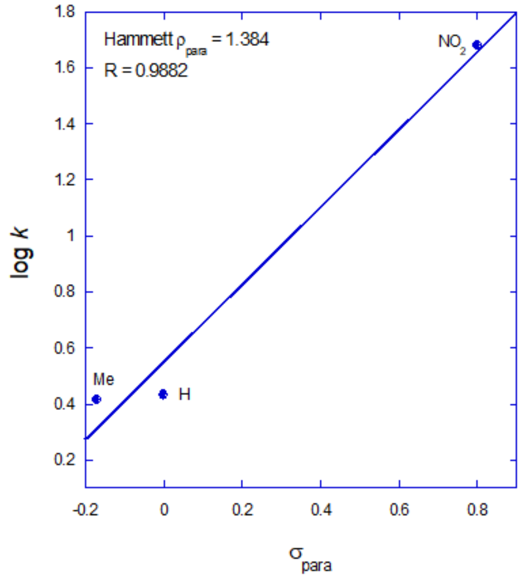


**Figure 30.** Plot of log k versus Hammett $\sigma_p$ for $MnO_4^-$ oxidation of 5-X-2-furfurals in aqueous medium at 25°C

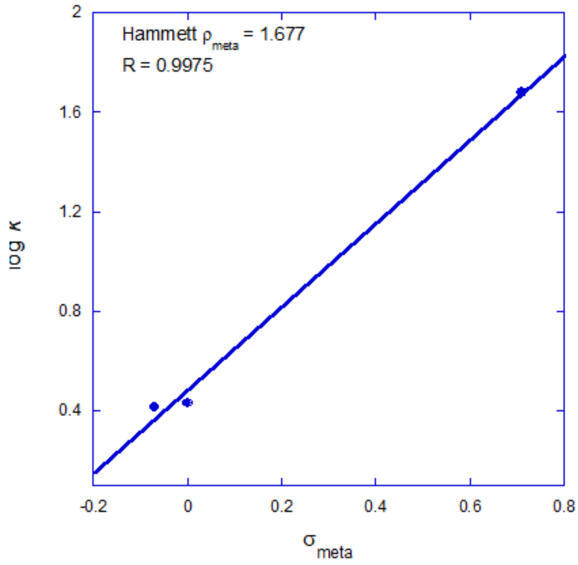


**Figure 31.** Plot of log k versus Hammett $\sigma_m$ for $MnO_4^-$ oxidation of 5-X-2-furfurals in aqueous medium at 25°C

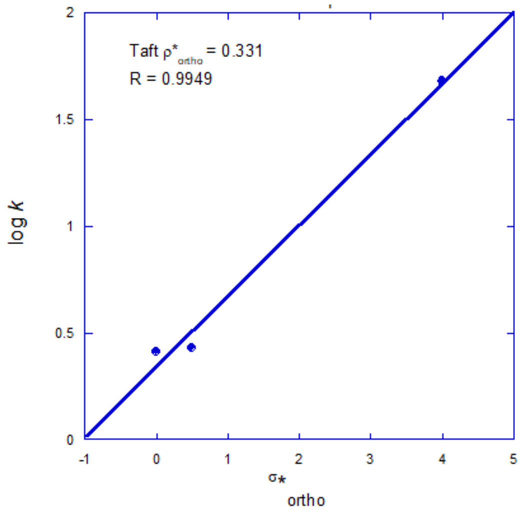
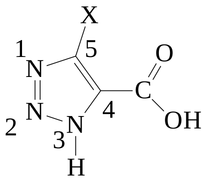


**Figure 32.** Plot of log *k* versus Taft $\sigma^*_{ortho}$ for $MnO_4^-$ oxidation of 5-X-2-furfurals in aqueous medium at 25°C

Rate data of $MnO_4^-$ oxidation of 5-X-furfurals in aqueous neutral medium [21] correlated well with all the Hammett and Taft substituent constants for which we could not give any explanation. Yet the correlation with Hammett $\sigma_{meta}$ is slightly better (R = 0.9975) than the other two. This could be possible as the substituent and the functional group are separated by a pair of non-bonded electrons which come from oxygen (see scheme 3 structure **E** and **F**).However, Freeman reported [21] the Hammett plot log $k_2$ versus σfor $MnO_4^-$ oxidation of 5-X-furfurals in aqueous neutral and basic medium with substituents X = H, Me, n-Bu, Et, Cl and Br. Though $MnO_4^-$ oxidation of 5-X-furfurals with X = $NO_2$ studied but not shown in the Hammett plot. But the data is not available in this publication except the Hammett plot. Therefore, it was not possible to analyze the data in detail in the present study.

*5-X-1, 2, 3-triazole-4-carboxylic acids:*

**Table 14. p$K_a$, Hammett Taft $\sigma^*_{ortho}$ values of 5-X-1,2,3-triazole-4-carboxylic acids**



| Sl. No. | X | p$K_a$ | Taft $\sigma^*_{ortho}$ | F[a] (field effect contribution) | R[a] (resonance effect contribution) | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| 1 | H | 3.22 | 0.49 | 0.00 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB1683581.htm |
| 2 | COOH | 1.86 | 2.08 | 0.44 | 0.66 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6756385.htm |
| 3 | $CF_3$ | 2.76 | 2.61 | 0.64 | 0.76 | https://m.chemicalbook.com/ChemicalProductPropertyEN_CB83172313.htm |

[a] F and R values are from J. March, Advanced organic Chemistry, 4th Edition, Wiley-Interscience, New York, 1992, page 284.

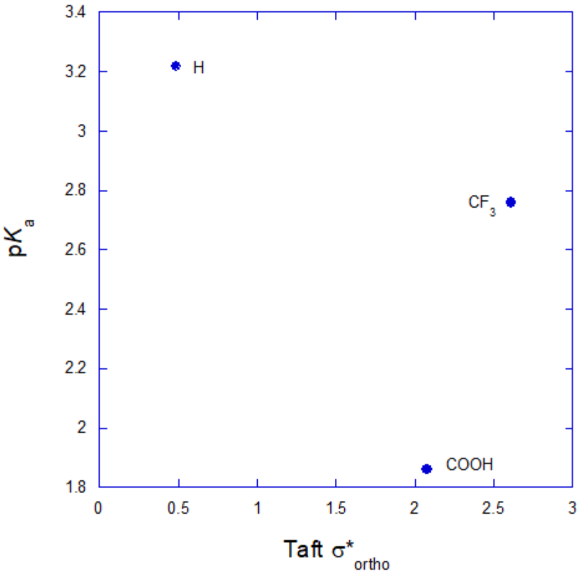


**Figure 33.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-1,2,3- triazole-4-carboxylic acid

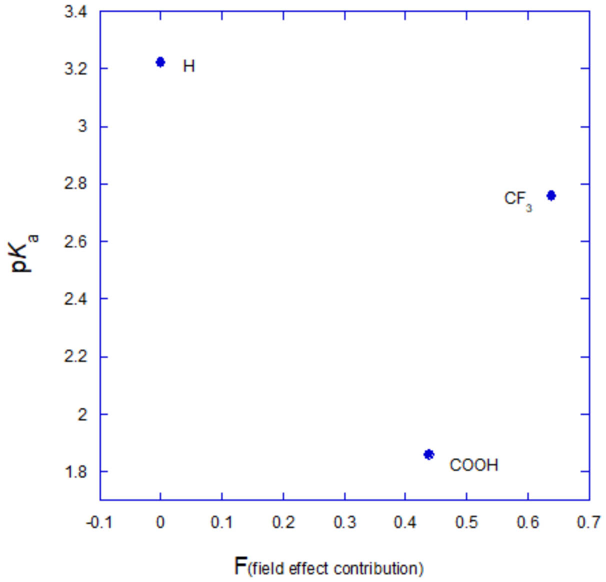


**Figure 34.** Plot of p$K_a$ versus F(field effect contribution) for 5-X-1,2,3-triazole-4-carboxylic acid

The plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ (figure 33) is not linear. Then we thought that using Swain and Lupton type equation ($\sigma = fF + rR$) [22] and plotting p$K_a$ versus F (field effect contribution) (figure 34) and p$K_a$ versus R (resonance effect contribution) (figure 35) to see the individual field and resonance effects on the acid dissociation. But none of them are linear. The non-linearity of any of the three plots could possibly be due to the involvement of various types of intramolecular hydrogen bonding in 5-X-1,2,3-triazole-4-carboxylic acids as shown below in scheme 11.

