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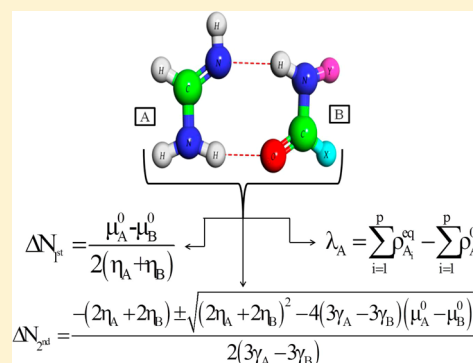**180** PUBLICATIONS   **2,831** CITATIONS

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Critical Study of the Charge Transfer Parameter for the Calculation of Interaction Energy Using the Local Hard−Soft Acid−Base Principle

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S *Supporting Information*

ABSTRACT: Local hard−soft acid−base (HSAB) principle is semiquantitative in nature due to the presence of an ad hoc charge transfer parameter. The accuracy of HSAB principle significantly depends on the definition of this ad hoc parameter. In this paper, for the first time we have introduced the second-order approximation of ΔN (ΔN_{second}) as an ad hoc parameter for charge transfer to calculate interaction energies of multiple site based interactions using local hard soft acid base principle. The second-order approximation of ΔN has been derived from Sanderson's electronegativity equalization principle. To validate our approach, we have studied interaction energies of some prototype molecules. The interaction energies obtained from our approach have been further compared with the interaction energies of those obtained using other charge transfer parameters (ΔN_{first} and λ) and the conventional methods. We have also discussed the advantages and limitations of the approach.

$$\Delta N_{1st} = \frac{\mu_A^0 - \mu_B^0}{2(\eta_A + \eta_B)} \qquad \lambda_A = \sum_{i=1}^{p} \rho_{A_i}^{eq} - \sum_{i=1}^{p} \rho_{A_i}^0$$

$$\Delta N_{2nd} = \frac{-(2\eta_A + 2\eta_B) \pm \sqrt{(2\eta_A + 2\eta_B)^2 - 4(3\gamma_A - 3\gamma_B)(\mu_A^0 - \mu_B^0)}}{2(3\gamma_A - 3\gamma_B)}$$

1. INTRODUCTION

Density functional theory (DFT) is popular due to its success in studying the molecular structure, chemical bonding,[1−11] interaction energy (IE), reactivity, and selectivity of molecules.[12−22] In recent years, DFT based reactivity descriptors have been extensively used to study the aromaticity, the intra- and intermolecular reactivity, regioselectivity, electrophilicity, nucleophilicity[23] of organic reactions, and prediction of the reactive site of various molecular systems.[24,25] DFT has also provided theoretical basis for concepts such as electronic chemical potential, electronegativity, hardness and softness, collectively known as global reactivity descriptors (GRD).[26−30] The global reactivity descriptors describe the molecule as a whole. These descriptors essentially determine the response of the energy of a system to the change of number of electrons at fixed external potential. The chemical potential of the two systems determines the flow of electrons. Global hardness[31,32] talks about the inertness of the whole molecule and can be seen as reluctance to the charge transfer. However, the interaction between molecules occurs through particular atoms (definite site) within the molecule, and thus, the interaction is always local. Therefore, to explain the interactions between molecules, we need local reactivity descriptors (LRD)[33−36] such as Fukui function and local softness. The Fukui function and local softness relate the change of electron density to the number of electrons and chemical potential respectively. LRDs have a direct relation with the Fukui frontier molecular orbitals, and the relevance has been verified in identifying electrophilic and nucleophilic reactive centers in a molecule. From the value of Fukui function of every atom in a molecule, we can predict the reactive atom of the system and higher the value of Fukui function, higher is the reactivity.[37,34]

Various theoretical approaches exist for correlating the reactivity of molecular system based on different quantities like molecular orbital theory, charge on the atom, bond order, etc. Pearson introduced hardness and softness parameter in the context to explain the reactivity of acids and bases.[41] He has tabulated reactivity trends of acids and bases in terms of hard soft acid base parameter. This concept is called Pearson's hard−soft acid−base (HSAB) principle. The principle says that soft acid-soft base and hard acid-hard base combination is more favorable than hard−soft combination. It became very popular among the chemists because of its simplicity and wide range of applicabilities. However, the theoretical quantification of qualitative HSAB principle is difficult. Many groups are working on this issue for explaining the relative bond strengths of acid−base complex.

Li and Evans have proposed a reactivity scheme[42] by using energy perturbation method within the framework of density functional theory. They have shown that the Fukui function is an important quantity, which relates frontier molecular orbital (FMO) theory to HSAB principle.[26,43,44] Later, Gazquez and Mendez also proposed the local HSAB principle,[45] which states that the interaction between two molecules will occur not necessarily through their softest atoms but rather through those atoms which have similar Fukui function values. Pal and co-workers have shown failure of Fukui function and local softness to describe intramolecular reactivity trend in several organic carbonyl compounds. They have proposed a new reactivity descriptor called relative electrophilicity and relative nucleophil-

icity to explain the reactivity of a particular site.[46] Nguyen and co-workers also noticed the failure of Fukui indices in rationalizing the regioselectivity of protonation in fluoro- and chloro-substituted phenol.[47] Roy et al.[48,49] have observed difficulty to obtain rank ordering of the reactivity of atoms in molecules where Fukui function becomes negative. They have prescribed the Hirshfeld population scheme[50] to obtain the non-negative Fukui functions. Fuentealba et al. have also discussed the possible existence of negative value of Fukui indices by computing Kohn−Sham frontier orbital density.[51] Chattaraj and co-workers have extended the applicability of these descriptors to describe the molecular excited states.[52−54] Toro-Labbé calculated bond energy of hydrogen bonded complexes by using Sanderson's principle of electronegativity equalization.[55]

