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RESEARCH ARTICLE

Application of Conceptual Density Functional Theory Descriptors for Electrophilic Aromatic Substitution

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Dedicated to Professor Gyorgy Keglevich on his 60th Birthday

Abstract

The conceptual density functional theory descriptors, namely Mulliken and Hirshfeld charges, global hardness and softness, Fukui functions, electronic chemical potentials, and nucleophilic indices of several mono-substituted benzene derivatives and electrophilic indices of some electrophiles have been calculated at the B3LYP/-31+G(d) level in the gas phase. Instead of the Mulliken charges, density of the Hirshfeld charges at the three positions are in accordance with the experimentally observed directing effects of the substituent groups in electrophilic aromatic substitution. The Fukui functions though explain the *ortho/para* directing effects, but fail to rationalize the *meta* directing effect. The chemical potential and the nucleophilicity indices are well in accordance with the experimentally observed activating/deactivating effect of the substituent groups. The electrophilicity indices of some electrophiles indicate their relative strengths.

Keywords: Conceptual DFT descriptors, Electronic chemical potential, Electrophilic aromatic substitution, Fukui function, Hirshfeld charges, Mulliken charges.

Introduction

Reactivity reflects the susceptibility of a particular site in the substrate towards a reagent in a chemical reaction, and thus plays a key role in designing synthesis of new compounds, understanding biological systems, and material science (Bultinck *et al*., 2007). The density functional theory (DFT) based on Hohenberg-Kohn theorems and later on the Kohn-Sham approximation made it possible to study progress of the organic reactions with manageable computational costs (Hohenberg and Kohn,1964; Kohn and Sham,1965). In continuation to this, Parr and co-worker (1995) developed 'Conceptual DFT', a sub-field of DFT, with the help of which, one can understand and predict the chemical reactivity of a molecule or a particular site therein. This field has allowed putting many important quantities such as electronegativity, electronegativity equalization, the theory of hard and soft acids and bases, chemical potential and many more, on a firmer theoretical footing. The field has even led to new concepts, e.g., the maximum hardness principle.

The Fukui function is among the most basic and commonly used reactivity indicators. It is defined as:

$$f(r,N) = \left(\frac{\partial(\delta E/\delta\vartheta_{ext})_N}{\partial N}\right)\vartheta_{ext}$$

where,

E is the energy,

N the number of electrons, and

ϑ_{ext} is the external potential

By the Hellmann-Feynman theorem and for non-degenerate cases, the Fukui function is given as the change in the density function ρ(r,N) of the molecule as a consequence of changing the number of electrons N in the molecule under the constraint of a constant external potential. Therefore,

The Fukui function can thus be regarded as a

$$f(r,N) = \left(\frac{\partial\rho(r,N)}{\partial N}\right)\vartheta_{ext}$$

generalization of Frontier Molecular Orbital (FMO) theory. It predicts how additional electron density will be redistributed in a molecule. The form of the function

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will depend on whether or not an electron was removed or added from the molecule.

Mendez and Gázquez (1994) extended the concept of hard-soft acid-base (HSAB) theory to explain the global and local reactivity of organic molecules towards nucleophilic and electrophilic reagents. Thus, the chemical reactivity at a particular molecular site could be rationalized by using a quantitative descriptor, the Fukui function (f(r)), arising from finite difference approximation. Thus, the Fukui function was defined as:

$$f^{+}(r) = \rho_{N+1}(r) - \rho_{N}(r) \quad \text{[nucleophilic attack]} \quad (1)$$

$$f^{-}(r) = \rho_{N}(r) - \rho_{N-1}(r) \quad \text{[electrophilic attack]} \quad (2)$$

Where ρ_N+1(r), ρ_N(r) and ρ_N-1(r) are the electron densities at a point r in the system with N+1, N and N-1 electrons, respectively, all with the ground state geometry of the N electron system.

They concluded, 'regions of a molecule where the Fukui function is large are chemically softer than the regions where the Fukui function is small and by invoking the HSAB principle in a local sense, one may establish the behaviour of different sites with respect to hard or soft reagents' (Mendez and Gázquez,1994).

