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Stockholders Charge Partitioning Technique. A Reliable Electron Population Analysis Scheme to Predict Intramolecular Reactivity Sequence

Ram Kinkar Roy†

Department of Chemistry, Birla Institute of Technology and Science (BITS), Pilani-333031, Rajasthan, India

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Stockholders charge partitioning (i.e., Hirshfeld population analysis) is used to evaluate the intramolecular reactivity sequence (i.e., site selectivity) of some chosen alkyl halides. It is shown that the local reactivity descriptors, e.g., condensed local softness (or condensed Fukui function indices) in general and “relative electrophilicity” and “relative nucleophilicity” in particular, when evaluated by Hirshfeld population analysis, correctly reproduce the strongest electrophilic center in all 18 systems chosen in the present study. No manipulation of the charge summation scheme, i.e., addition of H-charges on the carbon atoms to which they are bonded, is required here as was done in a previous study (Roy, R. K. *J. Phys. Chem*. **2003**, *107*, 397) on the same systems using Mulliken population analysis. Extension of the study to polyfunctional systems (e.g., *m*-chloroaniline and *m*-anisidine) also shows that HPA correctly predicts the gas phase protonation site although MPA fails. This clearly indicates that Hirshfeld population analysis is superior to Mulliken population analysis as a charge-partitioning scheme (i.e., Hirshfeld population analysis provides a more reliable definition of atoms in molecules) as long as the intramolecular reactivity trend is concerned.

1. Introduction

In the past few years there is renewed interest in the goodness of Hirshfeld population analysis (HPA)[1] and its comparative reliability to other charge partitioning schemes. Roy et al.[2] first showed that HPA produces nonnegative (and hence physically more realistic) condensed Fukui function (FF) indices.[3] Also, it was shown that electronic population derived on the basis of HPA produces more reliable intramolecular reactivity trends[2] when compared to those obtained from Mulliken population analysis (MPA),[4] natural bond orbital (NBO) analysis,[5] and molecular electrostatic potential (MESP) based methods.[6] Through analytical derivation of condensed FF indices in terms of HPA and MPA, it was shown that the stockholder nature of HPA is responsible for its superiority over other charge partitioning schemes.[7] Even when ΔN (i.e., electron change) tends to zero (thus making the relaxation effect negligible), the sign of condensed FF indices derived from MPA was shown to be unpredictable.[8] Subsequently, there are quite a number of studies in this area,[9−11] and some others have analytically shown that the HPA is a superior charge partitioning scheme because it suffers from minimum missing information when atoms form a molecule.[12−15]

Now coming to the point of a theoretical study of nucleophilic substitution reactions, the matter become complicated when molecular electrostatic potential (MESP)[6] is used as the reactivity descriptors (because the potential always shows the maximum over a nuclei and thus masking the real active site), although some alternative methods have been suggested to avoid it.[16] However, studies have shown that no such problem appears when density functional theory (DFT) based local reactivity descriptors, e.g., local softness[17] or FF’s,[3] are used.

Recently Parr et al.[18] have proposed a new global electrophilicity index of any chemical species, which is the square of its electronegativity divided by its chemical hardness. A successful application of this newly defined global reactivity index was made by Domingo et al.,[19] who could characterize quantitatively the global electrophilicity power of common diene/dienophile pairs used in Diels−Alder reactions. In a separate interesting study,[20] the same group has extended the concept of global electrophilicity index to define local electrophilicity index and successfully explained the regioselectivity in Diels−Alder reactions. Intermolecular reactivity trends in carbonyl compounds and organic acids was explained successfully by Krishnamurty and Pal[21] using “group softness” as the reactivity parameters. Chandrakumar and Pal[22] have proposed a model, based on the local hard and soft acid−base (HSAB)[23] principle, which explains the preferable site of attack in the case of multiple site interaction.

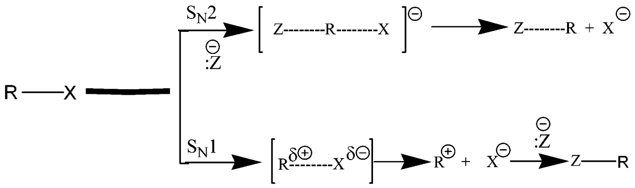

Figure 1. Scheme of S_N1 and S_N2 reactions of alkyl halides. Here $:Z^{(-)}$ is the attacking nucleophile (Nu^-).

The nucleophilic substitution reactions (both bimolecular, i.e., S_N2 and unimolecular, i.e., S_N1) at the C_{C-X} (C atom of the C−X moiety) of alkyl halides are among the most intensely studied of all chemical reactions and nowadays a textbook subject.[24] These two types of reactions are schematically represented in Figure 1. Now for S_N1 or S_N2, whichever way the substitution reaction proceeds, the most preferable center for nucleophilic attack should be C_{C-X}. So the concern is whether the condensed FF indices or local softness values of the atomic centers in the alkyl halides can really predict C_{C-X}

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† E-mail address: rkoy@bits-pilani.ac.in.

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to be the strongest electrophilic center to initiate a nucleophilic attack on it.