The working equations of local HSAB principle are based on the perturbative theory and the local descriptors of the reacting system. The local HSAB principle is semiquantitative[56] in nature due to presence of an ad hoc parameter (K). This principle works well for weak interacting systems viz. hydrogen bonded complexes, Lewis acid−base complexes, etc. Earlier, Gazquez and Mendez[45,57] have studied the reactivity of enolate anions and pyridine derivatives using an arbitrary value of $K = 0.5$. Similarly, Geerlings and co-workers[58] have studied the reactivity of benzonitrile oxides using the value of $K = 1.0$. The authors could relate the reactivity of various sites of a given molecule with the energy only at the qualitative level. Pal and co-workers[12] have made a critical study on the applicability of local reactive descriptors in the case of weak interactions. They have used the charge transfer parameter defined by Sanderson for the calculation of multiple site interaction energies.[59] This parameter is derived from the electronegativity equalization principle by truncating Taylor series expansion of energy at the second order. The interaction energy can be calculated by using another ad hoc charge transfer parameter denoted as λ. This parameter is defined as the net difference of the sum of the condensed electron population of each atom present in the system A having p-number of atoms, before and after the interaction.[12,59,60] Thus, to calculate λ, the actual geometry of reactants before and after interaction should be known. Therefore, it is difficult to calculate interaction energy using parameter λ, for the systems having a large number of interaction sites that interact simultaneously. Most of the biological interactions occur via multiple sites and are complex in nature. Thus, in that case the parameter λ cannot be useful. This has motivated us to extend our approach of calculation of interaction energy using second-order approximation of ΔN. In this paper, we have derived the second-order charge transfer parameter by truncating Taylor series expansion of energy up to third order. The calculation of ΔN requires information of reactant molecules only before interaction. Hence, it can be explicitly useful for any kind of interaction pattern. Recently, Anton used it for adsorbates and metal surface.[61] Theoretically, ΔN_{second} is supposed to be more accurate than ΔN_{first} because it includes higher order terms of the Taylor series expansion of energy. Therefore, we have investigated multiple site based interactions of prototype biological molecules using ΔN_{second} as an ad hoc parameter. We have further studied the IE of the same molecules using ΔN_{first}, as well as λ, and compared the results with the IE obtained using ΔN_{second}. The paper is organized as follows. In section 2, we present some important definitions of the reactivity descriptors and derivation of second-order approximation of ΔN. Section 3 provides the details about the computational methodology we have used. The elaborate discussion about the results obtained is

provided in section 4. The important conclusions are drawn in section 5.

2. THEORY

2.1. Derivation for Charge Transfer Parameter. Suppose reactants A and B are reacting to form a product AB. The energy of the reactants A and B can be written in Taylor series expansion as[1]

$$E_A = E_A^0 + \left(\frac{\partial E_A}{\partial N_A}\right)_{v(r)} (N_A - N_A^0)$$

$$+ \frac{1}{2!}\left(\frac{\partial^2 E_A}{\partial N_A^2}\right)_{v(r)} (N_A - N_A^0)$$

$$+ \frac{1}{3!}\left(\frac{\partial^3 E_A}{\partial N_A^3}\right)_{v(r)} (N_A - N_A^0)^3 + ... \quad (1)$$

$$E_B = E_B^0 + \left(\frac{\partial E_B}{\partial N_B}\right)_{v(r)} (N_B - N_B^0)$$

$$+ \frac{1}{2!}\left(\frac{\partial^2 E_B}{\partial N_B^2}\right)_{v(r)} (N_B - N_B^0)$$

$$+ \frac{1}{3!}\left(\frac{\partial^3 E_B}{\partial N_B^3}\right)_{v(r)} (N_B - N_B^0)^3 + ... \quad (2)$$

The term $(\partial E \partial N)_{v(r)}$ is called the chemical potential, which is defined as μ, $(1/2!(\partial^2 E/\partial N^2))_{v(r)} = \eta$ is the hardness and $(1/3!(\partial^3 E/\partial N^3))_{v(r)}$ is known as the hyperhardness,[64−67] denoted by γ and so on. Rewriting eqs 1 and 2 in terms of μ, η, and γ

$$E_A = E_A^0 + \mu_A^0 \Delta N + \eta_A^0 \Delta N_A^2 + \gamma_A^0 \Delta N_A^3 + ... \quad (3)$$

$$E_B = E_B^0 + \mu_B^0 \Delta N + \eta_B^0 \Delta N_B^2 + \gamma_B^0 \Delta N_B^3 + ... \quad (4)$$

If all other effects are ignored, then the total energy will have following form

$$E_A + E_B = E_A^0 + E_B^0 + (\mu_A^0 - \mu_A^0)\Delta N + (\eta_A^0 + \eta_B^0)\Delta N^2$$

$$+ (\gamma_A^0 - \gamma_B^0)\Delta N^3 + ... \quad (5)$$

where

$$\Delta N = (N_B^0 - N_B) = (N_A - N_A^0) \quad (6)$$

When a reaction takes place between two reactants with different chemical potentials, one of the reactants donates electrons and the other accepts electrons, leading to a change in the chemical potential. If $\mu_B^0 > \mu_A^0$ and ΔN is positive, electrons will flow from B to A.

