Application of LFER to pKₐs and Dipole Moments of 1H and 2H Tautomers of Tetrazole: Mimicking Structure-Function Relation as a Chemical Education Perspective

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Abstract:

Structure-function relation is a 155 years old concept to explain the dependence of biological activity of a drug molecule on its structure put forward by Crum-Brown and Fraser*. Similar line of interest is followed in the present work and it stimulates the understanding of structure-activity relation (SAR) among the graduate students. An attempt is made for the first time from our laboratory to apply the Hammett and Taft equations to a five membered ring system with four nitrogens as heteroatoms viz. tetrazole to identify the aqueous medium 1H and 2H Tautomers. For this purpose experimentally determined aqueous medium pKₐ values of NH-acidities of a total of fifteen 5-X-1,2,3,4-tetrazoles and DFT/B3LYP method at the 6-31G* level calculated dipole moments of seven 1H and 2H tautomers of 5-X-1,2,3,4-tetrazoles are used to correlate with Hammett σpara and σmeta, and Taft σortho values. Good correlations are obtained. The promising response of more abundant and more polar 1H tautomer with less susceptibility (ρ* = -1.38 in pKₐ correlations and ρ* = -0.55 in dipole moments correlation) to Taft equation and less abundant and less polar 2H tautomer with more susceptibility (ρpara = 6.56, ρmeta = 7.79 in pKₐ correlations, and ρpara = 2.69, ρmeta = 3.26 in dipole moments correlation) to Hammett equation of the tetrazole is well distinguished. Thus it mimics a principle of structure-function study on a chemical property like the ionization of NH proton of tetrazole and on a physical property like dipole moment for the first time. Therefore finding a way is achieved to get the equilibrium identification of 1H and 2H tautomers without using any expensive and time consuming experimental techniques.

*Crum-Brown, A; Thomas R. Fraser, "The connection of chemical constitution and physiological action". Trans. R. Soc. Edinb., Vol. 25, page 1968–69 (1865)
Keywords:
Structure-Function study; 1H and 2H Tautomers; pK\textsubscript{a} values; Dipole Moments; Hammett Equation; Taft Equation; Tetrazole

Introduction:

Much effort has been made by Wentrup et. al. [1] in the study of tautomeric equilibrium of 5-X-1,2,3,4-Tetrazoles both by theory and experiments specially on 1H and 2H tautomeric equilibrium of both in gas phase and solution phase. There was an excellent review on tetrazoles published by Trifonov and Ostrovskii [2] emphasizing the protolytic equilibriums. In both these studies importance is given mainly on the study of 1H ⇌ 2H tautomeric equilibriums. It is to be noted that UV-Vis, dipole moments and NMR techniques were employed in the entire study of 1H and 2H tautomeric equilibriums [1,2]. In earlier studies [2,3] while applying the LFER to pK\textsubscript{a} values and the dipole moments, information about the para, meta and ortho positions of the atoms in the five membered heterocyclic ring system are not referred. We have recently published a review where in one can find the visual interpretation and identification of the para, meta and ortho positions of the atoms in the five membered heterocyclic ring system is well explained [ref]. In the present study we have shown for the first time without using expensive and time-consuming methods like ¹H NMR, ¹³C NMR and dipole meters, a simple novel protocol is just handy to identify the 1H and 2H tautomers of tetrazole hitherto not reported earlier with the use of Linear Free Energy Relationships (LFER) knowing experimentally determined pK\textsubscript{a} values [2] and DFT/B3LYP method at the 6-31G* level calculated dipole moments [3]. And mimicking of principle of structure-function study on a chemical and a physical property for the first time is observed.

Methods:

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

Results and discussion:

In table 1 is the complete data of pK\textsubscript{a} values of 5-X-1,2,3,4-tetrazoles, Hammett σ\textsubscript{para}, σ\textsubscript{meta}, Taft σ\textsubscript{ortho} and E\textsubscript{g}\textsubscript{ortho} is given.

