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Chemical reactivity and selectivity using Fukui functions: basis set and population scheme dependence in the framework of B3LYP theory

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Abstract. The use of Fukui functions for the site selectivity of the formaldehyde molecule for nucleophilic, electrophilic and radical attacks has been made with special emphasis to the dependence of Fukui values on the basis sets as well as population schemes in the framework of B3LYP theory. Out of the five population schemes selected viz., Mulliken population analysis, natural population analysis, CHELP, CHELPG and atoms in molecules (AIM), it is found that the CHELPG and AIM schemes predict precise reactive site with less dependency on the basis sets. Charges derived from Hirshfeld partitioning, calculated using the BLYP/dnd method (implemented in the DMOL^3 package), provide non-negative Fukui values for all the molecular systems considered in this study. Supporting results have been obtained for acetaldehyde and acetone molecules at the 6-31 + G** basis set level. These results support the fact that high Fukui values correspond to soft–soft interaction sites. On the other hand, the correlation of the low Fukui value to the hard–hard interaction site merits further investigation.

Key words: Fukui function – Basis set – Population scheme – Reactivity – Soft–soft interaction

1 Introduction

A variety of local and global descriptors have been employed to rationalize chemical reactions [1, 2, 3]. Several reports have been published on the applications of the local hard–soft acid–base (HSAB) principle in analyzing the reactive-site selectivity in a molecule [4, 5, 6, 7, 8]. The frontier orbital (FO) theory proposed by Fukui [9] is a general approach to look at the chemical reactivity, which can be described as the ability of a molecule to involve itself in a chemical reaction. The important features of the FO theory can be explained from density functional theory (DFT). Parr and Yang [2] have defined the Fukui function (FF) of a molecule, providing information on the reactivity. The FF successfully predicts relative site reactivities for most chemical systems and as such it provides a method for understanding and categorizing chemical reactions [10]. FFs are used as the criteria for understanding chemical reactivity and site selectivity. The atom with the highest FF value is highly reactive when compared to the other atoms in the molecule [2]. These values represent the qualitative descriptors of reactivity of different atoms in the molecule. Ayers and Parr [11] have elucidated that molecules tend to react where the FF is the largest when attacked by soft reagents and in places where the FF is smaller when attacked by hard reagents. Lee et al. [12] have successfully used the FF for determining the reactive site for formaldehyde and some other molecules and mentioned that the application of these ideas to large molecules should be undertaken. The influence of solvent on the reactivity of the molecules, such as formaldehyde, methanol, acetone, formamide and DNA bases, has been studied [13, 14] using FFs in the framework of Hartree–Fock (HF) theory. FFs have also been employed in studies of weak interactions for calculating the interaction energies [4]. The intermolecular reactivity trends of some carbonyl compounds have been predicted using group softness, a FF-based descriptor [15].

It is evident from the previous results that the soft–soft interactions are preferred at the site of the maximum FF and hard–hard interactions take place at the sites where the FFs are a minimum [6, 16, 17]. Ayers and Parr [18, 19] have explored the effect of external potential on chemical reactivity, in particular, throwing light on hard–hard interactions where its effect dominates. Recently, Chattaraj [20] has pointed out that FFs are not proper descriptors of the hard–hard interactions since they are not frontier controlled and possible descriptors for such interactions have been discussed. The FFs are calculated using charges derived from various population schemes. Unfortunately, various populations

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schemes used in the FF calculation have inherent deficiencies related to arbitrariness in density partitioning while defining an atom in a molecule [21, 22, 23].

There are considerable debates about the best way of finding the partial charges on the atoms in a molecule to calculate FFs. Methods to assign charges to atoms in a molecule based on the wave function of the molecules have been pursued since the earliest quantum mechanical calculations. The Mulliken population analysis (MPA) scheme [24, 25] has been widely used and widely criticized for its basis set dependence and arbitrary division of the shared charges between two atoms. The natural population analysis (NPA) scheme [26, 27] developed by Weinhold and coworkers has also been used to obtain charges on atoms in molecules (AIM). The theory of AIM developed by Bader has also been used for deriving charges and other topological features of the electron density [28, 29, 30]. The molecular electrostatic potential (MESP) has also been used to obtain useful information about the reactivity of molecules [31, 32, 33], viz., CHELP and CHELPG schemes, which derive charges on atoms using an electrostatic potential. Charges on atoms can also be obtained by fitting the MESP of the molecules. Arulmozhiraja and Kolandaivel [34] have calculated the dependence of the condensed FF on atomic charges using the MPA and NPA. Recently, Kar and Sannigrahi [35] compared the predictive ability of MPA, NPA and Löwdin population analysis to determine local reactivity indices of free radicals within the framework of HF and B3LYP theories. Since there is no agreement in the charges obtained from these methods, the objective of this study is to understand how various schemes provide FF values using different basis sets in the framework of B3LYP theory. De Proft et al. [36] have shown that there is an effect of the basis set as well as partitioning on the description of the reactivity of the molecule. They have also found that the B3LYP and B3PW91 methods provide comparatively good results. Hence, in this study an attempt has been made to probe the effect of various basis sets and population schemes on the chemical reactivity of formaldehyde and other related molecules using the B3LYP method.