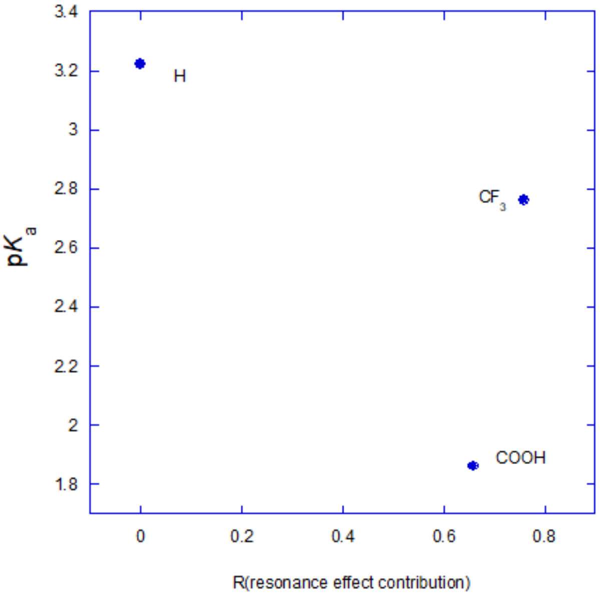
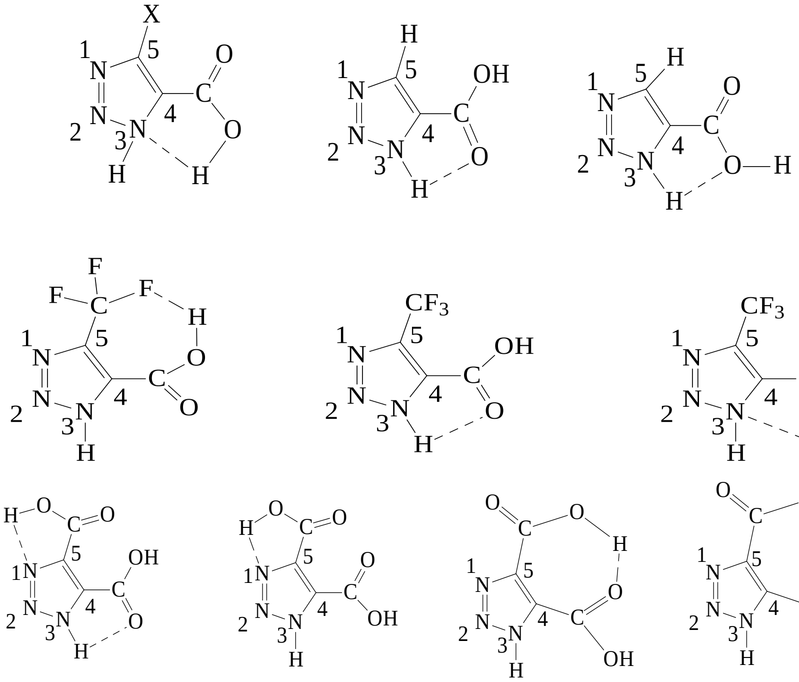


**Figure 35.** Plot of p$K_a$ versus R(resonance effect contribution) for 5-X-1,2,3-triazole-4-carboxylic acid

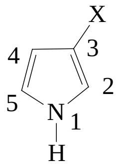


Scheme 11

Due to the presence of these hydrogen bonding any of the substituent does not behave as if it is a pure isolated substituent, hence the non-linearity in the p$K_a$ versus Taft $\sigma^*_{ortho}$, p$K_a$ versus F and p$K_a$ versus R plots.

*3-X-Pyrroles:*

**Table 15. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 3-X-Pyrroles**



| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^*_{ortho}$ | |
| 1 | H | 16.5 | 0.00 | 0.00 | 0.49 | https://en.wikipedia.org/wiki/Pyrrole<br>Gerhartz, W. (exec ed.). Ullmann's Encyclopedia of Industrial Chemistry. 5th ed. Vol A1: Deerfield Beach, FL: VCH Publishers, 1985 to Present., p. A22 (93) 453<br>Perrin DD; Dissociation constants of organic bases in aqueous solution IUPAC Chem Data Ser, Butterworths, London (1965) |
| 2 | Me | 17.3 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB5146220.htm |
| 3 | Br | 15.33 | 0.23 | 0.39 | 2.84 | https://m.chemicalbook.com/ProductChemicalPropertiesCB6339708_EN.htm |
| 4 | $NO_2$ | 13.96 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB3209956.htm |