In a recent article,[25] the present author has shown that when local reactivity descriptors were evaluated from MPA-based charges, C_{C-X} does not appear to be the strongest electrophilic center. The situation become more complicated when in several cases local reactivity descriptors appeared to be negatively valued. This failure to produce the correct intramolecular reactivity trends was attributed to improper charge partitioning adopted by MPA. However, C_{C-X} appears to be the strongest electrophilic center when charges on the H atoms were summed on the C atoms to which they are bonded and then intramolecular reactivity trends were evaluated. The logic behind adopting this new technique is that C_{C-X} pulls the electron density from the attached hydrogen atoms to compensate it's deficiency (generated due to C → X electron pull). However, this electron withdrawing is overestimated in MPA, causing unreliable intramolecular reactivity trends.

A critical analysis of the reliability of HPA is carried out in the present study. The local reactivity descriptors of the individual atomic centers are calculated on the basis of HPA derived charges to verify whether C_{C-X} really emerges as the most preferable electrophilic site. As an extension of the study, two polyfunctional systems, e.g., *m*-chloroaniline (*m*-ClC_6H_4-NH_2) and *m*-anisidine (*m*-$OMeC_6H_4NH_2$), are chosen. The prediction of the most preferable nucleophilic sites in these two systems is critical as experimental evidence suggests the existence of two such competing sites in each of them (for details, see section 4).

The article is structured as follows: In section 2.(i) a brief discussion on the background of DFT based local reactivity descriptors are made. Stockholder nature of HPA is discussed analytically in section 2(ii). The methodology adopted in the present study and the computational techniques have been elaborated in section 3. Section 4 contains the discussion on the results obtained in the study. In the concluding section (section 5), the final outcome of the study is summarized.

2. Theoretical Background

(i) A. Local Reactivity Descriptors Based on Softness and Fukui Function Indices. The density functional theory (DFT) based local reactivity descriptors which we will be using in the present study are the Fukui function (FF) indices ($f(\bar{r})$) introduced originally by Parr and Yang.[3] They are defined as

$$s(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v(\bar{r})}\left(\frac{\partial N}{\partial \mu}\right)_{v(\bar{r})} = f(\bar{r})S = \left(\frac{\partial \mu}{\partial v(\bar{r})}\right)_{N} S \qquad (1)$$

Here, N, μ, and $v(\bar{r})$ represent the number of electrons, chemical potential, and external potential (i.e., the potential due to the positions of the nuclei plus applied external field, if any) at position $\bar{r}$ of the chemical species. From eq 1 it is obvious that when $f(\bar{r})$ is multiplied by S, the global softness parameter, we get the local softness ($s(\bar{r})$), i.e.

$$s(\bar{r}) = f(\bar{r})S \qquad (2)$$

Thus, we can say that the information held by $f(\bar{r})$ and $s(\bar{r})$ is the same, i.e., the sensitivity of the chemical potential of the system to the local external perturbation.[26] However, $s(\bar{r})$ contains some additional information about the global molecular softness.

The details of S and its working equation are discussed in most of the other studies in this area including ref 25. In general, at some integral value of N_0, the derivative $\partial\rho/\partial N$ may produce three values, i.e., one value from the right, one from the left, and an average. Three such indices can be written as

$$f^{+}(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v}^{+}$$

$$\text{(derivative as } \Delta N \text{ increases from } N_0 \rightarrow N_0 + \delta) \qquad (3a)$$

$$f^{-}(\bar{r}) = \left(\frac{\partial \rho(\bar{r})}{\partial N}\right)_{v}^{-}$$

$$\text{(derivative as } \Delta N \text{ increases from } N_0 - \delta \rightarrow N_0) \qquad (3b)$$

$$f^{0}(\bar{r}) = \frac{1}{2}[f^{+}(\bar{r}) + f^{-}(\bar{r})]$$

$$\text{(mean of left and right derivatives)} \qquad (3c)$$

Yang and Mortier[27] have proposed approximate atomic $f(\bar{r})$ indices by applying the finite difference approximation to the condensed electronic population on any atom. Thus, we have three operational forms of approximate atomic $f(\bar{r})$ indices (from eq 3a−c) which, when multiplied by S, provide three different types of local softness for any particular atom k. These can be written as

$$s_k^{+} = [\rho_k(N_0 + 1) - \rho_k(N_0)]S$$

$$\text{(suited for studies of nucleophilic attack)} \qquad (4a)$$

$$s_k^{-} = [\rho_k(N_0) - \rho_k(N_0 - 1)]S$$

$$\text{(suited for studies of electrophilic attack)} \qquad (4b)$$

$$s_k^{0} = \frac{1}{2}[\rho_k(N_0 + 1) - \rho_k(N_0 - 1)]S$$

$$\text{(suited for studies of radical attack)} \qquad (4c)$$

where $\rho_k(N_0)$, $\rho_k(N_0 - 1)$, and $\rho_k(N_0 + 1)$ represent the electronic population on atom k for the N_0, $N_0 - 1$, and $N_0 + 1$ electron systems, respectively.