2 Calculation of Fukui function

2.1 Global hardness and softness

Parr and Pearson [1] first provided the analytical definition of global hardness of any chemical species as

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{V(r)} = \left(\frac{\partial \mu}{\partial N}\right)_{V(r)} , \tag{1}$$

where $\boldsymbol{E}$ is the total energy, $\boldsymbol{N}$ is the number of electrons of the chemical species and μ is the chemical potential, which is identified as the negative of the electronegativity, χ [1, 37], as defined by Iczkowski and Margrave [38].

The corresponding global softness is expressed as

$$S = \frac{1}{2\eta} = \left(\frac{\partial^2 N}{\partial E^2}\right)_{V(r)} = \left(\frac{\partial N}{\partial \mu}\right)_{V(r)} . \tag{2}$$

By applying the finite-difference approximation to Eq. (1), we get the operational definition of η and $\boldsymbol{S}$ as [1]

$$\eta = (\mathrm{IP} - \mathrm{EA})/2 \tag{3}$$

and

$$S = 1/(\mathrm{IP} - \mathrm{EA}) \tag{4}$$

or

$$S = 1/2\eta , \tag{5}$$

where IP and EA are the ionization potential and the electron affinity of the chemical species, respectively.

2.2 Local quantities

The site selectivity of a chemical system cannot, however, be studied using the global descriptors of reactivity. For this, appropriate local descriptors need to be defined. An appropriate definition of local softness, $s(r)$, is given by

$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{v(r)} , \tag{6}$$

such that

$$\int s(r)\mathrm{d}r = S , \tag{7}$$

Combining Eqs. (2) and (6),

$$\begin{aligned} s(r) &= \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)}\right)_{N} S \\ &= f(r)S \end{aligned} \tag{8}$$

where $f(r)$ is defined as the FF [2]. It is obvious that the local softness contains the same information as the FF (i.e., the sensitivity of the chemical potential of a system to a local external potential) as well as additional information about the molecular softness. Using left and right derivatives with respect to the number of electrons, electrophilic and nucleophilic FFs and local softness can be defined. To describe the reactivity of an atom in a molecule, it is necessary to condense the values of $f(r)$ and $s(r)$ around each atomic site into a single value that characterizes the atomic contribution in a molecule. Thus, for an atom k in a molecule, depending upon the types of electron transfer, three kinds of condensed FF of the atom k can be obtained. For an N-electron system, independent calculations have been made on N−1, N and N + 1 electronic systems with the same molecular geometry. Various population schemes yield $q_k(N-1)$, $q_k(N)$ and $q_k(N+1)$ for all the atoms. Then these values were substituted in the following equations and the corresponding FF values for f_k^+, f_k^- and f_k^0 were obtained. In a finite-difference approximation, the f_k values are calculated as [10, 11, 39]

$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{for nucleophilic attack} , \tag{9}$$

$$f_k^- = q_k(N) - q_k(N-1) \text{ for electrophilic attack} \tag{10}$$

and

$$f_k^0 = [q_k(N+1) - q_k(N-1)]/2 \text{ for radical attack} , \tag{11}$$

where q_k is the gross electronic population of atom k in the molecule. Parr and Yang have proposed that larger Fukui values indicate more reactivity [2, 21, 40]. Hence, the greater the value of the condensed FF, the more reactive is the particular atomic center in the molecule.

3 Computational details

The geometries for the HCHO, CH_3CHO and CH_3COCH_3 molecules were optimized using the 6-31G* basis set in the framework of B3LYP [41] theory. The atomic charges for all the molecules were obtained in the framework of B3LYP theory using various population schemes viz., MPA, NPA, AIM, CHELP [32] and CHELPG [33]. The DENSITY = CURRENT option was used in all the calculations of the atomic charges. The dependence of the FF values with basis set was studied by employing the 6-31G*, 6-31 + G**, 6-31 + + G** and 6-311 + + G** basis sets. To compute the FF values for the CH_3CHO and CH_3COCH_3 molecules, the 6-31 + G** basis set alone was used and the FF values are compared with those obtained for HCHO. All the calculations were performed using the Gaussian94W suite of programs [42] in PIII systems. Further, the Hirshfeld partitioning scheme [43] employing the BLYP/dnd method, which is included in the DMOL^3 program [44], was also used to derive the atomic charges and thereby the FFs for comparison.

4 Results and discussion

It is well established that the FF can be used as a descriptor for determining the chemical reactivity, especially the site selectivity of a molecule [20]. However, the influence of the population schemes and basis sets on the Fukui value is not yet been systematically studied. In this investigation, we employed various population schemes in four different basis set functions in the B3LYP framework for determining the charges as well as the FF for the formaldehyde molecule. In order to confirm the selection of the calculation methods, we calculated the charges as well as the FF for higher homologue aldehydes and ketones, such as acetaldehyde and acetone, in various population schemes using the 6-31 + G** basis set. Roy et al. [45] have shown that the Hirshfeld partitioning [43] provides only non-negative FF indices. In this study, we used this partitioning scheme for comparison.