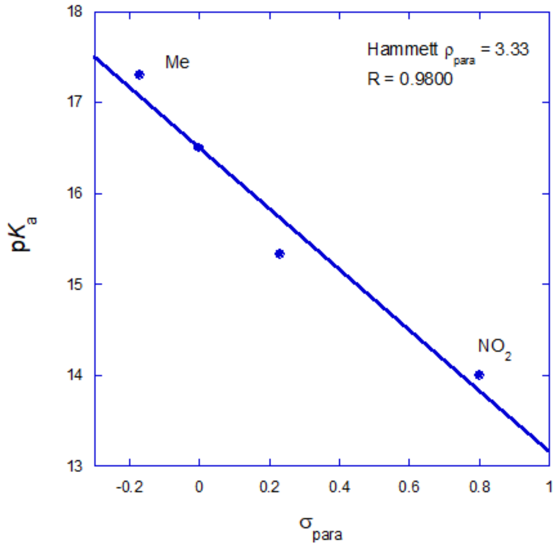


**Figure 36.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 3-X-pyrroles

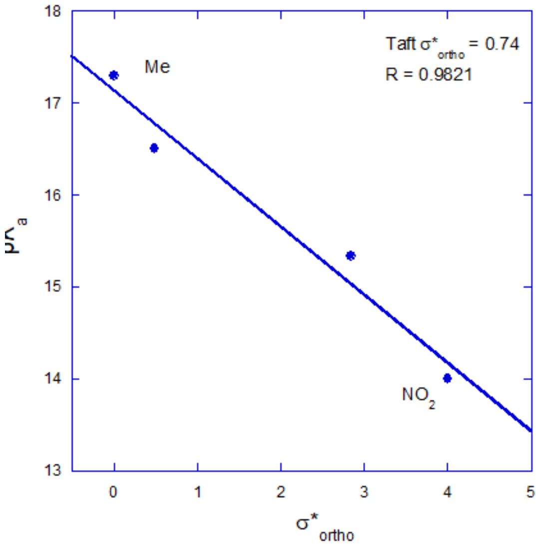


**Figure 38.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 3-X-pyrroles

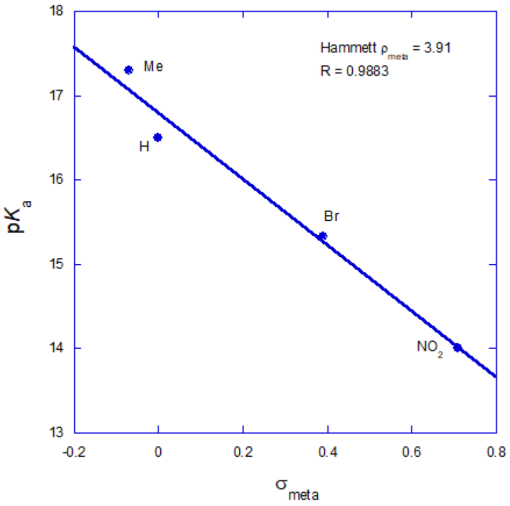


**Figure 37.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 3-X-pyrroles

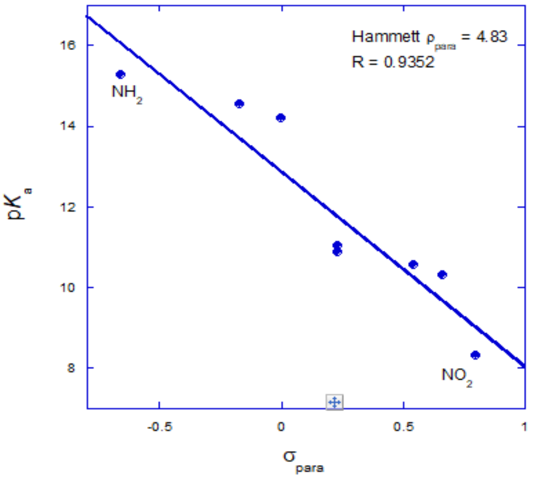
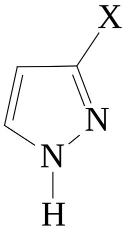


**Figure 39.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 3-X-pyrroles

In the figures 36-38 it is clear from the correlation coefficients, the p$K_a$ data of 3-X-pyrroles correlated well (Hammett $\rho_m$ = -3.91, R = 0.9883) with Hammett $\sigma_m$ values. Therefore the 3 position of the 3-X-pyrroles is best assumed as *meta*-position.

*3-X-pyrazoles:*

**Table 16. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 3-X-pyrazoles**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 14.2 | 0.00 | 0.00 | 0.49 | https://www.imperial.ac.uk/media/imperial-college/research-centres-and-groups/spivey-group/teaching/org2heteroaromatics/lecture81112.pdf |
| 2 | Cl | 11.04 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB42593960.htm |
| 3 | Me | 14.56 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB3198957.htm |
| 4 | Br | 10.88 | 0.23 | 0.39 | 2.84 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB1121665.htm |
| 5 | CN | 10.3 | 0.66 | 0.56 | 3.30 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6384364.htm |
| 6 | $NO_2$ | 8.32 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB7744572.htm |
| 7 | $NH_2$ | 15.28 | -0.66 | -0.16 | 0.62 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2322586.htm |
| 8 | $CF_3$ | 10.56 | 0.54 | 0.43 | 2.61 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB3681435.htm |

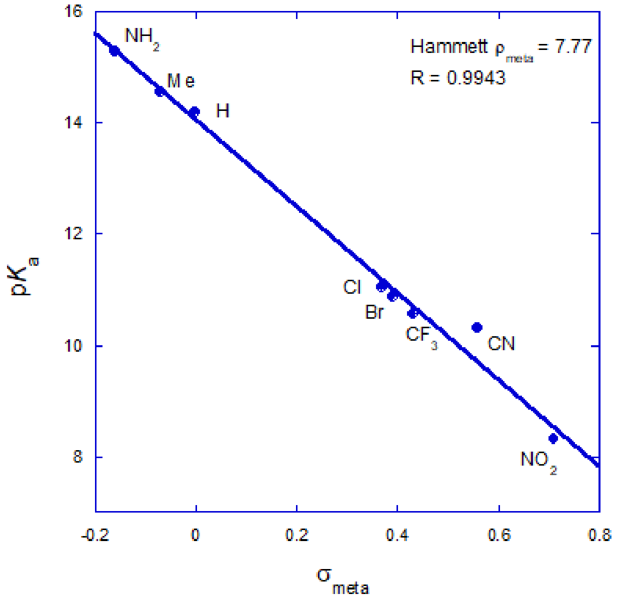


**Figure 40.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 3-X-pyrroles

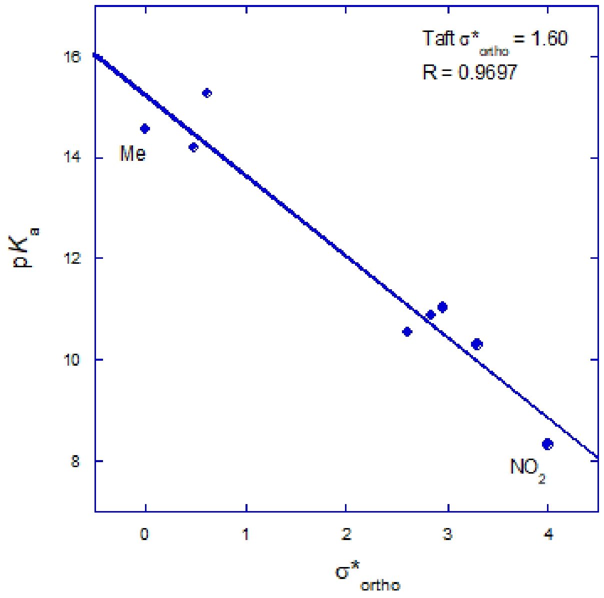
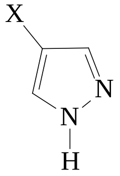


**Figure 41.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 3-X-pyrroles

In the figures 39-41 it is clear from the correlation coefficients, the p$K_a$ data of 3-X-pyrazoles correlated well (Hammett $\rho_{meta}$ = - 7.77, R = 0.9943) with Hammett $\sigma_m$ values. Therefore the 3 position of the 3-X-pyrazoles is best assumed as *meta*-position.

*4-X-pyrazoles:*

**Table 17. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 4-X-pyrazoles**



| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^*_{ortho}$ | |
| 1 | H | 14.2 | 0.00 | 0.00 | 0.49 | https://www.imperial.ac.uk/media/imperial-college/research-centres-and-groups/spivey-group/teaching/org2heteroaromatics/lecture81112.pdf |
| 2 | Cl | 12.71 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2212438.htm |
| 3 | Me | 14.95 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB8233079.htm |
| 4 | Br | 12.7 | 0.23 | 0.39 | 2.84 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6158239.htm |
| 5 | CN | 10.3 | 0.66 | 0.56 | 3.30 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6384364.htm |
| 6 | $NO_2$ | 9.63 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6418845.htm |