Yang and Mortier (1986) subsequently suggested the use of the gross charge (qr) at a particular atom r in a molecule obtained from Mulliken population analysis (MPA) to determine the condensed Fukui function (*f(r)*) at that atom. Thus

$$f^{+}(r) = qr(N+1) - qr(N) \quad \text{[nucleophilic attack]} \quad (3)$$

$$f^{-}(r) = qr(N) - qr(N-1) \quad \text{[electrophilic attack]} \quad (4)$$

Fuentealba *et al.* (2000) suggested that the DFT based on the Hohenberg–Kohn theorem could be used successfully in understanding the chemical reactivity correlated with the chemical potential μ defined in DFT as:

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{\vartheta}$$

The electrophilicity index ω as defined by Parr *et al.* (1999) is a measure of the stabilisation energy of a molecule on acquiring additional electron density ΔN. It is expressed by the equation

$$\omega = \frac{\mu^2}{2\eta}$$

where μ and η are the chemical potential and global hardness respectively.

On the other hand, the nucleophilicity index N represented the tendency of the molecule to donate electrons. Domingo *et al.* (2008) correlated the relative nucleophilicity index N with the HOMO energies obtainable from the Kohn-Sham scheme as

$$N = E_{HOMO}(\text{Nucleophile}) - E_{HOMO}(\text{TCNE})$$

tetracyanoethylene (TCNE), the most electrophilic neutral species was taken as the reference.

Electrophilic aromatic substitution reaction wherein a hydrogen atom attached to the aromatic ring such as benzene is replaced by an electrophile constitutes an important synthetic method for obtaining a variety of aromatic substituted products. The regioselectivity and the kinetics of the reaction are governed by the nature of the substituent group(s) already present in the aromatic ring. On the basis of these two parameters, the substituent groups have been broadly classified into two groups- the *ortho/para* directing and *activating* and the *meta directing* and *deactivating*. In the classical organic chemistry textbooks, (Carey and Sundberg, 2000; Solomons *et al.*, 2013) the directing and the activating/deactivating effects have been rationalised on the basis of the resonance and inductive effects. After the development of the conceptual DFT, it became tempting to correlate regioselectivity and activating/deactivating effect of the substituent groups in electrophilic aromatic substitution reactions with the reactivity descriptors obtainable from the DFT calculations. Liu (2014) investigated a large number of monosubstituted benzene derivatives for their directing effect towards electrophilic substitution and correlated the regioselectivity with the Hirshfeld charge- *ortho/para* directing groups were found to have greater negative charges on the *ortho/para* positions, whereas *meta* directing groups had the greater negative charge on the *meta* position. Furthermore, a strong correlation was found between the Hirshfeld charge and the HOMO energy level- greater the Hirshfeld charge, higher the HOMO energy level thereby making donation of the electrons to the LUMO of the electrophile easier resulting in the activating effect. However, no mention was made of the Fukui functions and the Mulliken charges at different positions of the monosubstituted benzene derivatives in this paper. Melin *et al.* (2004) calculated Fukui functions and charges (Mulliken and Hirshfeld) of hydroxylamine derivatives, their sulphur containing variants and amino acids and concluded that hard-hard

interactions are better explained in terms of charges. These results motivated us to calculate some DFT descriptors of a few selected monosubstituted benzene derivatives and electrophilic reagents besides Fukui functions and Mulliken and Hirshfeld charges at different positions of the mono-substituted benzene derivatives and examine their applicability to explaining the directing and activating/deactivating effects.

Material and Mehtods

Computational Methods

Gaussian 16 suite of programs(Frisch *et al.*, 2016)was used for all calculations and geometries were optimized in the gas phase at the B3LYP/6-31+G(d) level of theory. Frequency calculations were done at the same level to determine zero-point corrections and to characterize energy minimum by the presence of no imaginary frequency.

Natural bond orbital analysis as incorporated in Gaussian 16 was done at the B3LYP/6-31+G(d) level (Reed and Weinhold, 1985).

Chemical reactivity indices were calculated as follows:

$N = E_{HOMO}$ (nucleophile) - E_{HOMO} (TCNE)

$f^{+}(r) = qr_{(N+1)} - qr_{(N)}$

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

$$S = \frac{1}{2\eta}$$

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$f^{+}(r) = qr_{(N+1)} - qr_{(N)}$

$f^{-}(r) = qr_{(N)} - qr_{(N-1)}$

Results and Discussion

Directing Effect of the Substituent Groups

Mulliken and Hirshfeld charges

Mulliken and Hirshfeld charges at different positions in benzene and mono substituted benzene derivatives calculated at the B3LYP/6-31+G(d) level are given in Table 1.