Figures 1-6 are the Hammett and Taft plots. The effect of substituents (X) on the pK\textsubscript{a} values of 5-X-1,2,3,4-tetrazoles is rather complex (table 1) [2]. 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 below in scheme 1 [2]. In a nonpolar...
medium, both the 1H and 2H tautomers 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 [1]. From figures 1 and 2, it is clear that the correlation of \( pK_a \) 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.

\[
\begin{align*}
\text{1H-Tautomer} & \quad K_T \quad \text{2H-Tautomer} \\
\end{align*}
\]

Table 1: \( pK_a \) values of 5-X-1,2,3,4-tetrazoles, Hammett \( \sigma_{\text{para}}, \sigma_{\text{meta}} \), Taft \( \sigma_{\text{ortho}} \) and \( E_s^{\text{ortho}} \)

| Sl. No. | X     | \( pK_a \) | Hammett | Taft \( \sigma_{\text{ortho}} \) | \( E_s^{\text{ortho}} \) |
|--------|-------|------------|---------|-------------------------------|----------------------|
| 1      | H     | 4.86       | 0.00    | 0.00                          | 0.49                 | 1.24                |
| 2      | Me    | 5.56       | -0.17   | -0.07                         | 0.00                 | 0.00                |
| 3      | Et    | 5.59       | -0.15   | -0.07                         | -0.10               | -0.07               |
| 4      | i-Pro | 5.53       | -0.15   | -0.07                         | -0.19               | -0.47               |
| 5      | CF3   | 1.40       | 0.54    | 0.43                          | 2.61                | -1.16               |
| 6      | Cl    | 2.07       | 0.23    | 0.37                          | 2.96                | 0.27                |
| 7      | Br    | 2.13       | 0.23    | 0.39                          | 2.84                | 0.08                |
| 8      | I     | 2.85       | 0.28    | 0.35                          | 2.46                | -0.16               |
| 9      | NH\(_2\) | 6.00     | -0.66   | -0.16                         | 0.62                | 0.63                |
| 10     | C\(_6\)H\(_5\) | 4.83  | -0.01   | 0.06                          | 0.60                | -2.58               |
| 11     | NO\(_2\) | -0.83   | 0.80    | 0.71                          | 4.00                | -1.28               |
| 12     | 3-ClC\(_6\)H\(_4\) | 3.77  | 0.10\#  | 0.15\#                        | 0.85\#             | -                   |
| 13     | 3-NO\(_2\)C\(_6\)H\(_4\) | 3.50  | 0.20\#  | 0.21\#                        | 1.09\#             | -                   |
| 14     | 4-NO\(_2\)C\(_6\)H\(_4\) | 3.45  | 0.26\#  | 0.25\#                        | 1.14\#             | -                   |
| 15     | 4-MeOC\(_6\)H\(_4\) | 4.75  | -0.06\# | 0.03\#                        | 0.36\#             | -                   |

\(^*\)R. E. Trifonov and V. A. Ostrovskii, *Russian Journal of Organic Chemistry*, 2006, Vol. 42, No. 11, pp. 1585-1605

\(^*\)from Y. Nagai, H. Matsumoto, T. Nakano and H. Watanabe, *Bull. Chem. Soc. Jpn.*, vol. 45, 1972, page 2560
Though the content of 2H-tautomer is less than the 1H-tautomer in more polar solvents (since the pKₐ values are from water as the solvent [1]), yet the para and meta substituent effects originate from less polar and less abundant 2H-tautomer only. If one looks at the 2H-tautomer (scheme 1), the functional group (N2-H) is at meta to X at position 5 via nitrogen 1.
and it will be \textit{para} to X at position 5 via nitrogens 3 and 4. This is just similar to the visual observation for defining the \textit{para} and \textit{meta} positions of 5 membered heterocycles [ref] as given in scheme 2 and scheme 3 as shown below.

\begin{align*}
\text{Scheme 2} & \\
& \begin{array}{c}
\text{A} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array}
\end{array} \\
& \text{B} & \text{C}
\end{array}
\end{align*}

\begin{align*}
& \begin{array}{c}
\text{5-X-2-Y}
\end{array}
\end{align*}

\begin{align*}
\text{Scheme 3} & \\
& \begin{array}{c}
\text{D} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{X} \\
\text{Y}
\end{array}
\end{array}
\end{array} \\
& \text{E} & \text{F}
\end{array}
\end{align*}

This is the reason that the pK\textsubscript{a} values are well correlated in 2H tautomer with both Hammett \(\sigma\textsubscript{para}\) and \(\sigma\textsubscript{meta}\) substituent constants. The deviation of NH\textsubscript{2} in the correlation with \textit{para} substituents may be due to the intermolecular hydrogen bonding as shown in scheme 4A. Non deviation of NH\textsubscript{2} group in the correlation with \textit{meta} substituents could not be explained.