At equilibrium

$$\mu_B = \mu_A \quad (7)$$

where

$$\mu_A = \left(\frac{\partial E_A}{\partial N_A}\right)_{v(r)} = \mu_A^0 + 2\eta_A \Delta N + 3\gamma_A \Delta N^2 + ... \quad (8)$$

$$\mu_B = \left(\frac{\partial E_B}{\partial N_B}\right)_{v(r)} = \mu_B^0 - 2\eta_B \Delta N + 3\gamma_B \Delta N^2 + ... \quad (9)$$

Table 1. Value of Charge Transfer Parameters for the Multiple Bonded Complexes (Values in Atomic Units)

	ΔN_{first}			ΔN_{second}			λ
complex	DFT/6-311G(d,p)/ B3LYP	MP2/ 6-311G(d,p)	CCSD(T)/ 6-311G(d,p)	DFT/6-311G(d,p)/ B3LYP	MP2/ 6-311G(d,p)	CCSD(T)/ 6-311G(d,p)	DFT/6-311G(d,p)/ B3LYP
SUC-BUTL(1)	0.02940	0.01421	0.04151	0.02938	0.01420	0.04161	0.02142
FA-FD(2)	0.03092	0.02538	0.03307	0.03093	0.02536	0.03302	0.07620
AA-FD(3)	0.02570	0.01699	0.02488	0.02571	0.01697	0.02486	0.06871
FRM-FD(4)	0.01395	0.00805	0.00342	0.01396	0.00805	0.00342	0.02531
NFRM-FD(5)	0.00977	0.00204	0.00261	0.00982	0.00224	0.00261	0.01724
ATM-FD(6)	0.01114	0.00385	0.00121	0.01127	0.00385	0.00121	0.04448
NATM-FD(7)	0.00543	0.00095	0.00449	0.00552	0.00095	0.00449	0.12151
ACT-HCL(8)	0.05162	0.04440	0.03650	0.05165	0.04439	0.03647	0.02797
ACT-LICL(9)	0.06414	0.06320	0.06517	0.06417	0.06325	0.06513	0.02766
BUTY-HCL(10)	0.07564	0.06083	0.07449	0.07572	0.06085	0.07441	0.02766
BUTY-LICL(11)	0.09557	0.08588	0.10412	0.09593	0.08612	0.10417	0.02435

Considering terms up to second order of eqs 8 and 9, we have from eq 7

$$\mu_A^0 + 2\eta_A \Delta N = \mu_B^0 - 2\eta_B \Delta N$$

Consequently, the first-order approximation of charge transfer parameter will be

$$\Delta N_{first} = \frac{\mu_A^0 - \mu_B^0}{2(\eta_A + \eta_B)} \qquad (10)$$

The second-order approximation of charge transfer parameter is obtained from eqs 8 and 9, by considering terms up to third order.

$$\mu_A^0 + 2\eta_A \Delta N + 3\gamma_A \Delta N^2 = \mu_B^0 - 2\eta_B \Delta N + 3\gamma_B \Delta N^2$$

So,

$$(3\gamma_A - 3\gamma_B)\Delta N^2 + (2\eta_A + 2\eta_B)\Delta N + (\mu_A^0 - \mu_B^0) = 0 \qquad (11)$$

Equation 11 is a quadratic equation. It gives the second-order approximation of charge transfer parameter,

$$\Delta N_{second} = \frac{-(2\eta_A + 2\eta_B) \pm \sqrt{(2\eta_A + 2\eta_B)^2 - 4(3\gamma_A - 3\gamma_B)(\mu_A^0 - \mu_B^0)}}{2(3\gamma_A - 3\gamma_B)} \qquad (12)$$

Equation 11 has two roots; thus, eq 12 gives two values of ΔN_{second}. However, physically, ΔN is the amount of charge transfer from one molecule to another in the process of complex formation between two molecules. In this paper we have studied multiple site based hydrogen bonding interaction. The H-bonding interactions are weak interactions; thus the amount of charge transfer from one molecule to another during the complex formation is very small (<1). In such a case, out of possible root the acceptable value of ΔN_{second} is one that is less than 1. In Table 1, we have reported the acceptable value of ΔN_{second}. However, the values of both ΔN and ΔN_{second} are available in the Supporting Information (Table S1) of this paper.

2.2. Global and Local Reactivity Descriptors. In DFT, the ground state energy of an atom or molecule is written in terms of electron density, $\rho(r)$ as[62]

$$E[\rho] = F[\rho] + \int dr\, \rho(r)v(r) \qquad (13)$$

$F[\rho]$ is the universal Hohenberg−Kohn functional. It contains electronic kinetic energy and electron−electron repulsion term. $v(r)$ is the external potential which includes the nuclear potential. The first and second partial derivatives of $E[\rho]$ with respect to the number of electrons N under the constant external potential $v(r)$ are defined as the chemical potential μ and the global hardness η of the system respectively[26−30]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} \qquad (14)$$

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} \qquad (15)$$

The inverse of the global hardness is called global softness and it is denoted by letter S.

$$S = \frac{1}{2\eta} \qquad (16)$$

The global descriptor, hardness, measures the overall stability of the system.[43,63] It is customary to use a finite difference approximation for μ and η. By using the energies of N, $(N+1)$, and $(N−1)$ electronic systems, we get the operational definition of μ and η,[1]

$$\mu = \frac{E_{N+1} - E_{N-1}}{2} = -\frac{IP - EA}{2} \qquad (17)$$

$$\eta = \frac{E_{N+1} + E_{N-1} - 2E_N}{2} = \frac{IP - EA}{2} \qquad (18)$$

where IP and EA are the first vertical ionization energy and electron affinity of the chemical species, respectively. The third term is γ, which is hyperhardness, and it is the third derivative of energy with respect to total number of electrons

$$\gamma = \frac{1}{6}\left(\frac{\partial^3 E}{\partial N^3}\right)_{v(r)} \qquad (19)$$

Equation 19 has been defined by Fuentealba and Paar.[64] The value of hyperhardness is usually small and the reason behind the small value of γ is that the energy, E, often has nearly quadratic dependence on the number of electrons, N (cf. the rationalization in ref 68).