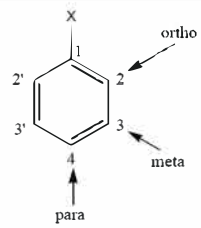
If we look closely at the Mulliken charges at the *ortho*, *meta* and *para* positions of the monosubstituted benzene derivatives having *ortho/para* directing group (CH_3, NH_2, OH, OEt, Cl), they are not consistent with the experimentally observed directing effect. For example, in toluene (X = CH_3), the negative charges at the *ortho*, *meta* and *para* positions are -0.002, -0.024 and -0.178 respectively. According to this pattern, the incoming electrophile should enter mainly at the *para* position followed by the *meta* position, which is contrary to the experimental results. Similarly in the case of aniline (X = NH_2), the charges at the *ortho*, *meta* and *para* positions are -0.123, -0.309 and -0.208 respectively indicating *meta* position as the preferred position for the electrophilic substitution which is not consistent with the experimental facts. Similar inconsistency is observed in the case of the benzene derivatives having *a meta*-directing group (X = -CHO, -$COCH_3$,-COOH, -NO_2, -CN, -SO_3H) when density of the negative charge is smaller at the *meta* position than at the *ortho* and/or *para* position(s). Thus, Mulliken charge cannot be used as the descriptor to rationalise the directing effect of the substituent groups in electrophilic substitution.

It is however noteworthy that densities of the Hirshfeld charges at the three positions both in the case of the *ortho/para* as well as *meta* directing groups are in complete accordance with the experimental observation. For example, in the case of toluene, density of the negative charges at the *ortho* (-0.047) and *para* (-0.048) is greater than at the *meta* (-0.043) position. Similarly in the case of the *meta* directing groups, density of the negative charge at the *meta* position is greater than at the *ortho/para* positions. For example, in the case of benzaldehyde (X = CHO), density of the negative charge at the meta position (-0.037) is greater than at the *ortho* (-0.027) and *para* (-0.024) positions making the meta position as the preferred site for further electrophilic substitution. From this it may be concluded that in contrast to the Mulliken charge, Hirshfeld charge is an appropriate descriptor for the directing effect of the substituent groups in electrophilic substitution. These results are in consonance with the earlier reported results (Liu, 2014).

Fukui Functions

As mentioned earlier, Mendez and Gázquez (1994) extended the concept of hard-soft acid-base (HSAB) theory to explain the global and local reactivity of organic molecules towards nucleophilic and electrophilic reagents and the descriptor, Fukui function

Table 1. Mulliken and Hirshfeld charges at different positions in benzene and monosubstituted benzene derivatives calculated at the B3LYP/6-31+G(d) level



X	Mulliken charges			Hirshfeld charges		
	Ortho	*meta*	*para*	*Ortho*	*meta*	*para*
-H	-0.178	-0.178	-0.178	-0.042	-0.042	-0.042
-CH_3	-0.002	-0.024	-0.178	-0.047	-0.043	-0.048
-NH_2	-0.123	-0.309	-0.208	-0.068	-0.042	-0.064
-OH	-0.042	-0.279	-0.174	-0.057	-0.037	-0.057
-OEt	-0.363	-0.268	-0.147	-0.059	-0.041	-0.060
-Cl	-0.269	-0.241	-0.163	-0.045	-0.034	-0.041
-CHO	-0.748	-0.164	-0.159	-0.027	-0.037	-0.024
-$COCH_3$	-0.892	-0.323	-0.173	-0.032	-0.040	-0.027
-COOH	-0.330	-0.207	-0.173	-0.022	-0.035	-0.026
-NO_2	-0.059	-0.253	-0.069	-0.025	-0.028	-0.019
-CN	-0.245	-0.092	-0.166	-0.019	-0.306	-0.024
-SO_3H	-0.414	-0.182	-0.254	-0.030	-0.030	-0.022

Table 2. Fukui functions at different positions in monosubstituted benzene derivatives calculated from the Mulliken and Hirshfeld charges for the electrophilic attack at the B3LYP/6-31+G(d) level