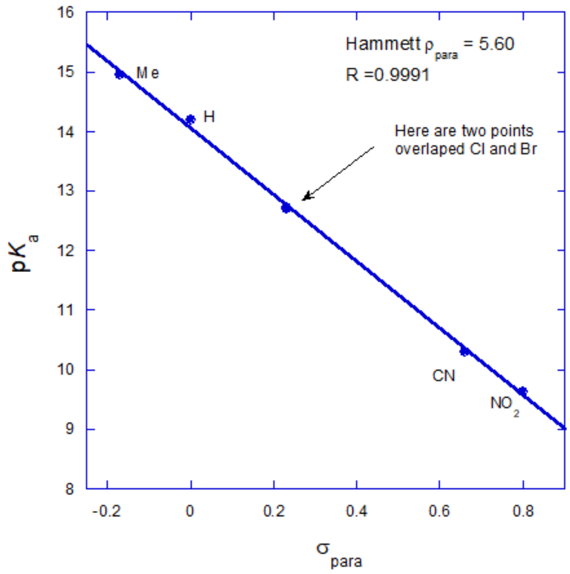


**Figure 42.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 4-X-pyrazoles

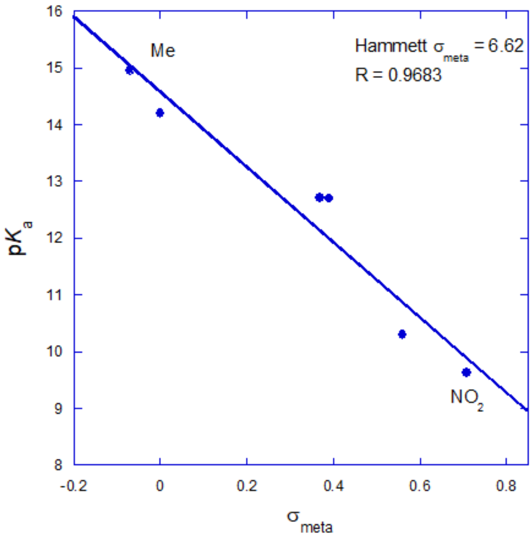


**Figure 43.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 4-X-pyrazoles

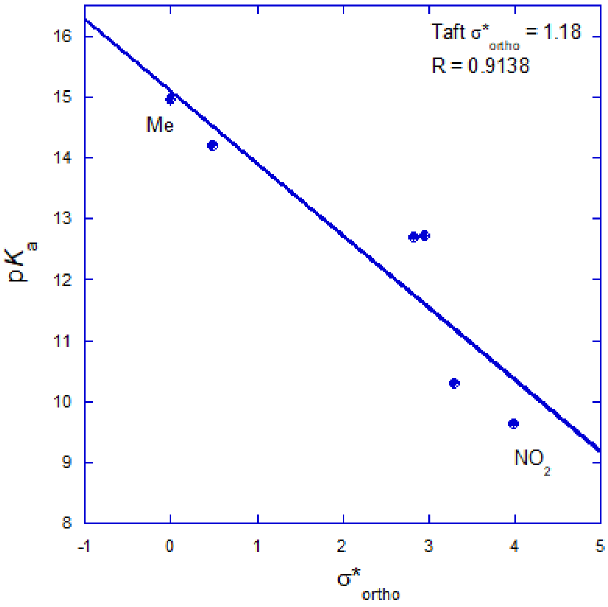
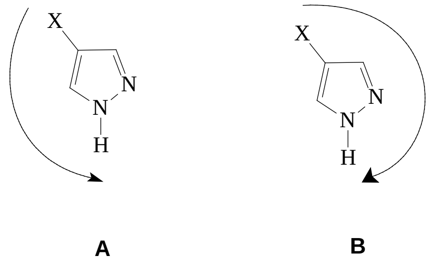


**Figure 44.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 4-X-pyrazoles

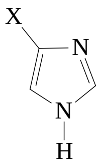
In the case of 4-X-pyrazoles the Hammett equation would have satisfied with $\sigma_{meta}$ values as the functional group (N1H) is only separated by a sp$^2$ carbon as shown in the scheme 12**A**. But in the figures 42-44 it is clear from the correlation coefficients, the p$K_a$ data of 4-X-pyrazoles correlated well (Hammett $\rho_{para}$ = - 5.60, R = 0.9991) with Hammett $\sigma_{para}$ values. Therefore the 4 position of the 4-X-pyrazoles is best assumed as *para*-position. And the substituent effect may best be transmitted via sp$^2$ carbon and sp2 nitrogen as shown in scheme 12 **B**.



Scheme 12

*4-X-imidazoles:*

**Table 18. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 4-X-imidazoles**



| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^*_{ortho}$ | |
| 1 | H | 14.5 | 0.00 | 0.00 | 0.49 | https://www.imperial.ac.uk/media/imperial-college/research-centres-and-groups/spivey-group/teaching/org2heteroaromatics/lecture81112.pdf |
| 2 | Cl | 11.7 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB2825830.htm |
| 3 | Me | 14.78 | -0.17 | -0.07 | 0.00 | https://www.drugbank.ca/drugs/DB03385 |
| 4 | Br | 11.7 | 0.23 | 0.39 | 2.84 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB4300919.htm |
| 5 | $NO_2$ | 8.31 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB8774477.htm |
| 6 | CN | 10.3 | 0.66 | 0.56 | 3.30 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB8763109.htm |
| 7 | $C_6H_5$ | 13.58 | -0.01 | 0.06 | 0.60 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6252973.htm |

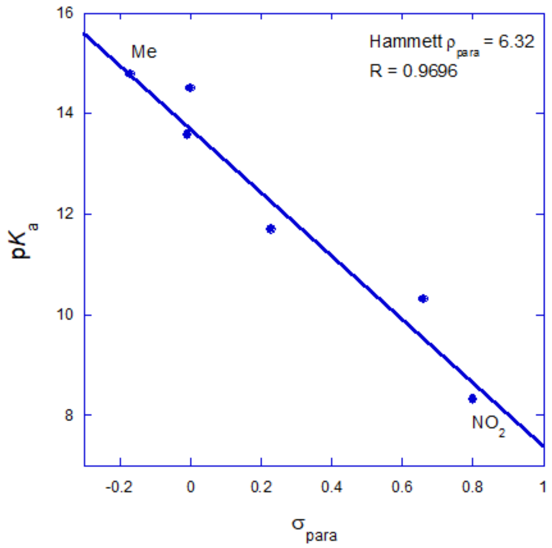


**Figure 45.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 4-X-imidazoles

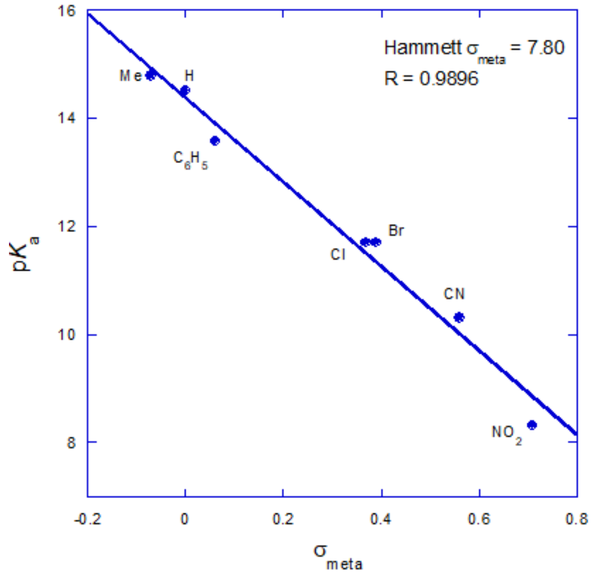


**Figure 46.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 4-X-imidazoles

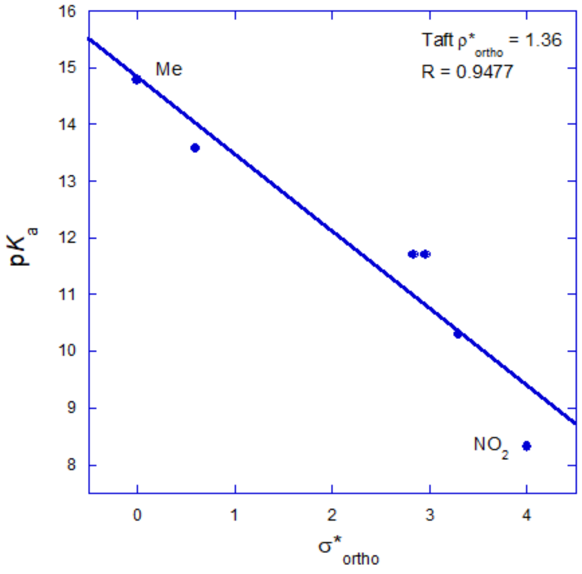
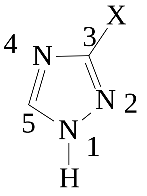


**Figure 47.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 4-X-imidazoles

In the figures 45-47 it is clear from the correlation coefficients, the p$K_a$ data of 4-X-imidazoles correlated well (Hammett $\rho_{meta}$ = - 7.80, R = 0.9896) with Hammett $\sigma_m$ values. Therefore the 4 position of the 4-X-imidazoles is best assumed as *meta*-position. The substituent effect may be better transmitted through the 5 positioned sp2 carbon.

