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Relationship between electrophilicity index, Hammett constant and nucleus-independent chemical shift

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Abstract. Inter-relationships between the electrophilicity index (w), Hammett constant (σ_p) and nucleus-independent chemical shift (NICS (1) – NICS value one ångstrom above the ring centre) have been investigated for a series of meta- and para-substituted benzoic acids. Good linear relationships between Hammett constant vs electrophilicity and Hammett constant vs NICS (1) values have been observed. However, the variation of NICS (1) against w shows only a low correlation coefficient.

Keywords. Electrophilicity; Hammett constant; NICS (1); reactivity; QSAR.

1. Introduction

Conceptual density functional theory (DFT) has been widely used to study the chemical reactivity and site selectivity of various molecular systems.^{1–3} The success of DFT is that it provides simple working equations to elucidate stability and reactivity. It is important to analyse the usefulness of DFT-based global reactivity descriptors in understanding the aromaticity of various hydrocarbons.³ In recent years, there has been tremendous interest in understanding the origin of the aromaticity. Schleyer *et al*^{4–8} have made seminal contributions in the field of aromaticity of hydrocarbons by proposing the idea of the nucleus-independent chemical shift (NICS). NICS is defined as the negative value of the absolute magnetic shielding calculated at the ring centre. NICS (0) represents the NICS value at the centre of the ring and NICS (1) is the NICS value of the molecule 1 Å above the ring centre. Schleyer and his coworkers⁶ have established that NICS (1) provides appropriate information about the aromaticity of various hydrocarbons. Within this model, the aromatic rings are assumed to be the rings with negative values of NICS. The more the negative value of this descriptor the greater is the aromatic character of the molecular

system. The success of NICS as a measure of the aromaticity is highly conspicuous and NICS has been employed as an effective index of aromaticity. Recently, the relevance of NICS in understanding the aromaticity in benzene and related compounds has been studied.⁹

Development of new chemical reactivity descriptors has gained significant momentum due to their application in various areas of chemistry, biology, rational drug design and computer-aided toxicity prediction.¹⁰ In quantitative structure activity and reactivity parlance, the use of Hammett constants is well known.^{11,12} The Hammett equation is given by

$$\log (k/k_0) = rS_p, \quad (1)$$

where k and k_0 are rate (or equilibrium) constants for the reactions of the substituted and unsubstituted compounds, S_p is the Hammett constant (substituent constant), and r is called the reaction constant. The Hammett equation has been one of the most widely used means for the study and interpretation of organic reactions and their mechanisms.

Several attempts have been made to relate the Hammett constant with various reactivity parameters for the development of new reactivity descriptors.¹³ The use of electrostatic potential in the QSAR parla-

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nce has also been attempted.¹⁴ Gadre and Suresh¹⁵ have probed the relation between S_p and the most negative valued MESP (V_{\min}) for several mono- and di-substituted aromatic compounds. It was found from these studies that electrostatic potential is a succinct tool in describing the reactivity of these substituted aromatic compounds.¹⁵

Formal definitions and working equations of global hardness, global softness and chemical potential are provided in several previous works.¹⁻³ In addition to these global quantities, recently, Parr *et al*¹⁶ have proposed the global electrophilicity power (electrophilicity index, w) of a molecule in terms of its chemical potential and chemical hardness as,

$$w = m^2/2h, \quad (2)$$

where $m \approx -(I + A)/2$ and $h = (I - A)/2$ are the electronic chemical potential and chemical hardness of the ground state of atoms and molecules respectively, approximated in terms of the vertical ionization potential (I) and electron affinity (A) using Koopmans' theorem. w describes the electrophilic power of a ligand and also its propensity to soak up electrons.¹⁶ This index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. By definition, it encompasses both the ability of an electrophile to acquire additional electronic charge and the resistance of the system to exchange electronic charge with the environment.

One of the important goals in physical organic chemistry is to have an appropriate description of the chemical substituents in the reactivity patterns of molecules.¹⁷ Several systematic linear relationships between substituent groups and chemical reactivities/properties have been developed.^{18,19} In this context, some important results relevant to reactivity descriptors based on DFT are mentioned. Electrophilicity index has been used to classify a series of reagents present in Diels–Alder reactions and 1,3-dipolar cycloadditions.²⁰ Good correlation between the difference in electrophilicity for diene and dienophile or dipole and dipolarophile pair and feasibility of cycloadditions has been found.²¹ Linear relationships between NICS and S_p , and NICS and chemical hardness have been recently obtained for *p*-substituted benzyl cations.^{13a} The relationship between various aromaticity indices and NICS has also been studied.^{13b} Recently Domingo *et al*^{13c} have compared the experimental S_p values and electronic electrophilicity

index w for a series of 42 substituted ethylenes. In their work, a statistical procedure has been developed to obtain intrinsic electronic contributions to S_p -based on the comparison between the experimental Hammett constant and electrophilicity index evaluated for a series of functional groups present in organic compounds. The aim of the present investigation is to extend and explore the possible inter-relationships between Hammett constant, NICS (1) and electrophilicity index for a series of meta- and para-substituted benzoic acids. Although the aromaticity–hardness relationship has already been investigated, such illustrations have not been probed in detail for electrophilicity index. Since electrophilicity contains an additional term namely chemical potential, its importance has been addressed in this study to develop a more, general descriptor of chemical reactivity which has been employed to get useful insights into various problems.^{22,23} From the linear relationships among the various descriptors, electronic contributions to Hammett constant have been assessed.