By using finite difference approximation of energy and using the energies of $(N+2)$, $(N+1)$, N, $(N−1)$, and $(N−2)$ systems, we obtain the expression for γ

$$\gamma = \frac{1}{12}(E_{N+2} - 2E_{N+1} + 2E_{N-1} - E_{N-2}) \tag{20}$$

The detailed derivation of γ has been given in the Appendix.

The site selectivity of a chemical reaction cannot be described by global reactivity descriptor. Thus, the appropriate local quantities need to be defined. Local softness is defined as[37,34]

$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{v(r)} \tag{21}$$

where

$$\int s(r)\, dr = S$$

Rewriting eq 21 we have

$$s(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \left(\frac{\partial N}{\partial \mu}\right)_{v(r)} \tag{22}$$

By using the definition of the global softness in eq 16, we can write

$$s(r) = f(r)S$$

where $f(r)$ is defined as the Fukui function (FF).[34,37−40] It can be defined as

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} \tag{23}$$

To describe the site selectivity or 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 atom in a molecule. This can be achieved by electronic population analysis. Depending upon the type of electron transfer, we have three different types of condensed Fukui function of the atom k,[35]

$$f_k^+ = [\rho_k(N+1) - \rho_k(N)] \quad \text{for nucleophilic attack} \tag{24a}$$

$$f_k^- = [\rho_k(N) - \rho_k(N-1)] \quad \text{for electrophilic attack} \tag{24b}$$

$$f_k^0 = \frac{1}{2}[\rho_k(N+1) - \rho_k(N-1)] \quad \text{for radical attack} \tag{24c}$$

where $\rho_k(N)$, $\rho_k(N+1)$, and $\rho_k(N-1)$ are defined as a gross electronic population of the atom k in neutral, anionic, and cationic system, respectively. Corresponding condensed local softness can be defined as

$$s_k^+ = f_k^+ S \tag{25a}$$

$$s_k^- = f_k^- S \tag{25b}$$

$$s_k^0 = f_k^0 S \tag{25c}$$

2.3. Expression for the Interaction Energy (IE). Multiple sites based interaction essentially, found to have two limiting cases, so-called localized reactive model (LRM) (Figure 1) and global (smeared) reactive models (SRM) (Figure 2). The expression for interaction energy of LRM is given as[59,60,69]
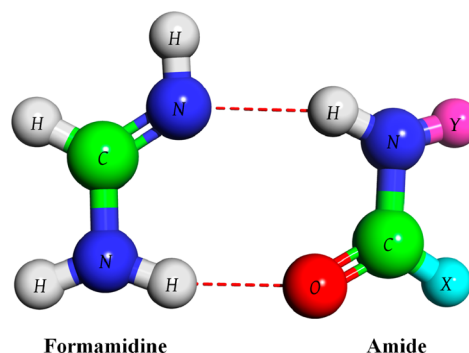

Figure 1. Multiple site based interactions pattern by localized reactive model (LRM) between acid, amide, and formamidine, where X = −H, −CH$_3$ refer to formamide and acetamide, respectively, and in all cases Y is −H. In the case of N-methyl derivatives, Y is −CH$_3$.
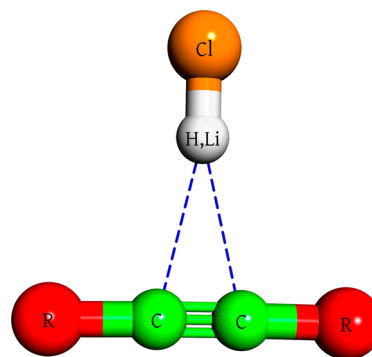

Figure 2. Multiple site based interactions pattern by smeared reactive models (SRM) between acetylene, butylene, H$^+$, and Li$^+$, where R = −H and −CH$_3$ refer to acetylene and butylene, respectively.

$$
\begin{aligned}
\Delta E_{int} \approx &-\frac{(\mu_A - \mu_B)^2}{2} \\
&\left(\frac{S_A S_B f_{Ax} f_{Bk}}{S_A f_{Ax} + S_B f_{Bk}} + \frac{S_A S_B f_{Ay} f_{Bl}}{S_A f_{Ay} + S_B f_{Bl}} + \frac{S_A S_B f_{Az} f_{Bm}}{S_A f_{Az} + S_B f_{Bm}} + ...\right)_{v(r)} \\
&-\frac{K}{4}\left(\frac{1}{S_A f_{Ax} + S_B f_{Bk}} + \frac{1}{S_A f_{Ay} + S_B f_{Bl}} + \frac{1}{S_A f_{Az} + S_B f_{Bm}} + ...\right)_{\mu}
\end{aligned}
\tag{26}
$$

Here the distinctive reactive sites of A and B are designated x, y, z, etc. and k, l, m, etc. respectively. It has been assumed that the interaction is taking place simultaneously between different pairs of reactive sites of the two systems as $x−k$, $y−l$, $z−m$, etc.