*3-X-1, 2, 4-triazole*

**Table 19. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 3-X-1,2, 4-triazole**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 10.3 | 0.00 | 0.00 | 0.49 | https://en.wikipedia.org/wiki/1,2,4-Triazole# |
| 2 | Cl | 7.96 | 0.23 | 0.37 | 2.96 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB5132779.htm |
| 3 | Me | 10.6 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB0692434.htm |
| 4 | Br | 7.84 | 0.23 | 0.39 | 2.84 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6770824.htm |
| 5 | CN | 6.82 | 0.66 | 0.56 | 3.30 | https://m.chemicalbook.com/ChemicalProductProperty_EN_CB6344463.htm |
| 6 | $NO_2$ | 5.92 | 0.80 | 0.71 | 4.00 | https://www.chemicalbook.com/ProductMSDSDetailCB7448098_EN.htm |
| 7 | $NH_2$ | 11.1 | -0.66 | -0.16 | 0.62 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB6767936.htm |

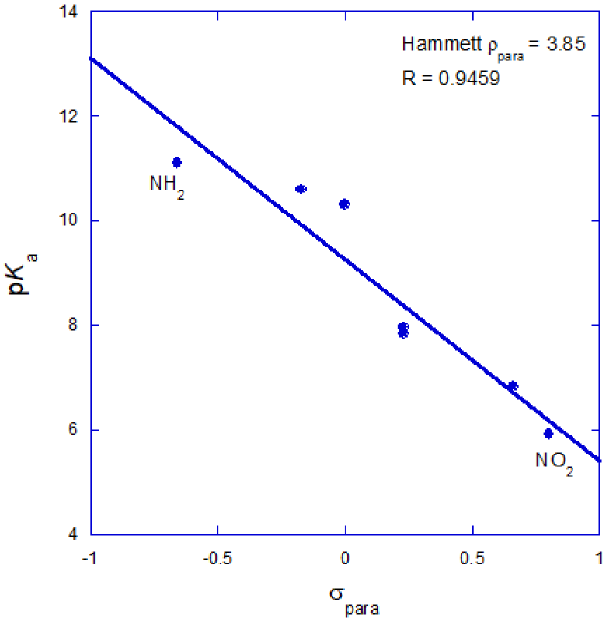


**Figure 48.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 3-X-1,2,4-triazole

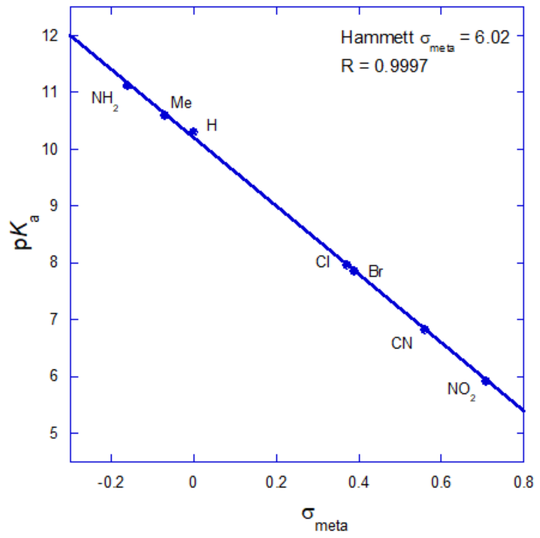


**Figure 49.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 3-X-1,2,4-triazole

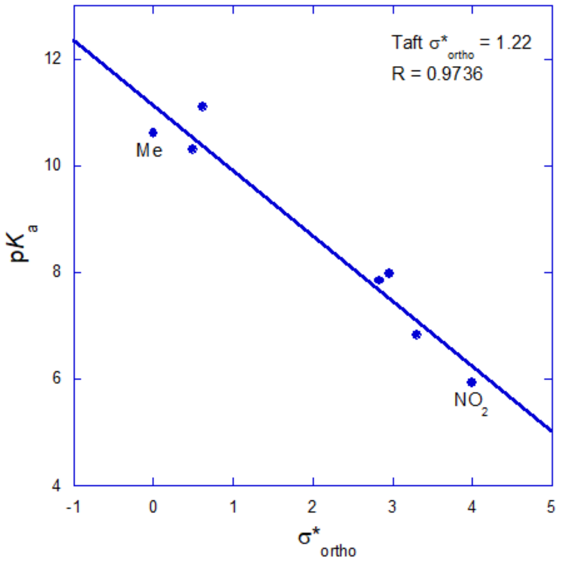
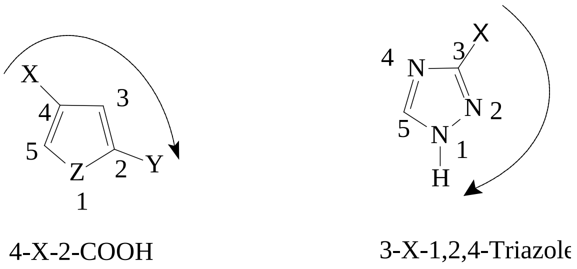


**Figure 50.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 3-X-1,2,4-triazole

In the figures 48-50 it is clear from the correlation coefficients, the p$K_a$ data of 3-X-1,2,4-triazole correlated well (Hammett $\rho_m$ = -6.02, R = 0.9997) with Hammett $\sigma_m$ values. Therefore the 3 position of the 1-substituted (N1H) 3-X-1,2,4-triazole is best assumed as *meta*-position. The situation here is analogous to structure **F** of scheme 3 as shown below in scheme 13.



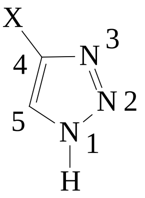
Structure **F** of scheme 3

Scheme 13

It is to be understood that when the substituent is at 2 position like Y in ***structure F of scheme 3***, 4 position becomes *meta*. Similarly, when the substituent (N1H) is at 1 position like in 3-X-1,2,4-triazole, 3 position becomes *meta*.