The condensed FFs for the formaldehyde system at the 6-31G* basis set level are given in Table 1. It is interesting to note that the condensed Fukui values using the MPA and NPA schemes for all the atoms in the formaldehyde molecule are very similar to the values obtained in an earlier study [13] using a HF-based approach. Lee et al. [12] predicted condensed Fukui values for the formaldehyde molecule at the 6-311G basis set level by employing the MPA scheme. It is observed that the AIM and CHELP schemes selected in our study are able to provide comparable Fukui values; however, the MPA scheme does not give comparable Fukui values. This could be due to the differences in the basis sets and it is known that the MPA scheme is sensitive to the basis set. The atom with the largest Fukui value is the most reactive one during chemical reaction; however, it would be difficult to identify the reactive atom in cases where the Fukui values are similar or comparable for two atoms. In this study, the MPA scheme exhibits more or less similar f_k^+ values for both carbon and oxygen at the 6-31G* level. It has been shown [46] in the mechanism of acid- and base-catalyzed hydration of aldehydes that the H^+ electrophilic attack occurs at the O atom (f_k^- largest for O) for the acid-catalyzed hydration, while the OH^- nucleophilic attack occurs at the C atom (f_k^+ largest for C) for the base-catalyzed hydration. At the 6-31G* level, the CHELPG scheme is able to produce the highest f_k^+ value for the C atom where the nucleophilic attack is expected, while for the electrophilic attack at the O atom, the NPA scheme is able to produce the highest f_k^- value. The NPA scheme is able to produce a comparatively high f_k^+ value for the C atom. Other schemes, such as CHELP, CHELPG and AIM, are generally able to predict similar trends for both electrophilic and nucleophilic attacks. All the population schemes suggest that the O atom is the most probable candidate for radical attack compared to any other atom.

The condensed FFs for the HCHO system at the 6-31 + G** level are presented in Table 2. At this level, the MPA scheme is able to produce the highest f_k^+ value for the C atom compared to other schemes; however, for the nucleophilic attack, the CHELP scheme is not able to produce a high f_k^+ value for the C atom compared to the values for other atoms. Other population schemes predict the correct trend in accordance with chemical intuition for nucleophilic attack. For the electrophilic attack at the O atom, the CHELPG scheme is able to produce the highest f_k^- value in contrast to the 6-31G* level. Similar to the 6-31G* level, all the population schemes predict the O atom for radical attack with the exception of the MPA scheme, which predicts the C atom for radical attack. The condensed FFs for the HCHO system at the 6-31 + + G** level are given in Table 3. Comparing all the Fukui values at the 6-31 + + G** level for various population schemes with those of the 6-31 + G**level, the magnitude of the Fukui values is not significantly altered except for the NPA method, which could be due to the fact that the 6-31 + G** level includes diffuse functions for the heavy atoms, whereas the 6-31 + + G** level includes diffuse functions for the hydrogen atoms in addition to for the heavy atoms. It seems that the addition of diffuse function to the hydrogen atom does not alter the charges on the atoms drastically. In other words, all the population

Table 1. Condensed Fukui functions for the HCHO system (6-31G* basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C	0.275	0.492	0.461	0.593	0.392	0.052	0.060	−0.093	−0.055	−0.096	0.163	0.276	0.184	0.269	0.148
O	0.276	0.287	0.262	0.216	0.235	0.434	0.533	0.529	0.528	0.518	0.355	0.410	0.395	0.372	0.376
H	0.225	0.111	0.139	0.096	0.187	0.257	0.203	0.282	0.263	0.289	0.241	0.157	0.210	0.179	0.238

Table 2. Condensed Fukui functions for the HCHO system (6-31 + G** basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C	0.740	0.656	0.246	0.438	0.502	0.063	0.037	−0.164	−0.118	−0.102	0.400	0.347	0.041	0.160	0.200
O	0.108	0.255	0.226	0.204	0.190	0.507	0.557	0.574	0.577	0.524	0.307	0.406	0.399	0.391	0.357
H	0.076	0.044	0.264	0.179	0.154	0.216	0.203	0.295	0.270	0.289	0.146	0.124	0.280	0.225	0.221

schemes behave in a similar manner in predicting the reactive site for all kinds of attack compared to the 6-31 + G** level. However, it is important to mention that the NPA scheme is unable to predict the precise reactive site for nucleophilic attack at the 6-31 + + G** level. This contradicts the general notion that the NPA is insensitive to the basis set [47, 48, 49].