Similarly, the IE of SRM is

$$
\begin{aligned}
\Delta E_{A_x - B_k} \approx &-\frac{(\mu_A - \mu_B)^2}{2}\left[\frac{\left(\sum_{i=1}^n s_{A_{x_i}}\right)\left(\sum_{j=1}^m s_{B_{k_j}}\right)}{\left(\sum_{i=1}^n s_{A_{x_i}}\right) + \left(\sum_{j=1}^m s_{B_{k_j}}\right)}\right]_{v(r)} \\
&-\frac{K}{4}\left[\frac{1}{\left(\sum_{i=1}^n s_{A_{x_i}}\right) + \left(\sum_{j=1}^m s_{B_{k_j}}\right)}\right]_{\mu}
\end{aligned}
\tag{27}
$$

where there are n participating atoms $x_1, x_2, ..., x_n$ in the site A$_x$, similarly, there are m atoms $k_1, k_2, ..., k_m$ in the site B$_k$. The detailed derivation of LRM and SRM are given in ref 69. In eqs 26 and 27 parameter K is a charge transfer parameter. It can be defined in various ways and in the literature K has been defined arbitrarily. To calculate IE by eqs 26 and 27, Pal and co-workers

Table 2. Values of the Chemical Potential (μ), Hardness (η), and Hyperhardness (γ) of All Monomers Calculated at the DFT, MP2, and CCSD(T) Levels (Values in Atomic Units)

reactants molecule	chemical potential, μ			hardness, η			hyperhardness, γ		
	DFT	MP2	CCSD(T)	DFT	MP2	CCSD(T)	DFT	MP2	CCSD(T)
succinamide (SUC)	−0.1517	−0.1345	−0.1400	0.2078	0.2100	0.2203	−0.0055	0.0001	−0.0313
butyrolactam (BUTL)	−0.1268	−0.1220	−0.1022	0.2146	0.2309	0.2345	−0.0103	−0.0096	−0.0137
formamidine (FD)	−0.1232	−0.1213	−0.1068	0.2464	0.2483	0.2555	−0.0128	−0.0184	−0.0207
formic acid (FA)	−0.1548	−0.1479	−0.1414	0.2648	0.2756	0.2682	−0.0167	−0.0076	−0.0069
acetic acid (AA)	−0.1485	−0.1387	−0.1322	0.2460	0.2638	0.2556	−0.0158	−0.0103	−0.0107
formamide (FRM)	−0.1368	−0.1293	−0.1103	0.2404	0.2523	0.2567	−0.0146	−0.0129	−0.0081
N-methylformamide (NFRM)	−0.1320	−0.1191	−0.1042	0.2335	0.2402	0.2461	−0.0106	−0.0064	−0.0114
acetamide (ATM)	−0.1337	−0.1250	−0.1056	0.2251	0.2390	0.2452	−0.0147	−0.0075	−0.0140
N-methylacetamide (NATM)	−0.1283	−0.1222	−0.1023	0.2174	0.2335	0.2384	−0.0113	−0.0107	−0.0178
Acetylene (ACT)	−0.1401	−0.1277	−0.1254	0.2785	0.2925	0.4150	−0.0201	−0.0184	−0.0237
Butylene (BUTY)	−0.1212	−0.1147	−0.0966	0.2272	0.2460	0.2570	−0.0121	−0.0132	−0.0196
HCl (HCL)	−0.1973	−0.1782	−0.1758	0.2755	0.2755	0.2749	−0.0165	−0.0159	−0.0146
LiCl (LICL)	−0.1985	−0.1862	−0.1851	0.1769	0.1701	0.1683	−0.0225	−0.0220	−0.0211

have replaced this ad hoc parameter K by λ which is the change in the electron densities at the interacting site before and after the interaction process. Thus, the expression for the term λ can be written for the system A as[12]

$$\lambda_A = \sum_{i=1}^{p} \rho_{A_i}^{eq} - \sum_{i=1}^{p} \rho_{A_i}^{0} \qquad (28a)$$

Similarly, the term λ can be defined for the system B,

$$\lambda_B = \sum_{j=1}^{q} \rho_{B_j}^{eq} - \sum_{j=1}^{q} \rho_{B_j}^{0} \qquad (28b)$$

where the first terms of the right-hand sides of eqs 28a and 28b refer to the sum of the electron densities of each atom in A and B in the molecule AB at equilibrium, respectively, and the second terms in eqs 28a and 28b refer to electron densities of each atom in the isolated systems A and B, respectively. The indices p and q are the number of atoms of the systems A and B, respectively. The ad hoc parameter K in eqs 26 and 27 is replaced in three different ways: (1) first-order approximation of ΔN (eq 10), (2) second-order approximation of ΔN (eq 12) and (3) parameter λ (eqs 28a or 28b).

3. METHODOLOGY AND COMPUTATIONAL DETAILS

In this study we have chosen various prototype molecules viz., succinamide (SUC), butyrolactam (BUTL), formamidine (FD), formic acid (FA), acetic acid (AA), formamide (FRM), N-methylformamide (NFRM), acetamide (ATM), N-methylaceta-mide (NATM). To investigate the charge transfer parameter in smeared reactive models (SRM), we have considered acetylene (ACT), butylene (BUTY), HCl (HCL), and LiCl (LICL) molecules. All the structures are optimized at MP2[70]/6-311G(d,p) and DFT[71−73]/B3LYP[75,76]/6-311G(d,p)[77] level of theory using Gaussian 09 software package.[74] The three-parameter hybrid functional of Becke[75] and Lee, Yang, and Parr correlation potential[76] has been used for DFT calculations. We have checked our geometries for nonimaginary vibrational frequencies. Single point calculations to calculate reactivity descriptors have been performed at DFT, MP2, and CCSD(T) level of theory. Optimized geometries of MP2 level are used for the single point calculations in CCSD(T) method. RHF calculations are carried out for all the neutral system with spin multiplicity 1. For the cationic (charge +1.0) and anionic (charge