*4-X-1, 2, 3-triazole:*

**Table 20. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 4-X-1,2, 3-triazole**



| Sl. No. | X | p$K_a$ | Hammett | | Taft $\sigma^*_{ortho}$ | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | | |
| 1 | H | 9.40 | 0.00 | 0.00 | 0.49 | https://en.wikipedia.org/wiki/1,2,3-Triazole |
| 2 | Me | 9.18 | -0.17 | -0.07 | 0.00 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB62468769.htm |
| 3 | Br | 6.98 | 0.23 | 0.39 | 2.84 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB82520209.htm |
| 4 | $NH_2$ | 9.87 | -0.66 | -0.16 | 0.62 | https://www.chemicalbook.com/ChemicalProductProperty_EN_CB02460781.htm |
| 5 | $C_6H_5$ | 7.68 | -0.01 | 0.06 | 0.60 | H. Wamhoff, in Comprehensive Heterocyclic Chemistry, 1984, Ed. By Alan R. Katritzky, Elsevier. |

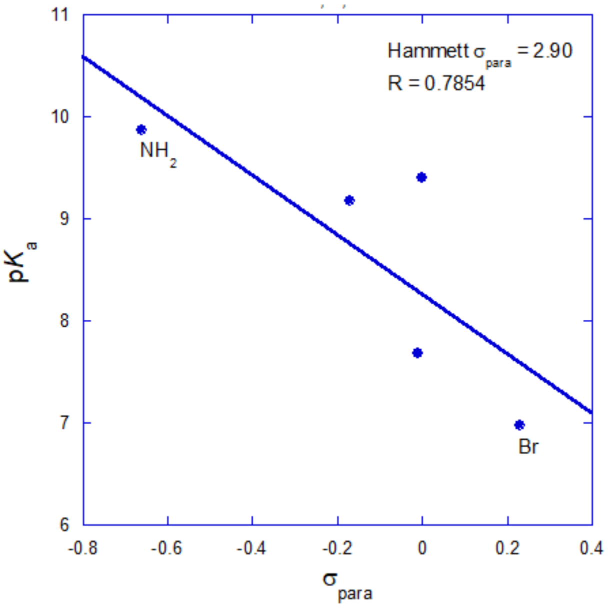


**Figure 51.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 4-X-1,2,3-triazole

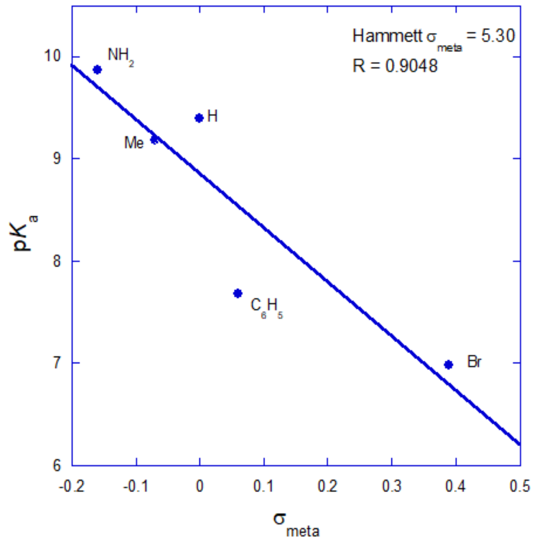


**Figure 52.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 4-X-1,2,3-triazole

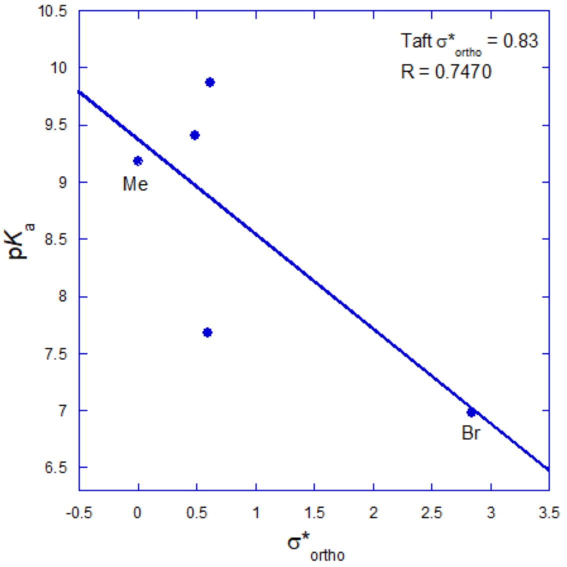
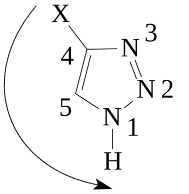


**Figure 53.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 4-X-1,2,3-triazole

In the figures 51-53 it is clear from the correlation coefficients, the p$K_a$ data of 4-X-1,2,3-triazole correlated well (Hammett $\rho_m$ = -5.30, R = 0.9048) with Hammett $\sigma_m$ values. Therefore the 4 position of the 1-substituted (N1H) 4-X-1,2,3-triazole is best assumed as *meta*-position. The situation again here is analogous to structure **F** of scheme 3 as shown below in scheme 14 but in the opposite direction via carbon 5.

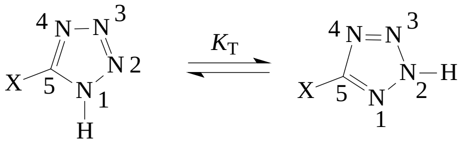


4-X-1,2,3-Triazole

Scheme 14

### *5-X-1, 2, 3, 4-tetrazoles*

**Table 21. p$K_a$, Hammett $\sigma_p$, $\sigma_m$ and Taft $\sigma^*_{ortho}$ values of 5-X-1,2, 3, 4-tetrazoles**



1H-Tautomer 2H-Tautomer

| Sl. No. | X | p$K_a$ | Hammett | | Taft | Literature for p$K_a$ values |
|---|---|---|---|---|---|---|
| | | | $\sigma_p$ | $\sigma_m$ | $\sigma^*_{ortho}$ | |
| 1 | H | 4.86 | 0.00 | 0.00 | 0.49 | R. E. Trifonov and V. A. Ostrovskii, *Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 11, pp. 1585-1605* |
| 2 | Me | 5.56 | -0.17 | -0.07 | 0.00 | |
| 3 | Et | 5.59 | -0.15 | -0.07 | -0.1 | |
| 4 | *i*-Pro | 5.53 | -0.15 | -0.07 | -0.19 | |
| 5 | CF3 | 1.40 | 0.54 | 0.43 | 2.61 | |
| 6 | Cl | 2.07 | 0.23 | 0.37 | 2.96 | |
| 7 | Br | 2.13 | 0.23 | 0.39 | 2.84 | |
| 8 | I | 2.85 | 0.28 | 0.35 | 2.46 | |
| 9 | $NH_2$ | 6.00 | -0.66 | -0.16 | 0.62 | |
| 10 | $C_6H_5$ | 4.83 | -0.01 | 0.06 | 0.60 | |
| 11 | $NO_2$ | -0.83 | 0.80 | 0.71 | 4.00 | |