The condensed FFs for the formaldehyde molecule at the 6-311 + + G** level are given in Table 4. For the nucleophilic attack at the C atom, the MPA scheme is able to produce the highest f_k^+ value compared to the other schemes; however, the CHELP method does not give a high f_k^+ value for the C atom and thus contradicts chemical intuition. Unlike the 6-31 + + G** level, the NPA scheme is able to predict the reactive site for nucleophilic attack correctly in accordance with chemical intuition at the 6-311 + + G** level. For the electrophilic attack at the O atom, the CHELPG scheme is able to give the highest f_k^- value compared to the other schemes. All the population schemes suggest the O atom for radical attack with the exception of the MPA scheme, which predicts that the radical attack would be on the C atom. Cioslowski et al. [50] have calculated atomic Fukui indices from the topological theory of AIM for the formaldehyde molecule using various approximations at the 6-311 + + G** level. They have computed spin-free, intraspin and interspin Fukui indices for nucleophilic and electrophilic attacks. The AIM scheme used in this study provides almost similar Fukui values for the electrophilic attack compared to that obtained using the unrestricted second-order Møller–Plesset perturbation theory approximation. Other population schemes selected in this study also provide comparable Fukui values; however, the atomic Fukui values for the nucleophilic attack are not in good agreement with those obtained in this study.

The FF values for the formaldehyde molecule using the Hirshfeld partitioning scheme employing the BLYP/dnd method are given in Table 5. It predicts the correct reactive sites for nucleophilic (highest f_k^+ for the C atom), electrophilic (highest f_k^- for the O atom) and radical (highest f_k^0 for the O atom) attacks as per chemical intuition.

4.1 Dependency on basis sets

It is known that the MPA scheme defines the single-particle density matrix over standard nonorthogonal atomic orbital basis sets [24, 25]; hence, it is very sensitive to the basis set. On the other hand, in the NPA scheme, the nonorthogonal atomic orbitals are transformed in to an orthogonal set by an occupancy-weighted symmetric orthogonalization procedure [26, 27], where the orbitals having the highest occupancy are strongly preserved in form, while an orbital of negligible occupancy can distort freely to achieve orthogonality. Hence the NPA scheme, in principle, should be insensitive to basis set. However, it has been reported that both the MPA and NPA schemes are

Table 3. Condensed Fukui functions for the HCHO system (6-31 + + G** basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C	0.736	0.133	0.238	0.427	0.501	0.081	0.037	−0.164	−0.119	−0.102	0.383	0.085	0.037	0.154	0.199
O	0.095	0.087	0.225	0.204	0.188	0.495	0.558	0.572	0.576	0.524	0.303	0.322	0.399	0.390	0.356
H	0.084	0.390	0.269	0.184	0.155	0.212	0.203	0.296	0.272	0.289	0.157	0.297	0.282	0.228	0.222

Table 4. Condensed Fukui functions for the HCHO system (6-311 + + G** basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C	0.689	0.666	0.248	0.444	0.481	0.076	0.022	−0.154	−0.106	−0.091	0.383	0.344	0.047	0.169	0.195
O	0.104	0.302	0.221	0.195	0.196	0.502	0.556	0.570	0.572	0.517	0.303	0.429	0.395	0.384	0.357
H	0.103	0.016	0.265	0.180	0.161	0.211	0.211	0.292	0.267	0.287	0.157	0.114	0.279	0.223	0.224

Table 5. Condensed Fukui functions for the HCHO system using Hirshfeld population analysis at the dnd basis set level

Atom	f_k^+	f_k^-	f_k^0
C	0.395	0.236	0.315
O	0.303	0.426	0.365
H	0.150	0.169	0.160

dependent on basis sets while changing from the 6-31G to the 6-31+G(3df, 3pd) level [51]. In this investigation, at the 6-31G* level, the MPA scheme is unable to predict the reactive site for the nucleophilic attack; however, at the 6-31+G** level, it is able to differentiate the C atom from other atoms for nucleophilic attack and produces the highest f_k^+ value compared to any other population schemes. The order and the magnitude of the f_k^+ values are not significantly altered while approaching higher basis sets, viz., the 6-31++G** and 6-311++G** levels. However, for the electrophilic attack, the f_k^- values are not significantly altered at all the selected basis sets in the MPA scheme. Site selectivity is also not hampered. For the radical attack, at the 6-31G* level, the MPA scheme is able to predict a similar reactive site compared to other schemes; however, at higher basis set levels, it is unable to predict the proper reactive site compared to the site predicted by the other schemes.

Comparing the Fukui values in the NPA scheme, there is no significant change in the magnitude of the Fukui values corresponding to electrophilic attack at all the basis set levels selected in this study in the framework of B3LYP theory. For the nucleophilic and radical attack, the magnitude of the Fukui values does not change significantly at all the basis set levels, with the exception of the 6-31++G** level. Most importantly, it could not predict the proper reactive site for the nucleophilic attack in accordance with chemical intuition and other population schemes at the 6-31++G** level.

Considering the electrophilic and radical attack, the CHELP scheme is able to produce more or less similar Fukui values and is able to predict the correct reactive site at all basis set levels. For the nucleophilic attack, the CHELP scheme is able to predict the precise reactive site in comparison with other population schemes as well as chemical intuition at the 6-31G* level; however, at the higher basis set levels, it is unable to predict the proper reactive site for the nucleophilic attack. The magnitude of the Fukui values seems to be comparable at the higher basis set levels.