From Taft plots given below in figures 3 and 4, it may be assumed that the \textit{ortho}-substituent effects originate from 1H-tautomer again with the deviation of NH\textsubscript{2} group (blue square, figure 3). The deviation is due to the fact that the 1H tautomer having larger dipole moment than 2H tautomer [2] becomes more favorable for solvation by solvent water as shown in scheme 4B below. In the solvation process of 1H tautomer of 5-aminotetrazole in the formation of hydrogen bonds, both the hetero ring and the amino group are involved (scheme 4B).
Scheme 4

A: Dimer of 2H Tautomer    B: solvated 1H Tautomer

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Taft $\rho_{\text{ortho}}^* = -1.34$
R = 0.9666
If one looks at the 1H-tautomer (scheme 1), 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 5 [ref].

Also it is noteworthy to see the correlation is improved without the bulky groups like CF₃, I and NO₂ (figure 4) is yet an additional evidence to say that position 5 of tetrazole is an ortho-carbon to N1-H.

Figure 5 is the plot of pKₐ versus Taft Eₛ. There is not at all any correlation of pKₐ with Taft Eₛ values.
Looking at figure 5 above, further the following conclusion can be drawn: Figure 6 given below is a re-plot of figure 3 plotting \((pK_a - \delta E_s)\) versus \(\sigma^*\) after deducting the steric effects from \(pK_a\) values using Taft-Pavelich equation [4].

\[
\text{Figure 5: Plot of } pK_a \text{ versus } E_s \text{ for 5-X-1, 2, 3, 4-tetrazoles}
\]

\[
\text{Figure 6: Plot of } (pK_a - \delta E_s) \text{ versus Taft } \sigma^*_{\text{ortho}} \text{ for 5-X-1, 2, 3, 4-tetrazoles}
\]

Taft \(\sigma^*_{\text{ortho}} = -1.36\)

\(R = 0.9763\)
For this, several iterations are done between zero and 1.0 for Taft $\delta$. Finally using a value of Taft $\delta = 0.25$ is best suited; the Taft steric reaction constant, figure 6 is made after subtracting the steric effects from $pK_a$. The correlation (figure 6) again with the deviation of NH$_2$ (blue square) indicating the strong solvation of 1H tautomer by water forming hydrogen bonding (scheme 4B). Application of Taft-Pavelich four parameter equation [4] to the $pK_a$ data is another strong indication of the $ortho$ effects originate from 1H-tautomer (scheme 1). The study of Taft-Pavelich four parameter equation from our group is frequently observed in several kinetic studies [5-8].

Table 2 gives the data of gas phase dipole moments, Hammett $\sigma_{para}$, $\sigma_{meta}$, Taft $\sigma^*_{ortho}$ and $E_{s/ortho}$ values of seven 5-X-1,2,3,4-tetrazoles. Figures 7-10 are the Hammett and Taft plots using dipole moments. From figures 7 and 8, it is clear that the correlation of dipole moments values with $para$ and $meta$ substituents is good ($R = 0.9652$ and 0.9517) with 2H tautomer. And from figure 9 it is clear that the correlation of dipole moments values with $ortho$ substituents is good ($R = 0.9375$) with 1H tautomer. And there was no correlation with Taft $E_{s/ortho}$ values (figure 10). The same explanations offered in the correlations of $pK_a$ values above with Hammett $\sigma_{para}$, $\sigma_{meta}$, Taft $\sigma^*_{ortho}$ and $E_{s/ortho}$ values will hold good in the correlations using dipole moments.

| Sl.No. | R     | Hammett $\sigma$ | Taft $\sigma^*_{ortho}$ | $E_{s}$ | Dipole moments ($\mu$D)$^a$ |
|--------|-------|------------------|-------------------------|--------|--------------------------|
|        |       | $para$ $meta$    | $sigma^*_{ortho}$ $E_{s}$ | 1H     | 2H                       |
| 1      | H     | 0.00             | 0.00                    | 0.49   | 1.24                     | 5.338 | 2.271 |
| 2      | CH$_3$| -0.17            | -0.07                   | 0.00   | 0.00                     | 5.738 | 2.106 |
| 3      | t-Bu | -0.20            | -0.10                   | -0.30  | -1.54                    | 5.725 | 1.991 |
| 4      | Ph    | -0.01            | 0.06                    | 0.6    | -2.58                    | 5.960 | 2.048 |
| 5      | Cl    | 0.23             | 0.37                    | 2.96   | 0.27                     | 4.636 | 2.821 |
| 6      | CF$_3$| 0.54             | 0.43                    | 2.61   | -1.16                    | 4.056 | 3.422 |
| 7      | NO$_2$| 0.80             | 0.71                    | 4.00   | -1.28                    | 3.374 | 4.860 |

$^a$from reference 3
Figure 7: Hammett plot of dipole moments ($\mu/D$) versus Hammett $\sigma_{\text{para}}$ for 5-X-1,2,3,4-tetrazoles (2H tautomer).