B. "Relative Electrophilicity" and "Relative Nucleophilicity". Although parts a−c of eq 4 are found to be very useful in generating the experimentally observed intramolecular reactivity trends in previously studied cases,[28,29] a few deviations have been reported by Roy et al.[30] On the basis of condensed FF (local softness) indices, Roy et al. introduced two different local reactivity descriptors, "relative electrophilicity" (s_k^{+}/s_k^{-}) and "relative nucleophilicity" (s_k^{-}/s_k^{+}) of any particular atom k, to locate the preferable site for nucleophilic and electrophilic attack on it, respectively. The advantage of this new proposition consists of the fact that the individual values of s_k^{+} and s_k^{-} are strongly influenced by the basis set or correlation effects. However, the ratio of s_k^{+} and s_k^{-}, involving two differences of electron densities (see eq 4, parts a and b) of the same system differing by one in their number of electrons, at constant nuclear framework, are expected to be less sensitive to the basis set and correlation effects.[30] These two newly proposed reactivity descriptors are shown to generate improved intramolecular reactivity trends than those obtained from condensed FF indices.[30,31] The general scheme to employ these two newly proposed local reactivity descriptors for predicting the preferable reactive site is as follows:

(i) Choose only the sites (i.e., atoms) having comparable and higher s_k^{+} and s_k^{-} values.

(ii) Then compare s_k^{+}/s_k^{-} and s_k^{-}/s_k^{+} values of these sites only.

(iii) If for any site, $s_k^{+}/s_k^{-} > s_k^{-}/s_k^{+}$, then it is the preferred electrophilic and vice versa.

However, when Mulliken population analysis (MPA) based charges are used to evaluate $s_k{}^+$ and $s_k{}^-$ values, the author observed that[25] neither $s_k{}^+$ nor $s_k{}^+/s_k{}^-$ could precisely detect the strongest electrophilic center (i.e., C_{C-X}) in all 18 chosen alkyl halides (to be discussed in section 3). The situation becomes more complicated because in several cases $s_k{}^-$ values come out to be negative thus making $s_k{}^+/s_k{}^-$ also negatively valued. After carefully analyzing the factors of this failure, a new scheme for evaluating $s_k{}^+$, $s_k{}^-$ and $s_k{}^0$ was proposed The equations for condensed FF indices following this new scheme for the C atom in CH_3-X molecules can be presented as

$$s_C{}^+ = [\rho_{CH_3}(N_0+1) - \rho_{CH_3}(N_0)]S \quad \text{(suited for studies of nucleophilic attack)} \tag{5a}$$

$$s_C{}^- = [\rho_{CH_3}(N_0) - \rho_{CH_3}(N_0-1)]S \quad \text{(suited for studies of electrophilic attack)} \tag{5b}$$

$$s_C{}^0 = \frac{1}{2}[\rho_{CH_3}(N_0+1) - \rho_{CH_3}(N_0-1)]S \quad \text{(suited for studies of radical attack)} \tag{5c}$$

Here, $\rho_{CH_3}(N_0)$, $\rho_{CH_3}(N_0-1)$ and $\rho_{CH_3}(N_0+1)$ represents the electronic population on the fragment $-(CH_3)$ for the N_0, N_0-1, and N_0+1 electron systems, respectively. It should be mentioned that similar kinds of approaches were adopted by Contreras et al.[32] to evaluate the local reactivity indices within a static reactivity picture.

(ii) Evaluation of Local Reactivity Descriptors Using Hirshfeld Population Analysis (HPA). As mentioned in the introductory section, Roy et al.[2] has shown that "relative electrophilicity" ($s_k{}^+/s_k{}^-$) and "relative nucleophilicity" ($s_k{}^-/s_k{}^+$), when evaluated through Hirshfeld's population analysis, produce the more reliable local reactivity trends than when the same reactivity descriptors are evaluated through MPA. Also HPA generates nonnegative condensed FF indices, which are physically more realistic than the negative condensed FF indices generated by MPA and other charge partitioning techniques in some cases. Here is a brief discussion of HPA.

This kind of charge partitioning technique is due to Hirshfeld,[1] in which the partitioned charges are defined relative to the "deformation density". The "deformation density" $\rho_d(\bar{r})$ is the difference between the "molecular" and the "un-relaxed" atomic charge densities (defined as "promolecular density") and is expressed as

$$\rho_d(\bar{r}) = \rho^{mol}(\bar{r}) - \rho^{pro}(\bar{r}) = \rho^{mol}(\bar{r}) - \sum_{\alpha}\rho_\alpha(\bar{r} - \bar{R}_\alpha) \tag{6}$$

Here, $\rho^{mol}(\bar{r})$ is the "molecular charge density" at a site $\bar{r}$, $\rho^{pro}(\bar{r})$ is the "promolecular charge density" at the same site, and $\rho_\alpha(\bar{r} - \bar{R}_\alpha)$ is the spherically averaged ground-state charge density of the free atom α suitably positioned at coordinate $\bar{R}_\alpha$.