At all the basis set levels, the CHELPG scheme is able to predict the precise reactive site in accordance with chemical intuition, with constancy in the magnitude of the Fukui values at higher basis set levels. In other words, the CHELPG scheme is completely insensitive to the higher basis set levels selected in this study. The AIM method predicts the correct reactive site for all types of attacks at all the basis set levels. Similar to the CHELPG scheme, the AIM method is less sensitive to the basis sets.

4.2 Dependency on population schemes

4.2.1 Based on a high Fukui value

For the nucleophilic attack at all the higher basis set levels viz., 6-31+G**, 6-31++G** and 6-311++G**, the MPA scheme is able to produce the highest f_k^+ values among all the selected population schemes. At the 6-31G* level, the CHELPG method is able to produce the highest f_k^+ value for the nucleophilic attack at the C atom; however, while considering the electrophilic attack at the O atom alone, the CHELPG scheme overrides all the other population schemes in terms of both the magnitude of the Fukui values and the independency on basis set except for the 6-31G* level. For the radical attack at the O atom, generally the NPA scheme is able to produce the highest f_k^0 value at all the selected basis set levels with the exception of the 6-31++G** level.

4.2.2 Based on the site selectivity

Although the magnitude of the Fukui value is important while selecting a particular population scheme, it is also necessary to verify that the selected method is able to give a high Fukui value for the actual reactive site at a given basis set level for all kinds of attack. Although the MPA scheme is able to give the actual reactive site for the electrophilic attack at all the basis set levels, it could not reproduce it for the remaining attacks. This could be due to the fact that the MPA scheme is sensitive to the basis set [47, 52]. Generally, the NPA scheme is able to predict the precise reactive site for the electrophilic and radical attack at all the basis set levels with a minimum variation in the magnitude of the Fukui values, thus proving that it is less sensitive to the basis sets. However, it remarkably fails to do the same for nucleophilic attack at a higher basis set level (6-31++G**). Such an observation has already been made by Nolan and Linck [51], who found that the charges on some atoms are quite sensitive to the change in basis set from 6-31G and 6-31+G. Likewise, the CHELP scheme is able to produce the correct reactive site for electrophilic and radical attack at all the basis set levels; however, it fails to predict the precise reactive site for nucleophilic attack at higher basis set levels. An interesting result of this investigation is that the CHELPG scheme has the ability to predict the precise reactive site for all kinds of attack at all the selected basis sets. It has already been shown that a large enough basis set incorporating polarization functions such as 6-31G** seems to be generally adequate for faithfully representing the molecular electrostatic-potential-based topography [53, 54]. Since the CHELPG scheme derives charges on atoms based on the molecular electrostatic potential, it is evident that CHELPG is less dependent on the basis sets. Similarly the AIM method is also able to predict the appropriate reactive site for all kinds of attack at all basis sets. Hence, it is worth noting that the electrostatic-potential-based CHELPG scheme and the topology of the electron-density-based AIM scheme are able to provide a high Fukui value for the precise reactive site for all kinds of attack at all the basis set levels in the framework of B3LYP theory. This fact is represented pictorially in Fig. 1.

4.3 Fukui minima versus hard–hard interactions

The maximum FF value of an atom in a molecule describes its reactivity, i.e., the local softness of the molecule. This means that the soft–soft interactions, which are frontier controlled, can be dealt with using the FF. Analogously, the minimum FF, which is charge controlled, should, in principle, predict the hard–hard interaction site; however, it has been shown [20] that for some systems it is unable to predict the reactive site for the hard–hard interactions. Hence, it was put forward that the hard–hard interaction can be well described by atomic charges rather than the Fukui minima [23]. Klopman [16] has derived the change in energy produced during the interaction of two systems, *R* and *S*, as a consequence of mutual perturbation of the molecular orbitals of both reactants, given in the form

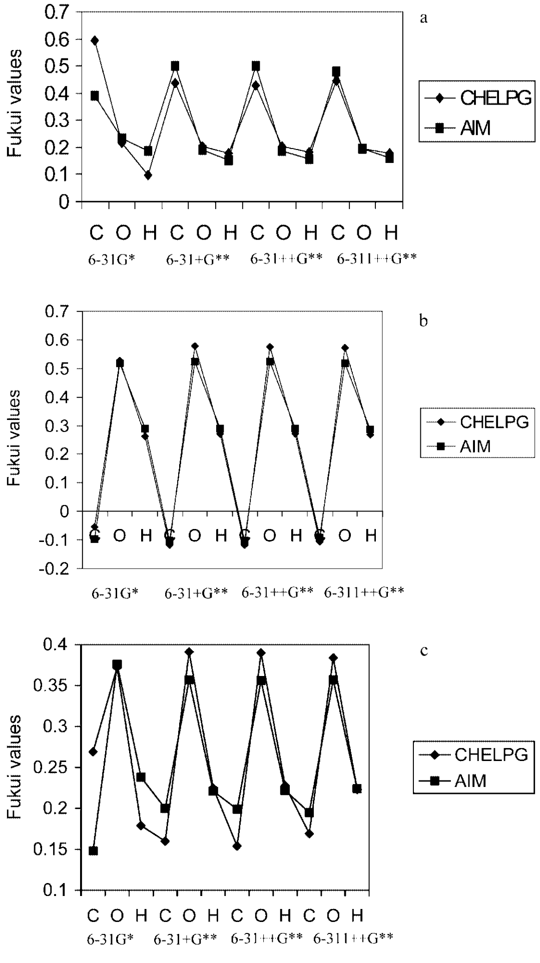

Fig. 1a–c. Comparison of condensed Fukui values from the CHELPG and atoms-in-molecules (*AIM*) schemes for all the basis set levels for HCHO. **a** Nucleophilic attack; **b** electrophilic attack; **c** radical attack