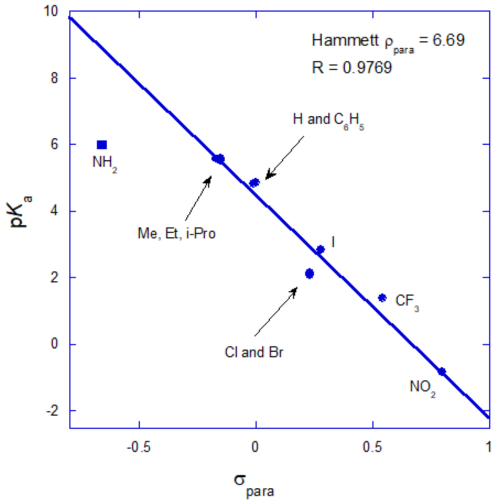


**Figure 54.** Plot of p$K_a$ versus Hammett $\sigma_p$ for 5-X-1,2,3,4-tetrazoles

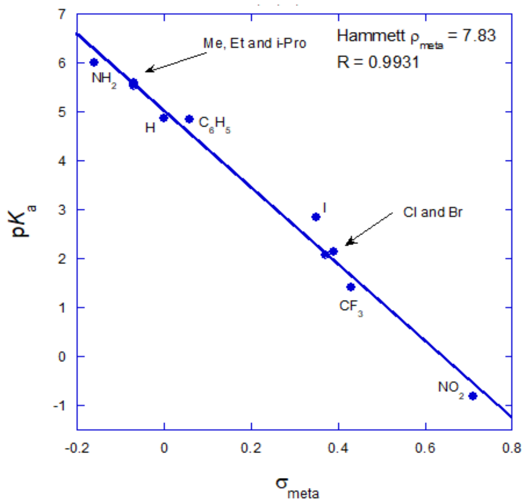


**Figure 55.** Plot of p$K_a$ versus Hammett $\sigma_m$ for 5-X-1,2,3,4-tetrazoles

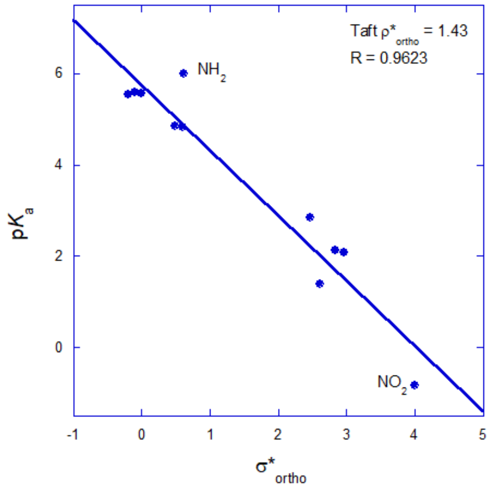


**Figure 56.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-1,2,3,4-tetrazoles

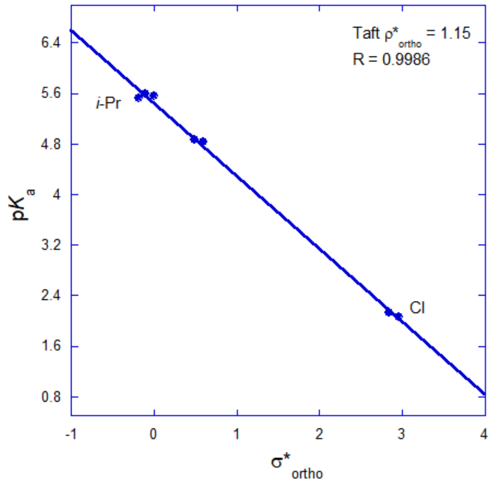
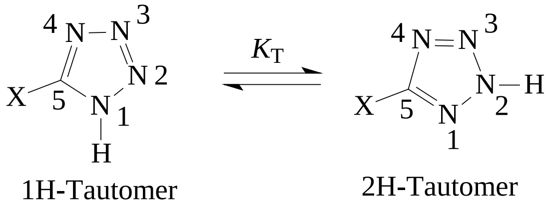


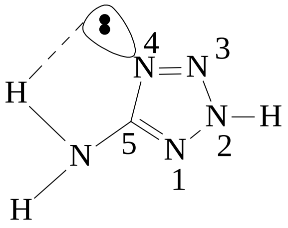
**Figure 57.** Plot of p$K_a$ versus Taft $\sigma^*_{ortho}$ for 5-X-1,2,3,4-tetrazoles without $NH_2$ and other three bulky groups like $CF_3$,I and $NO_2$

The effect of substituents (X) on the p$K_a$ values of 5-X-1, 2, 3, 4-tetrazoles is rather complex [23].Tetrazole itself is a strange molecule with 80% nitrogen of the total weight of the molecule. It is known that the tetrazole molecule exists in two tautomeric forms as shown in scheme 15 [24]. In a nonpolar medium, both the 1Hand 2Htautomers are predicted to exist in comparable amounts. In the solvents like water with high dielectric constant the existence of more polar 1H-tautomer is appreciable [24]. From figures 54-57, the correlation of p$K_a$ values with *para* and *meta* substituents is good (R = 0.9769 and 0.9931) with a deviation of $NH_2$ group with the *para*-substituents correlation.



Scheme 15

Though the content of 2H-tautomer is less than the 1H-tautomer in more polar solvents (since the p$K_a$ values are from water as the solvent [23]), yet the *para* and *meta* substituent effects originate from less abundant 2H-tautomer. If one looks at the 2H-tautomer (scheme 15), the functional group (N2-H) is at *meta* to X at position 5 via nitrogen 1 and it will be *para* to X at position 5 via nitrogen 3 and 4. This is just like the visual observation for defining the *para* and *meta* positions of 5 membered heterocycles as given in scheme 2 and scheme 3. This is the reason that the p$K_a$ values are well correlated with both Hammett $\sigma_{para}$ and $\sigma_{meta}$ substituent constants. The deviation of $NH_2$ in the correlation with *para* substituents may be due to the intramolecular hydrogen bonding as shown in scheme 16.

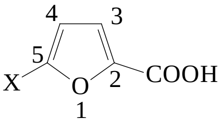


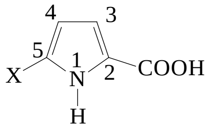
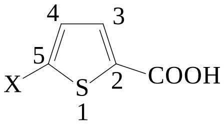
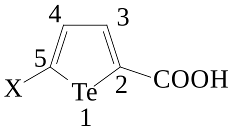
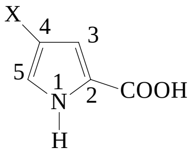
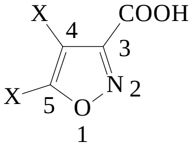
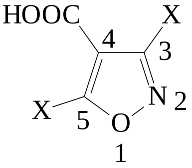
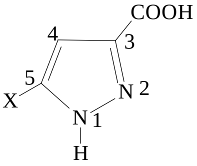
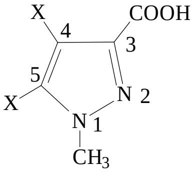
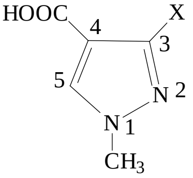
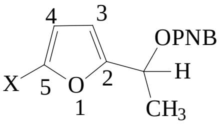
Scheme 16

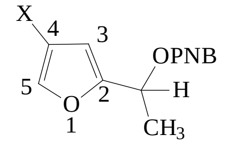
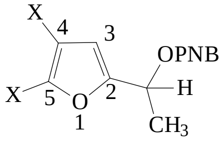
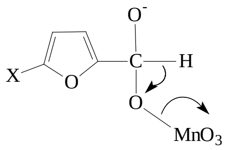
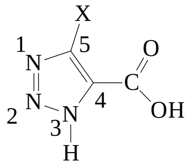
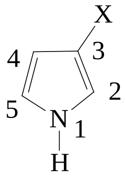
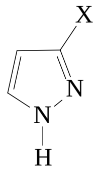
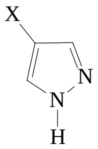
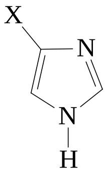
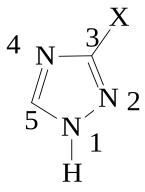
From Taft plots given in figures 56 and 57 it may be assumed that the *ortho*-substituent effects originate from 1H-tautomer. If one looks at the 1H-tautomer (scheme 15), the functional group (N1-H) is at *ortho* to X adjacent to nitrogen 1. This is just similar to the visual observation for defining the *ortho* position of 5 membered heterocycles as given in scheme 4. Also, it is noteworthy to see the correlation is improved without the bulky groups like $CF_3$, I and $NO_2$ (figure 57).

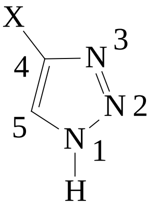
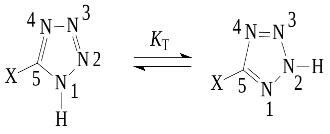
Table 22 gives a quick glance of the whole work. The readers should note that the Hammett and Taft reaction constants (ρ and ρ*) are given as positive numbers though as they were obtained as negative numbers in the plots because the plots were done using p$K_a$ (= - log $K_a$) values.