Now the effective atomic charge q_α, on a particular atom α, can be expressed as

$$q_\alpha = -\int \rho_d(\bar{r}) w_\alpha(\bar{r})\, d^3\bar{r} \tag{7}$$

Here, the negative sign obeys the convention of negative electron charge and $w_\alpha(\bar{r})$ is the "sharing function" which measures the relative share of the atom α in the "promolecular density" at the position $\bar{r}$. $w_\alpha(\bar{r})$ is expressed as

$$w_\alpha(\bar{r}) = \rho_\alpha(\bar{r} - \bar{R}_\alpha)\ [\sum_\beta \rho_\beta(\bar{r} - \bar{R}_\beta)]^{-1} \tag{8}$$

So, in the stockholders partitioning technique, the molecular charge density at each point is divided among the atoms of the molecule in proportion to their respective contributions to the "promolecular density" at that point. Thus, "like partners in a stockholders" corporation, each atom partakes of the local gain or loss in direct proportion to its share in the capital investment.

Subsequently, there are several numerical[9-11] and analytical[12-15] studies regarding the superiority of HPA over others as a charge partitioning schemes because HPA retains more information on atoms in molecules.

In the present study local reactivity descriptors of the chosen alkyl halides will be evaluated using the charges as defined by HPA and the reliability of the generated intramolecular reactivity trends will be analyzed.

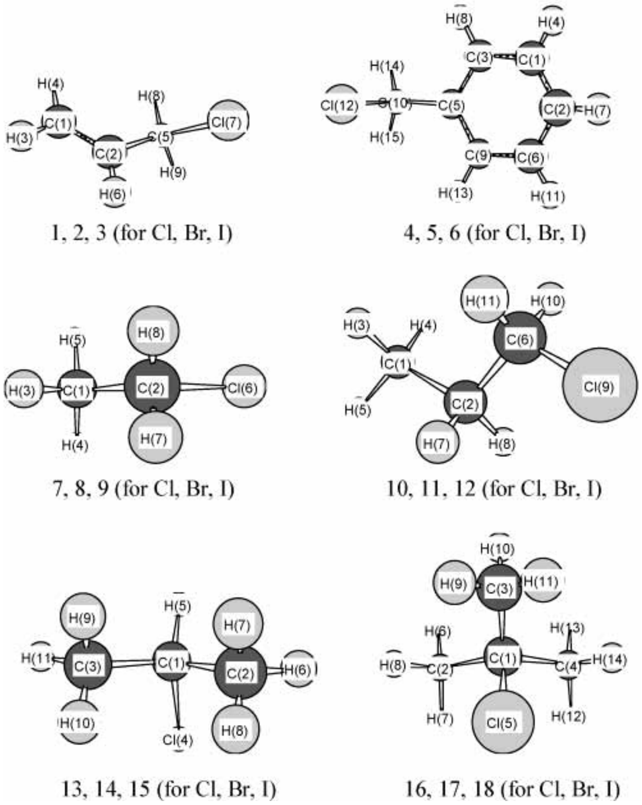
3. Methodology and Computational Details

To investigate the reliability of the local reactivity descriptors, evaluated from HPA based charges, 18 alkyl halides are chosen. They are the chlorides, bromides and iodides of six different alkyl groups. These are allyl ($-CH_2CH{=}CH_2$), benzyl ($-CH_2C_6H_5$), ethyl ($-CH_2CH_3$), *n*-propyl ($-CH_2CH_2CH_3$), isopropyl ($-CH(CH3)_2$), and *tert*-butyl ($-C(CH_3)_3$) groups. Incidentally these are the same alkyl halides chosen in ref 25. Apart from these halides two polyfunctional systems, *m*-$ClC_6H_4NH_2$ and *m*-$OMeC_6H_4NH_2$, are also chosen. Geometries are generated using the CHEM-3D program package[33] and optimized at lower level (semiempirical). For alkyl halides these geometries are further reoptimized at two higher levels: BLYP/dnd and BLYP/dnp. For *m*-$ClC_6H_4NH_2$ and *m*-$OMeC_6H_4NH_2$ geometries are reoptimized at four different higher levels: BLYP/dnd, BLYP/dnp, HF/6-31G*, and HF/6-31G**. Here in the BLYP method, gradient-corrected exchange and correlation functionals are used. The exchange functional is as proposed by Becke[34] and the correlation functional is as suggested by Lee, Yang, and Parr.[35] The "dnp" level basis set is of double-numeric quality (i.e., approximately two atomic orbitals for each one occupied in the free atom) augmented with polarization functions (i.e., functions with angular momentum one higher than that of highest occupied orbital in free atom). The "dnd" level basis set is similar to the "dnp" basis except that no "p" functions are used on hydrogen. The size of the "dnd" level basis is comparable to Gaussian 6-31G* basis sets, and "dnp" basis sets are comparable to 6-31G** sets. Both "dnd" and "dnp" are as included in the DMOL^3 program package.[36] Calculations at HF/6-31G* and 6-31G** levels are performed using the Gaussian 98 program package.[37]

The pictures of the alkyl halides with the numberings of the atoms are shown in Figure 2. Each of the 18 halides is denoted by an identification number e.g., $CH_2{=}CH-CH_2Cl$ = **1**, $CH_2{=}CH-CH_2Br$ = **2**, $C_6H_5CH_2I$ = **6**, etc. for simplicity of discussion in the latter part of the article.