$$\Delta E_{\text{total}} = -q_r q_s \frac{\Gamma}{\varepsilon} + \Delta\text{solv}(1) + \sum_{\text{occ}}^{m} \sum_{\text{unocc}}^{n} \left(\frac{2\left(c_r^m\right)^2 \left(c_s^n\right)^2 \beta^2}{E_m^* - E_n^*} \right), \tag{12}$$

where q_r and q_s are the total initial charges on the atoms *r* and *s*, Γ is the Coulomb interaction between *r* and *s* in a central field of approximation, ε is the dielectric constant of the medium, $c_r{}^m$ and $c_s{}^n$ are the coefficients of the atomic orbitals φ_r and φ_s, respectively, in the unperturbed orbitals ψ_m and ψ_n, β is the measure of perturbation, E_m^* and E_n^* are the energy of the molecular orbitals ψ_m of molecule *R* and ψ_n of molecule *S* under their mutual influence. For the hard–hard interactions, the energy difference between the FOs, $E_m^*–E_n^*$, is very large and hence the perturbation energy is primarily determined by the total charges on the two interacting atoms. Since very little electron transfer occurs, these reactions are charge controlled. On the other hand, for soft–soft interactions the $E_m^*–E_n^*$ term is very low and hence the perturbation energy will largely depend on the interaction of the FOs. Since the FFs are derived based on the atomic charges, it is logical to expect that the minimum FF may provide a site for charge-controlled reactions or hard–hard interactions. The DFT analogue of Klopman's Eq. (12) has been derived by Berkowitz [17]:

$$\mathrm{d}N = -\frac{\int \Delta\rho(\vec{r})\Delta v^{\mathrm{n}}(\vec{r})\mathrm{d}\vec{r}}{2\left(\eta_A^0 + \eta_B^0 - J_{\mathrm{f}}\right)}, \tag{13}$$

where d*N* is the amount of electronic charge transfer, which accompanies the formation of the complex *AB* from acid *A* and base *B*, η_A^{o} and η_B^{o} are absolute hardness of free molecules *A* and *B*, respectively, J_{f} is the Coulomb integral between the FFs, $\Delta\rho(\vec{r}) = \rho^{\mathrm{A}}{}_{\mathrm{LUMO}} - \rho^{\mathrm{B}}{}_{\mathrm{HOMO}}$ and $\Delta v^{\mathrm{n}}(\vec{r})$ is the difference in the external potential, where the superscript *n* stands for nuclei. It is possible to understand from Eq. (13) that small η_A^{o} and η_B^{o} facilitate charge transfer and hence soft–soft interaction. For hard–hard interaction, d*N* is small and the reaction will be controlled by Coulomb interaction between *A* and *B*.

It is important to mention that the local hardness is a more useful descriptor in understanding the hard–hard interactions; however, an unambiguous definition of local hardness is difficult and hence the application of other descriptors for hard–hard interactions needs to be considered [20]. The key concept of linking frontier molecular orbital theory and the HSAB principle in terms of FFs has been lucidly elucidated in the work of Li and Evans [6]. They concluded that the minimal Fukui site is the favored site for protonation. This evidence is also supported by the work of Yang and Mortier [39], who showed that the maximal Fukui site is not the site of protonation of the alkylamine. Using rigorous mathematical demonstrations, Li and Evans proved that the FF needs to be minimized in order for the reaction to proceed smoothly in the case of hard–hard interactions. The importance of charge–charge interactions in the local nature of selectivity has also been clearly explained. Though the minimal FF site is favored in the case of monofunctional systems, it fails in the case of polyfunctional systems [20]. Chattaraj [20] has proposed possible descriptors for chemical reactivity and selectivity. When two reactants approach each other, the energy change may be expressed as [21]

$$\Delta E = \Delta E_{\text{covalent}} + \Delta E_{\text{electronic}} + \Delta E_{\text{polarization}} \ . \tag{14}$$

For the soft–soft interactions, $\Delta E_{\text{covalent}}$ plays the significant role and hence these are frontier-controlled reactions. Since hard–hard interactions are charge controlled, the Hellmann–Feynman force on a particular nucleus may be a reliable descriptor owing to the importance of the $\Delta E_{\text{electronic}}$ term [20]. The dominant role played by the electrostatic interactions in hard–hard interactions has been clearly depicted through ab initio calculations [55]. Chattaraj [20] has proposed a local version of the Coulomb law of the form

$$F_{ij}^{AB} \propto \frac{q_i^A q_j^B}{r^2} \tag{15}$$

as an appropriate model for analyzing hard–hard interactions. q_i^{A} and q_j^{B} are the net charges on the atoms *i* and *j*, respectively.

