Research Article

A New Approach to Find Out the Correlation Between Nucleophilicity Index (N) and Hammett Constant

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Abstract

Nucleophilicity index (N) is a Conceptual Density Functional Theory-based reactivity descriptor which is used to define variety of physicochemical behaviours. Nucleophilicity index (N) is a measure of the electron donating power of an atom, molecule or ion and it is the inverse of electrophilicity index (ω) which is the electron attracting power of the species. In the present work we made an attempt to find out a correlation between Nucleophilicity index (N) and Hammett constant σ_p for 32CA reactions of a series of aromatic azides and alkynes, for this purpose we used a theoretical model to describe the Hammett substituent constants σ_p in terms of the nucleophilicity index (N). We have selected the B3LYP/6-31G(d) level of theory in most of the scales of the reactivity indices. We found a good linear correlation between them. The nucleophilic activation/deactivation is explained by theoretical scale of reactivity very nicely.

Keywords: Electrophilicity Index; Nucleophilicity Index; Hammett Constant

Introduction

As from the literature, we are familiar about the important application of triazloes in various fields like in bioconjugation problems, in drug designing [1-3]. Some [3+2] cycloaddition reactions which are recently introduced caught our attention [4]. These reactions occur in a regioselective pattern which provide the 1,4-disubstituted triazole isomer [5]. A variety of research has been done which depict the mechanistic pathways of these 32CA reactions [6,7]. 32CA reaction of between azides work as three atom component (TACs). TACs is categorised into different types [8]. In some recent work it is observed that substituent effect could alter the mechanism of a reaction from rigorous single step to stepwise pathway for few TAC azide compounds [9]. One of the empirical methods is linear free energy relationship which helps to understand the substituent effect on the reactivity of azides and alkynes. Hammett equation depict a linear free energy relationship and Hammett constant measure the electronic effects of replacing hydrogen by a given substituent [10]. Hammett constant provides useful information about structure-property and structure-activity studies [11]. There are various Conceptual Density Functional Theory-based reactivity descriptors which are used to describe a variety of of physicochemical properties [12].

Hammett equation [2,3] relates the reaction rates and equilibrium constants for many reactions with two parameters that are reaction constant (ρ) and substituent constant (σ_p) according to equation (1) [13].

$$\log \frac{K}{K_\circ} = \sigma \rho_P \quad \text{-----------(1)}$$

The electrophilic and nucleophilic behaviors of organic molecules can be described by using the reactivity indices which

are defined in conceptual DFT framework [12,14]. Electrophilicity can be calculated by using the approach of Parr., *et al.* [15].

$$\omega = \frac{\mu^2}{2\eta}$$ ------------ (2)

Here the term used that is μ and η refer to chemical potential and chemical hardness respectively. Electrophilicity index (ω), is a measure of the ability of a molecule to take up electrons. Some recent studies show a linear correlation between σ_p and ω [16,17].
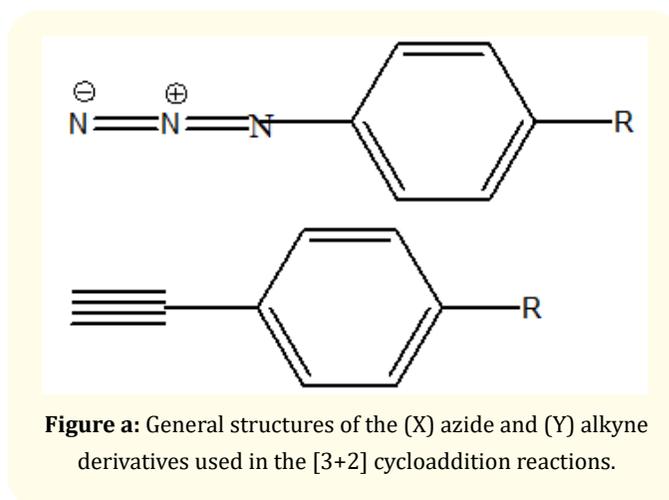

Figure a: General structures of the (X) azide and (Y) alkyne derivatives used in the [3+2] cycloaddition reactions.

Yi	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10	Y11	Y12
R	H	CH_3	F	$COOCH_3$	OPh	CHO	Br	Cl	COOH	$COCH_3$	CN	C_4H_9

Table 1: Substituent (R) for azide derivatives.