4. Results and Discussion

A. Electrophilicity of C_{C-X} at Equilibrium Geometry on the Basis of Hirshfeld Population Analysis (HPA) Derived Charges. In Table 1 a list of the atomic charges q_k and $s_k{}^+$ and $s_k{}^+/s_k{}^-$ values of C_{C-X} and X_{C-X} (halogen atom bonded to the C−X bond) are given. These values are based on HPA and for the equilibrium geometries of the alkyl halides. Only for allyl halides (i.e., **1**, **2**, **3**; see Figure 2) the corresponding values for another carbon atom (i.e., C_1) are also shown. This is because the C_1 atoms in these three halides also exhibit significant nucleophilicity, perhaps because of the presence of the conjugative allyl double bond. Values generated from BLYP/dnd and



1, 2, 3 (for Cl, Br, I)

4, 5, 6 (for Cl, Br, I)

7, 8, 9 (for Cl, Br, I)

10, 11, 12 (for Cl, Br, I)

13, 14, 15 (for Cl, Br, I)

16, 17, 18 (for Cl, Br, I)

Figure 2. Alkyl halides (with numbering of atoms) chosen in the present study.

BLYP/dnp methods are tabulated separately under two main columns. The negative charge values of C_{C-X} in several systems go against normal expectation as C_{C-X} should be the electrophilic center. So, nucleophilic attack on this carbon during the substitution process cannot be explained on the basis of charge values.

A careful analysis of s_k^+ values reveals some interesting outcomes. In the case of allyl halides (systems **1**, **2**, **3**), the s_k^+ values indicate that electrophilicity should have the order as follows:

$$X_{C-X} > C_1 > C_5 \text{ (i.e., } C_{C-X})$$

which again goes against our expectation as C_5 should be the strongest electrophilic center. The s_k^+ values of C_{C-X} and X_{C-X} of the remaining 15 systems also incorrectly predict X_{C-X} to be the strongest electrophilic center instead of C_{C-X}.

However, an interesting and very encouraging thing happens when we analyze s_k^+/s_k^- values. By comparing these values in the case of allyl halides, the trend of electrophilicity becomes as shown below:

$$C_5 \text{ (i.e., } C_{C-X}) > C_1 > X_{C-X}$$

This is the trend which we also expect for a nucleophilic attack on C_{C-X} in the course of substitution reaction process. For the remaining 15 systems, the trends of s_k^+/s_k^- values are also perfectly as expected. In all the systems, C_{C-X} emerges as the strongest electrophilic center.

It is also worthwhile to mention that the q_k, s_k^+, and s_k^+/s_k^- values of all the atoms are evaluated in the present study. However, values for C_1, C_5 (i.e., C_{C-X}) and X_{C-X} for allyl halides and C_{C-X} and X_{C-X} for other halides are shown in Table 1 because these are the atoms which show high s_k^+ values [please see section 2(i)B]. Also it is very encouraging that the s_k^-/s_k^+ values (i.e., "relative nucleophilicity") are highest for X_{C-X} in all 18 systems (values are not shown in Table 1 to reduce unnecessary space occupation), correctly predicting X_{C-X} to be the strongest electrophilic center. The above observations remain almost identical in either of the two methods, i.e., BLYP/dnd and BLYP/dnp, except for some minor numerical changes not affecting the trends.

TABLE 1: HPA-Based Charges (q_k), s_k^+, and s_k^+/s_k^- Values for Carbon and Halogen Atoms Attached to the C−X (X = Cl, Br, and I) Bonds of the Alkyl Halides Considered in the Present Study[a]