−1.0) systems, single point ROHF calculations are carried out with spin multiplicity 2. The optimized geometry of the neutral system was used to perform calculations on the cationic and anionic systems to satisfy the condition of constant external potential. The condensed Fukui function and local softness ($S_k^{\pm}$) for each reactive atom are computed via eqs 24 and 25 using Mulliken population analysis.[78] The reactive atoms in our study are hydrogen atom (electrophilic center) and oxygen atom (nucleophilic center). The parameter λ is calculated using eq 28 through Mulliken population scheme. In conventional methods, the interaction energy will be evaluated from the difference between the energy of the complex AB and sum of the energy of the monomer A and B,

$$\Delta E_{AB} = E_{AB} - (E_A + E_B) \qquad (29)$$

We have taken care of BSSE-counterpoise correction to calculate IE by conventional method.

4. RESULTS AND DISCUSSIONS

Hydrogen bonding interactions are extremely important in biological systems.[79−83] The helical structure of DNA molecule is due to the H-bonding between base pairs. In biological molecules such as proteins, polysaccharides, and lipids etc. the interactions are largely determined by multiple intra- and intermolecular H-bonding. To study such interactions, we have considered prototype complexes of formamide, acetamide, formic acid, acetic acid and their derivative with formamidine (FD) molecule as a simple nucleic acid base model. The amide−formamidine complex has been studied earlier by Bertran et al., Šponer et al., Kim et al., and Galetich et al.[84−87] They found that this is an important model complex having many features similar to those of the actual nucleic-acid base pair model. These complexes have two types of H-bonds: (a) −C═O group in amide and acid with formamidine −NH group; (b) amide −NH, acid −OH with formamidine N−C. The interaction between succinamide and butyrolactum has been studied by Uchimaru and co-workers.[88] Along with the above-mentioned complexes, we have also studied some multiple bonded interactions between π-electronic and electrophilic molecules. These molecules also show hydrogen-bonding interactions. The complexes formed between acetylene and butylene with HCl and LiCl are the examples of such multiple hydrogen bonded interactions.[89] Here H$^+$ of HCl and Li$^+$ of LiCl act as an electrophile interacting with the π-electron cloud of acetylene and butylene.

Table 3. Condensed Local Softness (S_k^+ and S_k^-)^a of the Reactive Atoms (Values in Atomic Units)

reactant molecule	A	B	DFT/6-311G(d,p)		MP2/6-311G(d,p)		CCSD(T)/6-311G(d,p)	
			A	B	A	B	A	B
succinamide (SUC)	O	H	0.5239	0.1890	0.5890	0.1641	0.6001	0.1549
butyrolactam(BUTL)	O	H	0.7140	0.5897	1.0106	0.2845	0.8416	0.1808
formamidine (FD)	N	H	0.6300	0.6513	0.6589	0.2326	0.6679	0.1873
formic acid (FA)	O	H	0.8346	1.4177	0.9496	0.1714	0.9825	0.1767
acetic acid (AA)	O	H	0.8119	1.0852	0.9494	0.1543	0.9853	0.1605
formamide (FRM)	O	H	0.8793	0.1955	1.0030	0.3490	0.9934	0.1973
N-methylformamide (NFRM)	O	H	0.8771	0.4714	0.9447	0.5379	0.6876	0.1691
acetamide (ATM)	O	H	0.8760	0.6299	1.0263	0.3488	1.0068	0.1785
N-methylacetamide (NATM)	O	H	0.7171	0.4430	1.0227	0.2040	1.0014	0.1612
acetylene (ACT)	C	C	0.6637	0.6637	0.6492	0.6492	0.6564	0.6564
butylene (BUTY)	C	C	0.4472	0.4472	0.5507	0.5507	0.5272	0.5272
HCl (HCL)	H		1.5986		1.6013		1.6032	
LiCl(LICL)	Li		2.5216		2.6515		2.6055	

^{a}For oxygen and nitrogen atoms S_k^- and for hydrogen and lithium atoms S_k^+ has been calculated. S_k^+ and S_k^- are same for the carbon atom.

In Table 2, the global properties of all prototype molecules are presented. These properties are calculated with DFT/B3LYP/6-311G(d,p), MP2/6-311G(d,p), and CCSD(T)/6-311G(d,p) levels of theory. For all the molecules the chemical potential (μ) obtained from DFT is higher than that of MP2 and CCSD(T) levels. Compared to chemical potentials for all other molecules, the chemical potential of HCl and LiCl calculated through DFT are much higher than that of MP2 and CCSD(T) methods. In the case of amide and acid complexes, the chemical potential difference is marginal in the range ≈0.012 to ≈0.027. However, hardness (η) does not follow a similar trend. The CCSD(T) values of hardness are higher for most of the molecules compared to DFT values. The MP2 values of hardness for acid molecules (viz. acetic acid and formic acid) are higher than those obtained with DFT and those of HCl and LiCl obtained from DFT are higher than those obtained with MP2 and CCSD(T) methods. In the case of hyperhardness, some molecules show higher values of γ at the CCSD(T) level and others show larger values at the DFT method. As per our observation, the values of γ are much lower than the chemical potential whereas μ and η values are in comparable magnitude for the all three methods. In 1991, Fuentealba and Parr[90] have also shown that in the case of atoms and their ions, the values of γ are smaller compared to μ and η. In contrast, Ordon and Tachibana[91] have shown in the case of diatomic molecules that γ can have a higher value than μ and η using maximum hardness principle. Thus, γ is not always lower than μ and η, and it varies from system to system. For the systems where γ is higher than μ and η, second-order approximation of ΔN will be more important to calculate the interaction energies. It is important to mention here that the sign of the γ can be either positive or negative. In the Table 2, all molecules have negative values of γ computed through three different methods viz. DFT, MP2, and CCSD(T). The η and μ values are positive and negative respectively for all the molecules. The γ values obtained using all the methods are significantly low and thus face a low profile existence in the interpretation of chemical bonding and reactivity.[67]