Xi	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12
R	H	CH_3	OCH_3	Br	F	CL	COOH	$COOCH_3$	$COCH_3$	C_4H_9	$CONH_2$	CN

Table 2: Substituent (R) for alkyne derivatives.

Methods of computation

In this particular work we have tried to find out a correlation between Hammett substituent constant and nucleophilicity index (N). For this purpose we have calculated the electrophilicity index by using equation (3).

$$\omega = \frac{\mu^2}{2\eta} = \frac{\left(\frac{E_H + E_L}{2}\right)^2}{(E_L - E_H)}$$ ----------(3)

We have computed frontier orbital energies (E_H and E_L) [18] at B3LYP/6-31G(d) level of theory [19]. Then according to Chattaraj and Maiti, Nucleophilicity is defined as the inverse of electrophilicity index (ω) which is the electron attracting power of the species [20].

$$N = \frac{1}{\omega}$$ --------------(4)

By using equation (4) we have calculated the nucleophilicty. This nucleophilicity is then correlated with Hammett substituent constants σ_p.

Results and Discussion

In tables 1 and 2, the nucleophilicity pattern of the substituted azide (X) and alkyne (Y) derivatives which are used in the [3+2] cycloaddition reaction can be seen. As expected, substitutions with electron withdrawing groups cause nucleophilic deactivation and substitution with electron donating group result in nucleophilic activation. This effect of substituent on nucleophilicity can be shown in table 3. For alkynes series this behaviour is also obtained. From the reference compound Y1 (N = 0.88), para substitution with ER groups (-CH_3) tend to increase the nucleophilic activation (N = 0.94) and the substitution of EW groups F, Cl, I tend to deactivate nucleophilicity. A linear correlation is found between the nucleophilicity index (N) and Hammett constant, it can be seen in figures 1 and 2. All the reactivity indices which are used in present study can be seen from table 1. Mayr., *et al.* [21,22] explains the importance of this reactivity scale.

Compound	R	μ	η	ω	N = 1/ω	σ_p^a
X1	H	-3.62	5.14	1.27	0.78	0.00
X2	Me	-3.48	5.03	1.21	0.82	-0.17
X3	MeO	-3.29	4.76	1.13	0.88	-0.27
X4	Br	-3.75	5.01	1.42	0.70	0.23
X5	F	-3.67	5.03	1.34	0.74	0.06
X6	Cl	-3.78	5.03	1.42	0.70	0.23
X7	COOH	-4.82	4.79	1.79	0.55	0.45
X8	COOMe	-4.05	4.82	1.71	0.58	0.45
X9	COMe	-4.16	4.65	1.86	0.53	0.50
X10	tert-butyl	-3.46	5.03	1.19	0.84	-0.20
X11	CONH2	-3.97	4.93	1.60	0.62	0.36
X12	CN	-4.33	4.82	1.94	0.51	0.66
Y1	H	-3.51	5.52	1.13	0.88	0.00
Y2	Me	-3.37	5.39	1.06	0.94	-0.17
Y3	F	-3.54	5.47	1.14	0.87	0.06
Y4	COOMe	-4.11	4.84	1.74	0.57	0.45
Y5	PhO	-3.24	5.12	1.03	0.97	-0.03
Y6	CHO	-4.41	4.63	2.10	0.47	0.42
Y7	Br	-3.73	5.22	1.33	0.75	0.23
Y8	Cl	-3.75	5.28	1.32	0.75	0.23
Y9	COOH	-4.22	4.87	1.82	0.54	0.45
Y10	COMe	-4.22	4.71	1.90	0.52	0.50
Y11	CN	--4.38	4.90	1.97	0.50	0.66
Y12	tert-butyl	-3.35	6.07	0.92	1.08	-0.089

Table 3: Electronic chemical potential (μ), chemical hardness (η), global electrophilicity (ω), Global nucleophilicity index (N) in ev,

Hammett constant σ_p^a.

[a] Hammett substituent constants σ_p taken from reference [14].

Figure 1: Plot of nucleophilicity (N) versus the Hammett constants for para substituents in the azide series.

Figure 2: Plot of nucleophilicity (N) versus the Hammett constants for para substituents in the alkyne series.

Conclusions

Our study presents a good linear correlation between the global nucleophilicity indices (N) and experimental Hammett substituent constants σ_p. The effect of substituent can determine the reactivity of both azide and alkyne derivatives. The present work suggests a new approach to find the correlations among various reactivity indices.

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