		methods					
		BLYP/dnd			BLYP/dnp		
alkyl halides	atomic centers	q_k	s_k^+	s_k^+/s_k^-	q_k	s_k^+	s_k^+/s_k^-
	C_1	−0.0748	0.4198	1.0574	−0.0740	0.4166	1.0542
1	C_5	−0.0143	0.2304	1.8355	−0.0175	0.2275	1.8175
	Cl	−0.1054	0.6354	0.6732	−0.1028	0.6431	0.6807
	C_1	−0.0714	0.4109	1.0620	−0.0703	0.4096	1.0660
2	C_5	−0.0267	0.2760	2.1504	−0.0284	0.2754	2.1315
	Br	−0.0975	0.9068	0.7301	−0.0971	0.9063	0.7283
	C_1	−0.0736	0.3971	1.0698	−0.0723	0.3862	1.0745
3	C_5	−0.0479	0.3041	2.3304	−0.0490	0.2965	2.3185
	I	−0.0676	1.2469	0.7688	−0.0677	1.2148	0.7663
4	C_{10}	−0.0154	0.1672	1.9676	−0.0188	0.1646	1.9510
	Cl	−0.1108	0.5132	0.7130	−0.1082	0.5160	0.7155
5	C_{10}	−0.0285	0.2160	2.3710	−0.0305	0.2151	2.3505
	Br	−0.1042	0.7540	0.7614	−0.1037	0.7503	0.7567
6	C_{10}	−0.0497	0.2464	2.5611	−0.0510	0.2472	2.5410
	I	−0.0743	1.0535	0.7883	−0.0749	1.0527	0.7831
7	C_2	−0.0095	0.3045	1.7233	−0.0117	0.3021	1.7034
	Cl	−0.1022	0.6777	0.6114	−0.1003	0.6887	0.6231
8	C_2	−0.0308	0.2862	1.8902	−0.0226	0.3174	2.0043
	Br	−0.0706	0.8459	0.6306	−0.0899	0.8946	0.6401
9	C_2	−0.0441	0.3889	2.3922	−0.0442	0.3768	2.3225
	I	−0.0581	1.4163	0.7445	−0.0586	1.3657	0.7273
10	C_6	−0.0132	0.2293	1.8117	−0.0157	0.2299	1.8238
	Cl	−0.1018	0.5979	0.6272	−0.0995	0.6048	0.6375
11	C_6	−0.0256	0.2736	2.1793	−0.0267	0.2750	2.1907
	Br	−0.0893	0.8447	0.6743	−0.0890	0.8459	0.6783
12	C_6	−0.0477	0.3073	2.3651	−0.0482	0.3019	2.3870
	I	−0.0582	1.1966	0.7085	−0.0583	1.1696	0.7117
13	C_1	0.0306	0.2050	1.7398	0.0318	0.2051	1.7438
	Cl	−0.1039	0.5833	0.5881	−0.1032	0.5955	0.6021
14	C_1	0.0211	0.2540	2.1873	0.0233	0.2562	2.2056
	Br	−0.0947	0.8349	0.6318	−0.0956	0.8371	0.6347
15	C_1	0.0021	0.2952	2.4342	0.0048	0.2992	2.4486
	I	−0.0649	1.2009	0.6778	−0.0663	1.2069	0.6801
16	C_1	0.0716	0.1621	1.8357	0.0760	0.1626	1.8448
	Cl	−0.1035	0.5475	0.5765	−0.1026	0.5595	0.5910
17	C_1	0.0642	0.2163	2.5028	0.0698	0.2196	2.5404
	Br	−0.0971	0.7954	0.6180	−0.0987	0.7990	0.6212
18	C_1	0.0478	0.2634	2.8112	0.0532	0.2663	2.8182
	I	−0.0695	1.1569	0.6587	−0.0710	1.1609	0.6808

[a] The s_k^+ values are in atomic units.

B. Electrophilicity of C_{C-X} on the Basis of Mulliken Population Analysis (MPA) Derived Charges. As mentioned earlier, in a previous study,[25] the present author has shown that the local reactivity descriptors, when evaluated on the basis of MPA-based charges, could not produce the expected trends of electrophilicity in most of the systems chosen here. The present study is extended to verify whether that was due to the artifact of methodology adopted apart from the population analysis scheme. In Table 2, the MPA-based q_k, s_k^+, and s_k^+/s_k^- values of the atoms concerned are tabulated. However, in this case, the methods used are BLYP/dnd and BLYP/dnp (unlike HF/6-31G* and HF/6-31G** in the previous study). It is claimed that numerical basis sets (i.e., "dnd" and "dnp") are superior to Gaussian basis sets of the same quality,[36] i.e., 6-31G* and 6-31G**,[38] respectively. A cursory glance at the values reveals that no improvement in the predictability of the electrophilicity trend is achieved in these methods also. Negative s_k^+/s_k^- values

TABLE 2: MPA-Based Charges (q_k), s_k^+, and s_k^+/s_k^- Values of Carbon and Halogen Atoms Attached to the C−X (X = Cl, Br, and I) Bonds of the Alkyl Halides Considered in the Present Study[a]