In this study, for the nucleophilic attack, the MPA, CHELPG and AIM methods predict the H atom as the hard species for all the basis sets covered; however, the NPA scheme predicts the H atom at all the basis set levels except the 6-31++G** level, while the CHELP scheme predicts it at the lowest basis set level. The Hirshfeld scheme also predicts the H atom as the reactive site for nucleophilic attack for hard–hard interaction using the BLYP/dnd method. It has been shown that for the protonation reactions, H^+, being a special hard acid, devoid of filled inner shells, possesses a minimum FF for hard–hard interactions [23, 56]. For the electrophilic attack, all the population schemes suggest that the C atom is the hard species at all the basis set levels only if the negative Fukui values are considered as meaningful, otherwise the H atom has the lowest Fukui value for all the population schemes except the MPA and NPA schemes. The Hirshfeld scheme suggests the H atom as the reactive site for electrophilic attack. It is known that the Hirshfeld scheme provides non-negative FF values [45]; hence, it can be concluded that the negative Fukui values obtained for the C atom is insignificant. However, the MPA and NPA schemes provide non-negative Fukui minima for the C atom, which does not support the previous conclusion. In the case of radical attack, at all the basis set levels most of the population schemes predict the C atom as the hard site except for the MPA, NPA and Hirshfeld schemes. Although these results are interesting, the lack of supporting evidence pertaining to hard–hard interactions of formaldehyde calls for further studies.

4.4 Confirmatory analysis with higher analogues of formaldehyde

We chose the 6-31+G** basis set for further calculations on the acetaldehyde and acetone molecules with all the selected population schemes. The choice of the 6-31+G** basis set is a compromise because it contains diffuse functions with moderate calculation time [57] apart form providing satisfactory Fukui values for all the population schemes as evidenced from the analysis for the formaldehyde molecule. The Fukui values for the acetaldehyde molecule at the 6-31+G** basis set level are given in Table 6. All the population schemes predict that the C atom of the aldehyde group is the reactive site for the nucleophilic attack. The MPA scheme provides the highest f_k^+ value for the C (of CHO) atom compared to the other schemes. For the electrophilic attack, all the population schemes provide a high f_k^- value for the O atom. Especially, the CHELP scheme provides the highest f_k^- value for the O atom. All the population schemes with the exception of the MPA predict that the O atom has the highest f_k^0 value for radical attack. These results are in agreement with those obtained for the formaldehyde molecule. The condensed FF for the acetaldehyde molecule employing the Hirshfeld partitioning scheme, calculated using the BLYP/dnd method, is given in Table 7. It predicts the correct reactive sites for electrophilic (highest f_k^- for the O atom) and radical (highest f_k^0 for the O atom) attacks in accordance with chemical intuition and other population schemes; however, it predicts the C atom of the methyl group for the nucleophilic attack unlike the other population schemes.

The condensed Fukui values for the acetone molecule at the 6-31+G** basis set level are given in Table 8. It is seen that only the NPA and CHELPG schemes predict the C atom of the carbonyl group for nucleophilic attack, while the remaining schemes produce ambiguous

Table 6. Condensed Fukui functions for the CH_3CHO system (6-31+G** basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C1	−0.224	−0.009	−0.812	−0.941	−0.017	−0.004	0.025	−0.161	−0.087	0.021	−0.114	0.008	−0.486	−0.514	0.002
C2	0.844	0.557	0.336	0.609	0.393	0.063	0.024	−0.123	−0.116	−0.136	0.453	0.291	0.106	0.247	0.128
H (C1)	0.060	0.049	0.265	0.266	0.077	0.072	0.059	0.149	0.125	0.099	0.066	0.054	0.207	0.195	0.089
H (C1)	0.061	0.061	0.333	0.349	0.101	0.101	0.082	0.156	0.134	0.132	0.081	0.071	0.245	0.241	0.116
H (C1)	0.061	0.061	0.333	0.349	0.101	0.101	0.082	0.156	0.134	0.132	0.081	0.071	0.245	0.241	0.116
O	0.127	0.226	0.297	0.231	0.177	0.467	0.527	0.548	0.546	0.491	0.297	0.376	0.422	0.388	0.334
H (C2)	0.070	0.055	0.248	0.137	0.167	0.201	0.200	0.275	0.265	0.262	0.136	0.128	0.262	0.201	0.214

Table 7. Condensed Fukui functions for CH_3CHO using Hirshfeld population analysis at the dnd basis set level