Hammett $\rho_{\text{para}} = 2.69$

$R = 0.9652$

Figure 8: Hammett plot of dipole moments ($\mu/D$) versus Hammett $\sigma_{\text{meta}}$ for 5-X-1,2,3,4-tetrazoles (2H tautomer).

Hammett $\rho_{\text{meta}} = 3.26$

$R = 0.9517$
Our analysis further gets support from the previously reported tentative ρ-σ analysis [3] in studying the existence of high percentage of 1H tautomers of 5-X-1,2,3,4-tetrazoles in solution compared to 2H tautomers.
Reactivity-Selectivity principle:

| Sl. No. | with pKₐ values | 2H Tautomer (a)15-22% in solvents whose dielectric constant > 2 | 1H Tautomer (a)78-85% in solvents whose dielectric constant > 2 |
|---------|------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| 1       | ρ<sub>para</sub> | ρ<sub>meta</sub> | ρ<sub>ortho</sub>* | 6.56       | 7.79       | 1.36       |
| 2       | with dipole moments | 2.69       | 3.26       | -0.55       |

*a*(1) Butler, R.N., *Comprehensive Heterocyclic Chemistry, II*, Katritzky, A.R., Rees, C.W., and Scriven, E.F.V., Eds., Oxford: Pergamon, 1996, vol. 4, p. 621.

(2) Butler, R.N., *Comprehensive Heterocyclic Chemistry, I*, Katritzky, A.R. and Rees, C.W., Eds., New York: Pergamon, 1984, vol. 4, p. 791.

(3) Elguero, J., Marzin, C., Katritzky, A.R., and Linda, P., *The Tautomerism of Heterocycles*, New York: Academic Press, 1976, p. 287.

From the table 2 it can be seen that the dipole moments of 1H-tautomer are higher than that of 2H-tautomer by 2-3 orders of magnitude indicating that the 1H-tautomer is more polar than the 2H-tautomer [3]. From the table 3 it can be seen that the Taft reaction constants (ρ*) of more polar 1H-tautomer are less than the Hammett reaction constants (ρ) of less polar 2H-tautomer by a factor of 5. Therefore, as a principle of structure-function study it can be stated that the more polar is the 1H-tautomer of tetrazole less is its susceptibility to substituent effects (Taft ρ*) and less polar is the 2H-tautomer more is its susceptibility to substituent effects (Hammett ρ = 7.18 average of the ρ<sub>para</sub> and ρ<sub>meta</sub>). Probably mimicking of principle of structure-function study is for the first time on a chemical property like NH deprotonation and on a physical property like dipole moment from our laboratory. There was a report by one of the authors (JV) on the application of similar study like reactivity-selectivity principle on a chemical property of reactivities of unstable carbocation intermediates [9].

**Therefore, Hammett and Taft equations are proved to be novel tools for the first time in identifying the 1H and 2H tautomers of tetrazole. And mimicking principle of structure-function relation on a chemical property like NH deprotonation and on a physical property like dipole moment for the first time is observed.**
The readers should note that the Hammett and Taft reaction constants (\(\rho\) and \(\rho^*\)) are given as positive numbers though as they were obtained as negative numbers in the plots because the plots are done using \(pK_a (= - \log K_a)\) values.

**Conclusions:** The Hammett and Taft equations are proved to be simple novel tools for the first time in identifying the 1H and 2H tautomers of tetrazole. And mimicking of structure-function relation on a chemical property like NH deprotonation and on a physical property like dipole moment for the first time is observed. Hence the authors believe that their study recalls the Reactivity-Selectivity Principle as Professor Herbert Mayer [10] pointed out is still an “Imperishable myth in Organic Chemistry”.

**Conflict of interest:** The authors declare that they don’t have any kind of competing interest.
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