alkyl halides	atomic centers	methods					
		BLYP/dnd			BLYP/dnp		
		q_k	s_k^+	s_k^+/s_k^-	q_k	s_k^+	s_k^+/s_k^-
1	C_1	−0.438	0.2871	1.0083	−0.140	0.2855	0.9756
	C_5	−0.391	0.0119	−0.1191	−0.123	0.0071	−0.1200
	Cl	−0.191	0.6288	0.6250	−0.204	0.6044	0.6210
2	C_1	−0.436	0.4109	1.0620	−0.135	0.3008	1.0551
	C_5	−0.414	0.2760	2.1504	−0.112	0.0131	−0.2000
	Br	−0.212	0.9069	0.7301	−0.233	0.9442	0.7308
3	C_1	−0.437	0.3030	1.1556	−0.130	0.3162	1.2065
	C_5	−0.560	−0.0612	1.1667	−0.268	−0.1367	2.6667
	I	−0.106	1.3838	0.8333	−0.126	1.2220	0.7500
4	C_{10}	−0.432	0.0990	−1.5000	−0.136	0.0965	−2.3333
	Cl	−0.192	0.4951	0.6429	−0.204	0.4771	0.6455
5	C_{10}	−0.456	0.0735	−1.5625	−0.130	0.0618	−1.3125
	Br	−0.215	0.7845	0.7629	−0.236	0.7827	0.7578
6	C_{10}	−0.605	−0.0095	0.2727	−0.284	−0.0160	0.4167
	I	−0.110	1.1748	0.8545	−0.131	1.1771	0.8502
7	C_2	−0.345	−0.1264	1.0702	−0.119	−0.1497	2.8800
	Cl	−0.201	0.7705	0.6447	−0.211	0.7486	0.6510
8	C_2	−0.356	−0.0985	1.3636	−0.102	−0.0382	0.7083
	Br	−0.212	0.8490	0.6016	−0.242	0.9087	0.6244
9	C_2	−0.516	−0.0850	2.9091	−0.265	−0.0978	3.3636
		−0.106	1.6124	0.8327	−0.127	1.5406	0.8008
10	C_6	−0.337	0.0464	−0.5116	−0.099	0.0317	−0.6250
	Cl	−0.198	0.5823	0.5644	−0.205	0.5625	0.5672
11	C_6	−0.356	0.0232	−0.3704	−0.082	0.0116	−0.1923
	Br	−0.215	0.8911	0.6773	−0.237	0.8973	0.6844
12	C_6	−0.515	−0.0712	1.9286	−0.252	−0.1958	5.4286
	I	−0.099	1.3574	0.7803	−0.120	1.1206	0.6600
13	C_1	−0.185	−0.0772	0.5069	−0.126	−0.0607	0.5800
	Cl	−0.204	0.5630	0.5143	−0.206	0.5359	0.5100
14	C_1	−0.201	−0.0786	0.6667	−0.120	−0.0789	0.6939
	Br	−0.226	0.8604	0.6118	−0.240	0.8651	0.6153
15	C_1	−0.342	−0.1569	1.9032	−0.262	−0.1551	1.8710
	I	−0.119	1.3485	0.7327	−0.133	1.3582	0.7352
16	C_1	−0.029	−0.0801	0.4066	−0.170	−0.0434	0.3077
	Cl	−0.209	0.5412	0.5040	−0.198	0.5168	0.5042
17	C_1	−0.038	−0.1032	0.6515	−0.149	−0.0843	0.5738
	Br	−0.234	0.8355	0.6000	−0.241	0.8428	0.6066
18	C_1	−0.160	−0.1907	1.6047	−0.268	−0.1691	1.5250
	I	−0.137	1.3184	0.7130	−0.144	1.3247	0.7166

[a] The s_k^+ values are in atomic units.

(due to negative s_k^- values in the denominator) make the situation complicated in several cases [**1**, **2** (only in the case of BLYP/dnp), **4**, **5**, **10**, and **11**]. There are also cases where both s_k^+ and s_k^- values are negative but s_k^+/s_k^- has the highest positive (obviously) value (**3**, **6**, **7**, **8**, **9**, **12**, **13**, **14**, **15**, **16**, **17**, **18**). There is also a case [**2** (only in BLYP/dnd method)], where s_k^+ has a low value (and so cannot be the strongest electrophilic), but the s_k^- *value is so low that the overall* s_k^+/s_k^- is very high and thus wrongly projects "k" to be a strong electrophilic center. All these observations simply point to the fact that the reliability in local reactivity descriptors in general and nonnegativity of s_k^+ and s_k^- values in particular primarily depends on the charge partitioning scheme and not on the basis sets or methods (i.e., HF or DFT) used to evaluate these values.

C. Prediction of the Strongest Nucleophilic Sites in Polyfunctional Systems. To test the superiority of HPA over MPA, the present study is extended to polyfunctional systems. Most preferable nucleophilic sites in *m*-$ClC_6H_4NH_2$ and *m*-$OMeC_6H_4NH_2$ are evaluated by both HPA and MPA. An experimental gas-phase protonation study by Summerhays et al.[39] suggests that in *m*-$ClC_6H_4NH_2$ the protonation takes place preferably on the N_{NH_2} (i.e., the N atom of the $-NH_2$ group), whereas for *m*-$OMeC_6H_4NH_2$ it is the C atom in the para position (i.e., C_{para}) which is protonated mainly. The explanation in favor of above observations is that in *m*-$ClC_6H_4NH_2$ the Cl atom in the meta position pulls the electron density from the two ortho carbon atoms (i.e., from the ortho and para carbon atoms with respect to the NH_2 group) due to its high electronegativity. As a result partial positive charges will be developed on these two sites, making N_{NH_2} the most electron-rich site for protonation

For *m*-$OMeC_6H_4NH_2$, the most electron-rich site is C_{para} because of the +R effect of the −OMe group (due to the presence of two lone pair of electrons on the O atom). So, in this case, C_{para} is preferably attacked by a proton.

In Table 3, the s_k^- and s_k^-/s_k^+ values, based on HPA and calculated by methods BLYP/dnd and BLYP/dnp, are reported. It is obvious from both s_k^- and s_k^-/s_k^+ values that for *m*-chloroaniline N_{NH_2} is the most preferable protonation site. However, for *m*-anisidine s_k^- values in both the methods fail to produce the experimental trends (as s_k^- value for N_{NH_2} is the highest). However, s_k^-/s_k^+ values in both methods correctly predict that C_{para} is the preferable center of protonation.