Atom	f_k^+	f_k^-	f_k^0
C1	0.297	0.161	0.229
C2	0.081	0.111	0.096
H (C1)	0.122	0.154	0.138
H (C1)	0.056	0.061	0.059
H (C1)	0.056	0.061	0.059
O	0.272	0.376	0.324
H (C2)	0.087	0.069	0.078

results. The CHELPG scheme is able to give the highest f_k^+ value for the C (of CO) atom compared to the other schemes. All the population schemes suggest the O atom as the candidate for electrophilic attack. The CHELP scheme provides the highest f_k^- value compared to the other schemes. As expected, for the radical attack, all the schemes provide a high f_k^0 value for the O atom. In a previous study [15] using local and group softness as descriptors, it was revealed that the reactivity of ketones is much lower than aldehydes for the nucleophilic addition reaction. The use of FFs as descriptors for determining the reactivity of aldehydes and ketones provides comparable results with the previous study. For the nucleophilic attack at the C atom, the NPA, CHELPG and AIM methods provide lower f_k^+ values compared to the other schemes at the 6-31+G** level for the acetone molecule compared to acetaldehyde. For the electrophilic attack at the O atom, all the population schemes provide lower f_k^- values. Further, as expected from the normalization condition that the sum of the FF indices is always 1, it was observed in this study that there is a reduction in the FF indices with an increase in molecular size. Roy et al. [58] have reported this fact using relative nucleophilicity, which is a measure of local polarizability, while finding the preferable protonation sites of aniline and substituted anilines. The FF values for the acetone molecule using the Hirshfeld partitioning scheme employing the BLYP/dnd method are given in Table 9. The methyl carbon is predicted to be the most probable reactive site for all attacks. Although the Hirshfeld scheme provides interpretable FFs, it is unable to predict the reactive site for all the attacks in comparison with the other population schemes.

5 Conclusion

The present study provides an in-depth analysis in the interpretation of FFs for the reactive site of an aldehyde and corroborates the observed results with higher homologues of aldehydes as well as ketones. It has been found from our analysis that the condensed FF depends highly on population analysis schemes, which in turn depend on the basis sets. Among the selected population schemes, the AIM and CHELPG schemes are completely insensitive to all the selected basis sets in the framework of B3LYP theory. This is in accordance with the findings of Gadre et al. [53] and Kulkarni [54]. For

Table 8. Condensed Fukui functions for the CH_3COCH_3 system (6-31+G** basis set)

Atom	f_k^+					f_k^-					f_k^0				
	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM	MPA	NPA	CHELP	CHELPG	AIM
C1	−0.111	0.292	0.357	0.542	0.037	0.012	0.045	−0.085	−0.090	−0.155	−0.050	0.169	0.136	0.226	−0.059
O	0.222	0.212	0.283	0.247	0.127	0.440	0.506	0.536	0.523	0.469	0.331	0.359	0.409	0.385	0.298
C2	0.299	0.057	−0.925	−1.093	0.109	0.033	0.032	−0.104	−0.050	0.023	0.166	0.045	−0.514	−0.571	0.066
C3	0.299	0.057	−0.925	−1.093	0.109	0.033	0.032	−0.104	−0.050	0.023	0.166	0.045	−0.514	−0.571	0.066
H (C2)	0.049	0.035	0.305	0.338	0.083	0.059	0.047	0.118	0.106	0.084	0.054	0.041	0.211	0.222	0.083
H (C3)	0.049	0.035	0.305	0.338	0.083	0.059	0.047	0.118	0.106	0.084	0.054	0.041	0.211	0.222	0.083
H (C2)	0.048	0.078	0.400	0.430	0.113	0.091	0.073	0.130	0.114	0.118	0.070	0.075	0.265	0.272	0.116
H (C2)	0.048	0.078	0.400	0.430	0.113	0.091	0.073	0.130	0.114	0.118	0.070	0.075	0.265	0.272	0.116
H (C3)	0.048	0.078	0.400	0.430	0.113	0.091	0.073	0.130	0.114	0.118	0.070	0.075	0.265	0.272	0.116
H (C3)	0.048	0.078	0.400	0.430	0.113	0.091	0.073	0.130	0.114	0.118	0.070	0.075	0.265	0.272	0.116

Table 9. Condensed Fukui functions for CH_3COCH_3 using Hirshfeld population analysis at the dnd basis set level

Atom	f_k^+	f_k^-	f_k^0
C1	0.065	0.091	0.078
O	0.221	0.116	0.168
C2	0.068	0.091	0.079
C3	0.236	0.355	0.296
H (C2)	0.075	0.062	0.068
H (C3)	0.075	0.062	0.068
H (C2)	0.049	0.051	0.050
H (C2)	0.049	0.059	0.055
H (C3)	0.081	0.056	0.069
H (C3)	0.081	0.056	0.069

most of the population schemes, high FF values give the exact reactive site for the HCHO molecule. Interestingly, the CHELPG and AIM schemes provide similar or comparable Fukui values for the formaldehyde molecule at all the basis set levels. Further, for higher aldehydes and ketones namely, CH_3CHO and CH_3COCH_3, all the population schemes predict the precise reactive site for the electrophilic and radical attacks, however, with some exceptions for the nucleophilic attack. Further it is noted that that the Hirshfeld partitioning provides non-negative Fukui values for all the molecular systems considered in this study as reported earlier [45]. However, it is unable to predict the correct reactive sites for higher molecular systems in comparison with other population schemes. Hence, further numerical studies need to be carried out to probe the effect of the basis set and the theoretical framework in which the Hirshfeld partitioning has to be performed.

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