**Table 22. Hammett and Taft parameters of different systems**

| Sl. No. | Heterocycle | Number of substitu-ents | Hammett | | Taft | Correlation coefficients with | | |
|---|---|---|---|---|---|---|---|---|
| | | | $\rho_{para}$ | $\rho_{meta}$ | $\rho^*_{ortho}$ | $\sigma_{para}$ | $\sigma_{meta}$ | $\sigma^*_{ortho}$ |
| 1 |  <br>5-X-Furan-2-COOH | 8 | 1.38 | 1.72 | 0.30 | **0.9982** | 0.9469 | 0.8953 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2 | <br>5-X-Pyrrole-2-COOH | 8 | 1.54 | 1.79 | 0.30 | **0.9873** | 0.8664 | 0.7630 |
| 3 | <br>5-X-Thiophene-2-COOH | 8 | 1.06 | 1.34 | 0.21 | **0.9939** | 0.8657 | 0.7345 |
| 4 | <br>5-X-Tellurophene-2-COOH | 5 | 1.59 | 2.08 | 0.38 | 0.9303 | **0.9778** | 0.9566 |
| 5 | <br>4-X-Pyrrole-2-COOH | 5 | 1.32 | 1.50 | 0.26 | **0.9931** | 0.9824 | 0.9352 |
| 6 | <br>4,5-X-Isoxazole-3-COOH | 5 | | | 0.58 | | | **0.9924** |
| 7 | <br>3,5-X-Isoxazole-4-COOH | 5 | | | 0.46 | | | **0.9964** |
| 8 | <br>5-X-Pyrazole-3-COOH | 3 | 0.88 | 1.04 | 0.19 | 0.9723 | **0.9988** | 0.9742 |
| 9 | <br>1-Methyl-4,5-X-Pyrazole-3-COOH | 3 | Correlation is not good with $\sigma_m$ (figure 21) | | | | | |
| 10 | <br>3-X-Pyrazole-4-COOH | 3 | | | 0.23 | | | 0.8491 |
| 11 | <br>5-X-2-FurylmethylcarbinylOPNB | 5 | 8.21 | 9.10 | 1.65 | **0.9862** | 0.9136 | 0.8592 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 12 | <br>4-X-2-FurylmethylcarbinylOPNB | 3 | 6.95 | 7.06 | 1.15 | **0.9655** | **0.9574** | 0.8520 |
| 13 | <br>4,5-X-2-FurylmethylcarbinylOPNB | 7<br>All 4 and 5 'X's are used | Brown's $\rho^+ = -7.4$ | | | R with Brown's $\sigma^+$ = **0.9906** | | |
| 14 | <br>5-X-Furfural-MnO$_4^-$ | 3 | 1.38 | 1.68 | 11.9 | 0.9882 | **0.9975** | 0.9939 |
| 15 | <br>5-X-1,2,3-Triazole-4-COOH | 3 | Neither of the plots of p$K_a$ versus Taft $\sigma^*_{ortho}$ (figure 33), or F (field effect contribution) (figure 34) or R (resonance effect contribution) (figure 35) is linear. For explanation see text on page 22. | | | | | |
| 16 | <br>3-X-pyrroles | 4 | 3.33 | 3.91 | 0.74 | 0.9800 | **0.9883** | 0.9821 |
| 17 | <br>3-X-pyrazoles | 8 | 4.83 | 7.77 | 1.60 | 0.9352 | **0.9943** | 0.9697 |
| 18 | <br>4-X-Pyrazoles | 6 | 5.60 | 6.62 | 1.18 | **0.9991** | 0.9683 | 0.9138 |
| 19 | <br>4-X-Imidazoles | 7 | 6.32 | 7.80 | 1.36 | 0.9696 | **0.9896** | 0.9477 |
| 20 | <br>3-X-1,2,4-Triazole | 7 | 3.85 | 6.02 | 1.22 | 0.9459 | **0.9997** | 0.9736 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 21 |  <br>4-X-1,2,3-Triazole | 5 | 2.90 | 5.30 | 0.83 | 0.7854 | **0.9048** | 0.7470 |
| 22 |  <br>1H-Tautomer 2H-Tautomer | 11 | 6.69 | 7.83 | 1.43<br>1.15 | **0.9769** | **0.9931** | 0.9623<br>**0.9986** |

## Conclusions

Hammett and Taft equations are applied to a total of 22 five-membered heterocyclic ring systems.

## Conflict of Interest

The authors declare that they don't have any kind of competing interest.

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## References

[1] Hammett. L. P., *J. Am. Chem*. Soc., vol. 59, page 96 (1937).

[2] Hammett. L. P., "Physical Organic Chemistry." McGraw Hill Book Co., Inc., New York, 1940, P. 184.

[3] Jaffé, H. H, *Chem. Rev.*, 53, 191 (1953).

[4] Wells, P. R., *Chem. Rev.*, 63, 171 (1963).

[5] Taft, R. W.*J. Am. Chem. Soc.*1952, 74, 2729 and 3120.

[6] Taft, R. W.*J. Am. Chem. Soc.*1953, 75, 4538.

[7] L. P. Hammett, *Chem. Revs.*, vol. 17, page 125, 1935.

[8] Imoto, E. and Motoyama, R., *Bull. Naniwa* Univ., *Series A*. 2. 127 (1954).

[9] F. Freeman, *J. Chem. Edn.*, vol. 47, page 140, 1970.

[10] Catlin, W.E., *Iowa State Coll. J. Sci*., 10, 65 (1935).

[11] Salo Gronowitz, Thiophene and its derivatives part 2 in The Chemistry of Heterocyclic Compounds, an Interscience publication, 1986 by John Wiley &Sons, Inc.

[12] A. Kekulé, *Justus Liebigs Ann. Der Chemie*, Vol. 162, page 77-124, 1872, https://en.wikipedia.org/wiki/Benzene#cite_note-18.

[13] Melander L. *Ark. Kemi*, 11, 397 (1957).

[14] Ram Keswani and Henry Freis, *J. Am. Chem.* Soc.,71, I789 (1949)

[15] (a) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, 35,731 (1961), (b) Tetrahedron Letters, 468, 1961.

[16] A.Halasa, L. Lapinski, I. Reva, H. Rostkowska, R. Fausto, and M. J. Nowak, *J. Phys. Chem. A* 2015, 119, 1037-1047.

[17] Advances in heterocyclic chemistry, Ed. A. R. Katritzky and A. J. Boulton, Vol. 20, page 37, Academic Press, New York, 1976.

[18] Zhou P, Tian F, Lv F, Shang Z., *Proteins*, 2009, 76, page 151-63.

[19] The bacterial response to the chalcogen metalloids Se and Te by D. Zannoni, F. Borsetti, J. J. Harrison and R. J. Turner in Advances in microbial physiology, Ed. By Robert K. Poole, Academic Press, First Edition 2008, page 4.

[20] Donald S. Noyce and Gary V. Kaiser, *J. Org. Chem.*, vol. 34, page 1008, 1969.

[21] F. Freeman, J. B. Brant, N. B. Hester, A. A. Kamego, M. Kasner, T. G. Mclaughlin, and E. W. Paull, *The Journal of Organic Chemistry*, vol. 35, page 985, 1970.

[22] C. G. Swain and E. C. Lupton, Jr., *Journal of the American Chemical Society*, 90,4328, 1968.

[23] R. E. Trifonov and V. A. Ostrovskii, *Russian Journal of Organic Chemistry*, 2006, Vol. 42, No. 11, pp. 1585-1605.

[24] Ming Wah Wong, Regis Leung Toung and Curt Wentrup, *J . Am. Chem.* Soc. 1993, 115, 2465-2472.