The corresponding MPA-based values of s_k^- and s_k^-/s_k^+ through methods HF/6-31G* and HF/6-31G** are shown in Table 4. Here we notice that in the case of *m*-$ClC_6H_4NH_2$ both the methods erroneously predict C_{para} to be the preferable site

TABLE 3: HPA-Based s_k^-, and s_k^-/s_k^+ Values of N_{NH_2} and C_{para} and C_{ortho} in *m*-Chloroaniline (Denoted as 1) and *m*-Anisidine (Denoted as 2) (for Details of the Atomic Positions See the Text)[a]

amino compounds	atomic centers	BLYP/dnd s_k^-	BLYP/dnd s_k^-/s_k^+	BLYP/dnp s_k^-	BLYP/dnp s_k^-/s_k^+
1	N_{NH_2}	0.4150	2.1278	0.4125	2.1627
	C_{para}	0.3457	1.7595	0.3444	1.7529
2	N_{NH_2}	0.3621	1.8467	0.3600	1.8650
	C_{ortho}	0.3146	1.7172	0.3130	1.6972
	C_{para}	0.3481	2.1002	0.3474	2.0806

[a] The s_k^- values are in atomic units.

TABLE 4: MPA-Based s_k^-, and s_k^-/s_k^+ Values of N_{NH_2} and C_{para} and C_{ortho} in *m*-Chloroaniline (Denoted as 1) and *m*-Anisidine (Denoted as 2) (for Details of the Atomic Positions See the Text)[a]

amino compounds	atomic centers	HF/6-31G* s_k^-	HF/6-31G* s_k^-/s_k^+	HF/6-31G** s_k^-	HF/6-31G** s_k^-/s_k^+
1	N_{NH_2}	0.2694	5.2293	0.2800	5.1645
	C_{para}	0.3835	−2.6172	0.3873	−2.6127
2	N_{NH_2}	0.1930	3.8064	0.2018	3.7702
	C_{ortho}	0.3121	46.7273	0.3153	34.4644
	C_{para}	0.3794	7.2865	0.3838	

[a] The s_k^- values are in atomic units.

of protonation because it has highest s_k^- value. Prediction on the basis of s_k^-/s_k^+ is not possible as these values are coming negative.

Prediction of preferable protonation site for *m*-$OMeC_6H_4NH_2$ appears to be more complicated. In this case, s_k^- values derived from both methods correctly predict that C_{para} is the most preferable site of protonation, although s_k^-/s_k^+ values wrongly predict it to be the C_{ortho} (i.e., the carbon atom ortho to the $-NH_2$ and para to the $-OMe$ group) position. Even if we accept that prediction on the basis of s_k^- values is correct the observed nucleophilicity trend of $C_{para} > C_{ortho} > N_{NH_2}$ is difficult to establish.

5. Conclusion

The present study clearly establishes the superiority of HPA over MPA as a charge partitioning scheme. That is why we observe unambiguous and expected trends of intramolecular reactivity in all the 18 chosen alkyl halides. This expected trend reconfirms that C_{C-X} of alkyl halides is the primary target of attack by a nucleophile (Nu^-) at the initial stage of substitution reaction.

The author and his collaborators has since past few years claimed that "relative electrophilicity" (s_k^+/s_k^-) and "relative nucleophilicity" (s_k^-/s_k^+) are more reliable local reactivity descriptors when compared to only s_k^+ and s_k^-. This claim is again established undoubtedly in the present study. That is why in Table 1 we observe that although in most cases only s_k^+ values fail to indicate C_{C-X} to be the strongest electrophilic center, s_k^+/s_k^- values do so. It is also encouraging that in both BLYP/dnd and BLYP/dnp methods X_{C-X} appears to be the strongest nucleophilic center (from s_k^-/s_k^+ values, not shown in Table 1). Even for polyfunctional systems the HPA based s_k^-/s_k^+ values appear to be the most reliable reactivity descriptors because the dominant gas-phase protonation sites in *m*-chloroaniline and *m*-anisidine can be predicted by using these descriptors.

Also, the present study reveals that electronic charge is not always a reliable indicator of the preferable site of electrophilic or nucleophilic attack. However, it is the system's response to the change of charge during nucleophilic and electrophilic attack (i.e., s_k^+ and s_k^- respectively) that dictates the preferable site for attack in the initial stage of the reaction.

The numerical values of s_k^+ and s_k^+/s_k^- in Tables 1 and 2 as well as s_k^- and s_k^-/s_k^+ in Tables 3 and 4 establish the fact that it is the Hirshfeld population analysis (HPA), and not methodology, which is responsible for superior reactivity trends. This become obvious when we see that the same methods make a very poor show when Mulliken population analysis (MPA) is adopted to evaluate those values. The superiority of HPA over other charge partitioning schemes (at least for predicting intramolecular reactivity trends) probably is due to its stockholder nature. A clear proof regarding this was given by Parr and Nalewajski,[12] which shows that when atoms combine together to form molecules, information loss is at a minimum when charges are partitioned according to HPA. In one of their earlier studies,[2] the author and his collaborators have clearly demonstrated that local reactivity descriptors based on HPA excel in predicting intramolecular reactivity trends where MPA-, MESP-, and NBO-based values make a poor show. It is interesting to note that HPA is successful in generating nonnegative (and so physically more realistic) Fukui function indices and very reliable intramolecular reactivity trends although it always underestimates atomic charges as was pointed out by Davidson and Chakravorty.[40]

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