Table 3 shows the values of local softness ($S_k^\pm$) of all monomers calculated by DFT, MP2, and CCSD(T) levels of theory using the 6-311G(d,p) basis. The molecules reacting through the localized reactive model and smeared reactive model (Figures 1 and 2) have two and one reactive atoms, respectively. The local softness value for the reactive atom A of the molecules SUC, FD,

FA, AA, ACT, and HCL are higher at the CCSD(T) level than at DFT and MP2. On the other hand, FRM, NFRM, ATM, NATM, BUTL, and LICL have higher values of $S_k^\pm$ for atom A at the MP2 level. In the case of reactive atom B, DFT gives larger values of $S_k^\pm$ for most of the molecules except FRM, NFRM, and BUTY, which have higher values at the MP2 level. Compared to values for other molecules, the LRD values (S_k^+) of HCl and LiCl are exceptionally high, which confirms the higher reactivity of HCl and LiCl. The effect of methylation to the amide −NH$_2$ group on μ and η can be seen from Table 2. The same effect is observed on the condensed local softness value of carbonyl oxygen (S_k^-) and hydrogen (S_k^+). The condensed local softness of reactive atoms A and B of FRM and ATM molecules are greater than their N-methyl derivative. Due to the +I effect of the methyl group, methylation leads to depletion of positive charge on the reactive H atom, which results into the lowering of GRD and LRD values of the reactive O-atom and H-atom. Hence, the reactivity of the methylated system is reduced and the corresponding value of IE is expected to be lower than those of the unsubstituted amide complex.

The first-order and second-order approximation of ΔN calculated through DFT, MP2, and CCSD(T) using eqs 10 and 12, respectively, are reported in Table 1. We have also presented DFT results of λ using eq 28. The CCSD(T) values of ΔN_{first} and ΔN_{second} for all the complexes are higher than those of other two methods. The difference between first-order and second-order approximation of the charge transfer parameter has been discussed in section 2.1. We note in the present study that the values of ΔN_{second} are slightly different from the ΔN_{first}. However, DFT results of ΔN_{first} and ΔN_{second} are higher for most of the complexes compared to CCSD(T) results except for the complexes 1, 2, 9, and 11 (Table 1). It should be mentioned here that the third term, γ, is very small for all the molecules we studied here. Hence, ΔN_{second} does not show significant improvement in IE in our study. However, the ΔN_{second} will be very useful to calculate IE for the molecules that have a larger value of γ. Further, we see that the charge transfer is less in the methylated −NH$_2$ group than in the unmethylated species. In the case of the LiCl interaction with acetylene and butylene, the value of charge transfer parameters (ΔN_{first}, ΔN_{second}, and λ) are greater than those for the corresponding HCl complex. This observation is consistent with our earlier discussion on the value of GRD and LRD (Tables 2 and 3). However, among the acetylene and butylene complexes, butylene complexes (BUTY−

Table 4. ΔE_v, ΔE_μ, and Total Interaction Energies of All Complexes As Described in the Text, Calculated by the Parameters ΔN_{first}, ΔN_{second}, and λ Using the DFT/6-311G(d,p) Method[a]

complex	ΔE_v			ΔE_μ			ΔE_{total}			$\Delta E_{\text{conventional}}$
	ΔN_{first}	ΔN_{second}	λ	ΔN_{first}	ΔN_{second}	λ	ΔN_{first}	ΔN_{second}	λ	
SUC-BUTL(1)	−0.0826	−0.0826	−0.0826	−9.2480	−9.2434	−6.7387	−9.3306	−9.3260	−6.8215	−14.8663
FA-FD(2)	−0.2513	−0.2513	−0.2513	−5.6326	−5.6347	−13.8829	−5.8859	−5.8839	−14.1343	−20.6473
AA-FD(3)	−0.1527	−0.1527	−0.1527	−5.1059	−5.1071	−13.6514	−5.2586	−5.2598	−13.8041	−19.8042
FRM-FD(4)	−0.0303	−0.0303	−0.0303	−4.0822	−4.0825	−8.1825	−4.1125	−4.1128	−8.2128	−16.2580
NFRM-FD(5)	−0.0177	−0.0177	−0.0177	−2.3940	−2.3939	−6.7789	−2.4118	−2.4116	−6.7966	−16.3290
ATM-FD(6)	−0.0238	−0.0238	−0.0238	−2.5310	−2.5312	−6.2852	−2.5548	−2.5550	−6.3090	−15.9840
NATM-FD(7)	−0.0048	−0.0048	−0.0048	−1.4154	−1.4154	−6.3517	−1.4202	−1.4202	−6.3565	−15.9421
ACT-HCL(8)	−0.7450	−0.7450	−0.7450	−2.7691	−2.7677	−1.4107	−3.5141	−3.5127	−2.1556	−2.1773
ACT-LICL(9)	−0.9307	−0.9307	−0.9307	−2.6143	−2.6156	−6.5106	−3.5449	−3.5463	−7.4412	−5.5990
BUTY-HCL(10)	−1.0409	−1.0409	−1.0409	−4.7599	−4.7648	−2.7990	−5.8008	−5.8056	−3.8399	−4.2221
BUTY-LICL(11)	−1.2358	−1.2358	−1.2358	−4.3893	−4.4057	−5.5804	−5.6251	−5.6415	−6.8162	−14.9459

[a]Energy values are in kcal/mol. The corresponding values of ΔN_{first} and ΔN_{second} are given in Table 1. LRM (eq 26) and SRM (eq 27) have been used to calculate the IE of the complexes SUC-BUTL(1) to NATM-FD(7) and ACT-HCL(8) to BUTY-LICL(11), respectively.