2. Computational details

Figure 1 shows the structural representation of all the substituted benzoic acid molecules considered in this study. Geometries of the molecules are optimised using Gaussian 98²⁴ employing HF method with four different basis sets. To probe the effect of basis set in the calculated values of various descriptors and the correlation coefficient, four different basis sets such as 6-311G*, 6-31G**, 6-31+G** and 6-31G* have been chosen. The calculated vibrational frequencies for all the molecules ensured that the geometries corresponding to the minimum energy are achieved. Various reactivity descriptors have been calculated using the standard working equations described earlier.¹⁻³ Adopting the procedure suggested by Schleyer *et al*.⁴ NICS (1) values have been calcula-

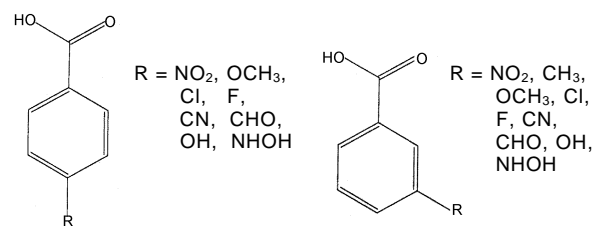


Figure 1. Structures of eight para-substituted benzoic acids and nine meta-substituted benzoic acids.

ted. Linear regression analysis has been performed to obtain the relationship between Hammett constant and NICS (1) with w . The S_p values for the various molecular systems have been taken from the earlier reports.¹¹

3. Results and discussion

Calculated R^2 values for various interrelations between the S_p , NICS (1), and w are presented in table 1. Figure 2a represents the calculated Hammett constants (S_p^{fit1}) vs experimental S_p . The S_p^{fit1} are obtained from the following linear regression equation,

$$S_p^{\text{fit1}} = 0.027 * w + 0.865. \quad (3)$$

It is evident from the R^2 values presented in table 1 and the plot represented in Figure 2a that there is fairly good linear relation between the Hammett constants and the electrophilicity index. The reason for good correlation between S_p and w can be attributed to the fact that w is a measure of the electrophilic power of the group and the sign of S_p describes electron-withdrawing or -donating nature of the substituent group. A positive value of S_p ensures that the substituent group is electron-withdrawing in nature and the reactivity of the molecule is expected to be high, on the other hand a negative value implies the electron-donating nature of the substituent and the reactivity of the molecule is thus less. In a recent study, Domingo *et al*^{13c} have observed a logarithmic relation between S_p and w . However, for the substituent groups considered in this study, we have found a linear correlation between the Hammett constants and electrophilicity index. The close agreement between S_p^{fit1} and S_p ensures good correlation between these descriptors of chemical reactivity and stability. The calculations have also been made using different basis sets to obtain the best estimates of various parameters. There is no unique basis set that provides better estimates of correlation coefficient for various interrelationships. In this case, the 6-311G* basis set yields better correlation between S_p and w values.

NICS (1)^{fit} represents the NICS (1) values obtained from linear regression analysis between NICS (1) values calculated using Schleyer's approach and w .⁴ The variation of NICS(1)^{fit} vs NICS (1) is depicted in figure 2b. Although there is a linear relationship between NICS (1) and electrophilicity index, the R^2 value for this fit is 0.51. It is an established

fact that individually NICS (1) and w describe the aromaticity and chemical reactivity respectively. Hence it is natural to expect a better correlation bet-