X	Fukui function calculated from Mulliken charges			Fukui function calculated from Hirshfeld charges		
	Ortho	*meta*	*Para*	*ortho*	*meta*	*para*
-CH_3	-0.064	-0.001	-0.136	-0.082	-0.068	-0.150
-NH_2	-0.115	0.007	-0.149	-0.657	-0.024	0.002
-OH	-0.114	0.016	-0.153	-0.09	-0.065	-0.143
-OEt	0.02	-0.055	0.005	-0.023	-0.084	-0.056
-Cl	-0.092	-0.005	-0.129	-0.019	0.068	-0.037
-CHO	0	-0.026	-0.047	-0.044	-0.044	-0.072
-$COCH_3$	0.04	-0.029	-0.049	-0.039	-0.043	-0.065
-COOH	-0.138	0.001	-0.051	-0.138	-0.063	-0.093
-NO_2	-0.172	-0.072	-0.025	-0.12	-0.128	-0.049
-CN	-0.04	-0.033	-0.112	-0.066	-0.069	-0.355
-SO_3H	-0.017	-0.026	-0.041	-0.027	-0.040	-0.060

was used for this purpose. Recently, we rationalised the addition of amines across the carbonyl group (1,2-addition) instead across the -CH=CH- functionality on the basis of Fukui functions (Kour *et al*., 2017). In view of this, we considered it prudent to calculate Fukui functions at the three positions of monosubstituted benzene derivatives and examine if it can also be used as a descriptor for predicting the directing effect of the substituent groups. The values of the Fukui functions at different positions in benzene and monosubstituted benzene derivatives calculated from the Mulliken and Hirshfeld charges at the B3LYP/6-31+G(d) level are given in Table 2.

As mentioned earlier, a smaller value of the Fukui function reveals harder character of a particular site in the molecule. It is interesting to find that the values of the Fukui functions both calculated from the Mulliken and Hirschfeld charges at the *ortho* and *para* positions of the monosubstituted benzene derivatives having *ortho/para* directing group (X = CH_3, NH_2, OH, OEt, Cl) are smaller than at the *meta* position revealing their comparatively harder character. For example, in the case of toluene, values of the Fukui functions at the *ortho*, *meta* and *para* positions are -0.064, -0.001, -0.136 (calculated from Mulliken charges) and -0.082, -0.068 and -0.150 (calculated from Hirshfeld charges) respectively. In both case, values at the *ortho* and *para* positions are smaller showing their harder character. Thus, a hard electrophile such as the nitronium ion (N^+O_2) will attack preferentially the *ortho/para* positions which is in agreement with the experimental results. However, in the case of the *meta* directing substituent groups, pattern of the values of the Fukui functions is contrary to the experimental observation. For example, in the case of benzaldehyde (X = CHO), values of the Fukui functions at the *ortho*, *meta* and *para* positions are 0.0, -0.026, -0.047 (calculated from Mulliken charges) and -0.044, -0.044 and -0.15 (calculated from Hirshfeld charges) respectively. In both cases, value of the Fukui function is smallest at the *para* position indicating it to be the hardest site. Thus, according to it, the electrophile should attack *para* position preferentially, which is contrary to the experiments observation. Thus, Fukui function cannot be used as the descriptor to explain the directing effect of the substituent groups in electrophilic aromatic

Table 3. Energies of Frontier Molecular Orbitals, Global hardness, global softness, electronic chemical potential, electrophilicity and nucleophilicity indices computed at the B3LYP/def2-SVP level

Species	E_{HOMO} (eV)	E_{LUMO} (eV)	Global hardness	Global softness (S ev)	Electronic chemical potential	Electrophilicity index (ω eV) x10 ²	Nucleophilicity index (N eV)* x 10²
Ph-H	-0.2571	-0.0144	0.121	4.132	-0.136	-	8.87
Ph-CH_3	-0.2452	-0.0141	0.115	4.347	-0.130	-	10.06
Ph-NH_2	-0.2101	-0.0104	0.100	5.00	-0.110	-	13.57
Ph-OH	-0.2320	-0.0178	-0.107	4.672	-0.124	-	12.22
Ph-OEt	-0.2236	-0.0126	0.105	4.761	-0.118	-	12.22
Ph-Cl	-0.2552	-0.0285	0.113	4.424	-0.141	-	9.06
Ph-CHO	-0.2686	-0.0784	0.0951	5.257	-0.173	-	7.72
Ph-$COCH_3$	-0.2599	-0.0709	0.0945	5.29	-0.165	-	8.99
Ph-COOH	-0.2720	-0.0651	0.103	4.854	-0.168	-	7.38
Ph-NO_2	-0.2899	-0.1072	0.091	5.494	-0.198	-	5.59
Ph-CN	-0.2775	-0.0658	0.105	4.761	-0.171	-	6.83
Ph-SO_3H	-0.2749	-0.1435	0.065	7.692	-0.209	-	7.09
N^+O_2	-0.7668	-0.4242	0.171	2.923	-1.191	414.76	-
CH_3COCl	-0.3098	-0.0563	0.128	3.906	-0.182	12.94	-
$CH_3COAlCl_4$	-0.1942	-0.1338	0.030	16.55	-0.164	44.83	-
CH_3Cl	-0.3026	-0.0085	0.147	3.401	-0.155	8.27	-
CH_3AlCl_4	-0.3137	-0.0584	0.127	3.937	-0.186	13.62	-
SO_3	-0.3616	-0.1253	0.118	4.237	-0.243	25.02	-