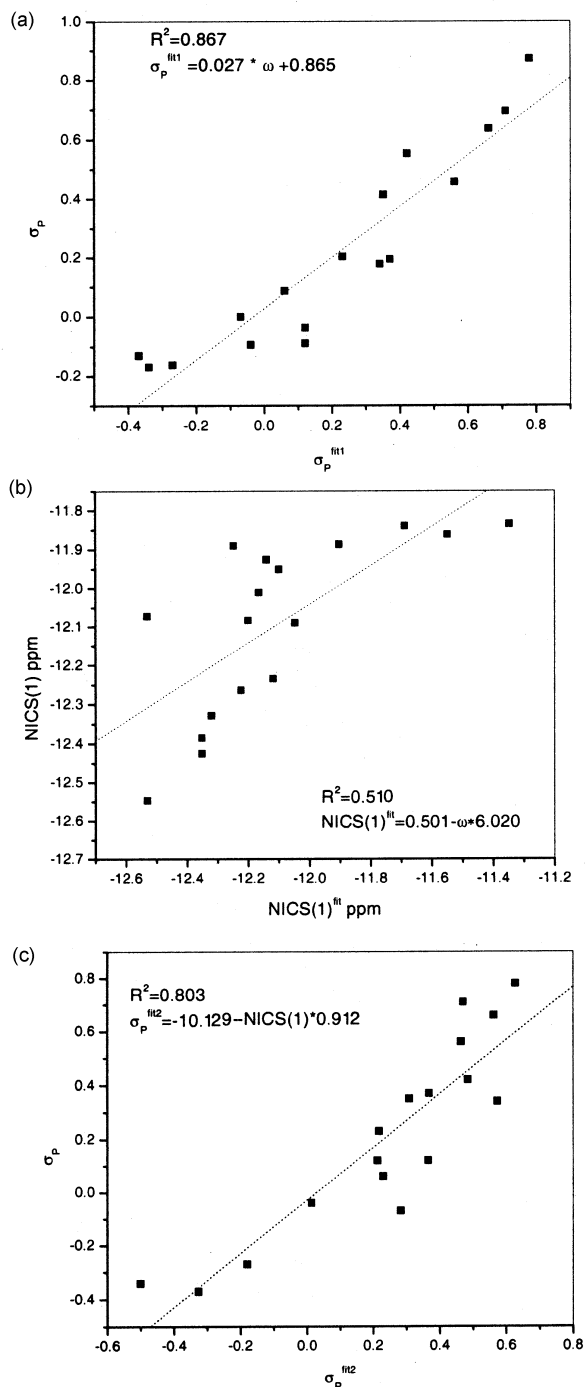


Figure 2. Linear plots between (a) S_p vs calculated S_p^{fit1} at HF/6-311G* level, (b) NICS (1) vs NICS (1)^{fit} at HF/6-311G* level, and (c) S_p vs S_p^{fit2} at HF/6-31+G** level.

Table 1. R^2 values for various plots between S_p , NICS (1), and w at HF level with four different basis sets.

	S_p	w	NICS (1)
S_p	1.000*		
	1.000°		
	1.000+		
	1.000•		
w	0.867*	1.000*	
	0.857°	1.000°	
	0.854+	1.000+	
	0.753•	1.000•	
NICS (1)	0.740*	0.473*	1.000*
	0.721°	0.445°	1.000°
	0.753+	0.508+	1.000+
	0.803•	0.438•	1.000•

HF/6-311G, °HF/6-31G**; +HF/6-31G*; •HF/6-31+G**

ween these two quantities. Contrary to this expectation, regression analysis reveals that there is no good correlation between aromatic criteria and w . However, the inverse relations between NICS (1) values for all molecules and w indicate that highly aromatic systems have low reactivity as exemplified by the w values. Since w contains a hardness term in the denominator which is a descriptor of stability, it is expected that aromaticity and w will exhibit an inverse linear relationship. However, the electrophilicity encompasses a chemical potential term in addition to hardness. It is possible to note from the R^2 value obtained from the linear least square analysis that chemical potential has profound influence on the relationship. It is important to point out here that the dimensions of chemical hardness and electronegativity are the same and that the square of the chemical potential is the same as the square of the electronegativity. It is expected that electrophilicity and electronegativity will show the similar trends in most cases which is in conformity with chemical intuition.

The plot of S_p^{fit2} vs S_p is depicted in figure 2c. From the regression analysis between S_p and NICS (1) values, S_p^{fit2} has been calculated. It is evident from the results that there is a good correlation between S_p and NICS (1) values.

4. Conclusion

It is possible to obtain linear relationships between Hammett constants of various substituted benzoic acids with their corresponding electrophilicity indices. Evidently, electrophilicity index can be used in

QSAR parlance. In this context, it is pertinent to mention that electrophilicity contains information about both electron transfer (chemical potential) and stability (hardness), it is expected to be a better descriptor of global chemical reactivity, as has been authenticated in many studies.^{13c,22,23} Similarly the linear regression analysis of the data between NICS (1) and δ_p showed good correlation confirming the high aromaticity–low reactivity pattern. When compared to these linear variations, the correlation coefficient of NICS (1) vs w is found to be lower. This may be attributed to the role of the chemical potential term present in the definition of electrophilicity index. Results from the linear regression analysis and S_p^{fit1} and S_p^{fit2} values indicate that it is highly feasible to obtain information about electronic contributions to the Hammett constants which may serve as an effective tool to forecast chemical reactivity.

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