* N = E_{HOMO} (species) – E_{HOMO}(TCNE) (E_{HOMO} TCNE = 0.3458 eV calculated at the same level)

substitution. It is in agreement with the observation that Fukui function explains soft-soft interactions but not the hard-hard interactions (Melin *et al.*, 2004).

Activating/deactivating effect

The values of global hardness (η), softness(S), chemical potential (μ), electrophilicity (ω) and nucleophilicity(*N*) indices of monosubstituted benzene derivatives and some electrophiles calculated at the B3LYP/6-31+G(D) are given in Table 3.

The activating/deactivating effects of the substituent groups in electrophilic aromatic substitution can be rationalized on the basis of two descriptors, namely electronic chemical potential (μ) and nucleophilicity index (N). Similarly, the electrophilicity of an electrophile can be adjudged quantitatively from its electrophilicity index (ω).

The electronic chemical potential (μ) is a measure of efficacy of charge transfer from a species of higher chemical potential to the system having lower chemical potential. It may be noted that chemical potential of benzene (- 0.136 eV) is higher than that of the nitronium ion (N^+O_2, - 0.191) indicating that there will be effective electron transfer from the former to the latter. This gap further increases in the case of $PhNH_2$ > PhOEt > PhOH > $PhCH_3$ and hence rate of nitration is expected to decrease in this order. The gap between the chemical potentials of chlorobenzene (- 0.141) and nitronium ion is smaller than between benzene and nitronium ion. Thus, nitration of chlorobenzene is expected to occur less readily than of benzene, which is in accordance with the experimental results. On this basis, the deactivating effects of the substituent groups –CHO, $COCH_3$, COOH, NO_2, CN and SO_3Hcan be rationalized.

The electrophilicity (ω) and nucleophilicity (*N*) indices have been found useful indicators to explain relative reactivities of molecules in chemical reactions (Perez *et al.*, 2007; Domingo and Perez, 2011; Domingo *et al.*, 2016). A conclusion similar to the one obtained from the chemical potential can be drawn from the nucleophilicity index, N about the activating/deactivating effect of the substituent group. It may be noted that the N values of $PhNH_2$ > PhOEt ~ PhOH > $PhCH_3$ are greater than that of benzene confirming the activating effect of the substituent group. On the other hand, values of the nucleophilicity indices of monosubstituted benzene derivatives having deactivating substituent group are smaller than that of benzene with the exception of chlorobenzene. Thus, these derivatives are expected to undergo electrophilic substitution less readily as compared to benzene. The unexpected value of the nucleophilic index of chlorobenzene possibly results due to +M effect of the chlorine atom.

Likewise, values of the electrophilic indices of the electrophiles reveal their relative electrophilic strength. A high value of the electrophilic index of nitronium ion (ω = 414.76) reveals its quite strong electrophilic character. It may be noted that in the presence of the Lewis acid $AlCl_3$, the electrophilicities of acetyl chloride and methyl chloride are increased manifold.

Conclusions

In electrophilic aromatic substitution reactions, the directing effect and the activating/deactivating effect are two principal variables depending on the nature of the substituent group already present. Conceptual DFT descriptors can be used to rationalize these effects with some limitations. Although Mulliken charges fail to rationalize the directing effect, Hirshfeld charges calculated at the same theory level are well in accordance with the experimentally observed results. The electronic chemical potential of the monosubstituted benzene derivative can be successfully used to explain the observed activating/deactivating effect. Similarly, conclusions drawn about the activating/deactivating effects from nucleophilicity indices are also similar with the exception of chlorobenzene. The unexpected greater value of the nucleophilic index of chlorobenzene as compared to benzene possibly results due to +M effect of the chlorine atom. Electrophilicity indices of a few electrophilic species are in accordance with their observed electrophilic strengths.

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