Table 5. ΔE_v, ΔE_μ, and Total Interaction Energies of All Complexes As Described in the Text, Calculated by the Parameters ΔN_{first} and ΔN_{second} Using the MP2/6-311G(d,p) Method[b]

complex	ΔE_v		ΔE_μ		ΔE_{total}		$\Delta E_{\text{conventional}}$
	ΔN_{first}	ΔN_{second}	ΔN_{first}	ΔN_{second}	ΔN_{first}	ΔN_{second}	
SUC-BUTL(1)	−0.0164	−0.0164	−4.4483	−4.4463	−4.4647	−4.4626	−10.9489
FA-FD(2)	−0.0717	−0.0717	−8.1643	−8.1579	−8.2360	−8.2296	−13.4694
AA-FD(3)	−0.0296	−0.0296	−5.5336	−5.5314	−5.5633	−5.5610	−12.9607
FRM-FD(4)	−0.0085	−0.0085	−2.2762	−2.2759	−2.2847	−2.2844	−10.5835
NFRM-FD(5)	−0.0008	−0.0008	−0.6741	−0.6741	−0.6749	−0.6749	−11.0741
ATM-FD(6)	−0.0019	−0.0019	−1.0794	−1.0793	−1.0813	−1.0811	−10.7523
NATM-FD(7)	0.0009	0.0009	−0.2918	−0.2918	−0.2919	−0.2919	−10.1012
ACT-HCL(8)	−0.5725	−0.5725	−2.4023	−2.4016	−2.9748	−2.9741	−1.5980
ACT-LICL(9)	−0.9350	−0.9350	−2.5102	−2.5120	−3.4452	−3.4470	−4.3785
BUTY-HCL(10)	−0.8240	−0.8240	−3.5306	−3.5322	−4.3546	−4.3563	−3.4168
BUTY-LICL(11)	−1.2471	−1.2471	−3.5902	−3.6000	−4.8373	−4.8471	−12.9545

[b]Energy values are in kcal/mol. The corresponding values of ΔN_{first} and ΔN_{second} are given in Table 1. LRM (eq 26) and SRM (eq 27) have been used to calculate the IE of the complexes SUC-BUTL(1) to NATM-FD(7) and ACT-HCL(8) to BUTY-LICL(11), respectively.

HCL and BUTY−LICL) show higher charge transfer during the complexation. This is due to the +I effect of −CH$_3$ group, which increases electron density of adjacent triple bonded C atoms, resulting in greater affinity of butylene toward H$^+$ and Li$^+$.

Tables 4 and 5 show the IEs obtained from the DFT and the MP2 methods, respectively. Three different charge transfer parameters, viz. ΔN_{first}, ΔN_{second}, and λ are used for the calculation of the IEs. Looking at the results, it is observed that the MP2 IEs are lower than those of the DFT IEs. In light of the HSAB principle, the interaction between the molecules takes place in two steps: (a) step 1 (referred to as ΔE_v) occurs at a constant external potential leading to equilibration of chemical potential; (b) step 2 (referred to as ΔE_μ) involves the change in the electron density of the complex leading to an equilibrium state with constant chemical potential. The charge transfer parameter is involved in the ΔE_μ, which is the dominating term in the total IE and is computed through eq 26 (SUC−BUTL to NATM−FD) and eq 27 (ACT−HCL to BUTY−LICL), known as LRM and SRM, respectively.[47] In the case of amide−formamidine (FRM−FD, NFRM−FD, ATM−FD, and NATM−FD), acid−formamidine (FA−FD and AA−FD), and succinamide−butyrolam (SUC− BUTL), the reactive atoms are not directly connected to each other and thus the reactivity of each atom will be more or less independent of each other. For such complexes, the IE can be considered as a sum of the IE

arising from each pair of reactive atoms and that is the reason LRM (eq 26) gives reasonable results. The results are further compared with the interaction energy calculated by the conventional method using eq 29. Because the reactive C atom in acetylene and butylene are directly connected through a triple bond and act as a group,[16] the IE of these molecules with HCl and LiCl have been calculated by SRM (eq 27). It is gratifying to note that the IE of LiCl with this triply bonded system is greater compared to the IE of the HCl complex. The IE values of the ACT−HCL(8) complex are −3.5141 kcal/mol (by ΔN_{first}), −3.5127 kcal/mol (by ΔN_{second}), and −2.1556 kcal/mol (by λ) obtained from DFT calculations. and conventionally (using DFT) they are −2.1773 kcal/mol, whereas the IE values of the ACT−LICL(9) complex computed through ΔN_{first}, ΔN_{second}, and λ are −3.5449, −3.5462, and −7.4412 kcal/mol, respectively, and conventional IE is −5.5990 kcal/mol. The higher IE of ACT−LICL(9) is due to the higher electron affinity of Li$^+$ as compared to that of the H$^+$ ion. As mentioned earlier, the effect of methylation reduces the reactivity of the molecule. This is also supported by values of IE that are −4.1128 and −2.5550 kcal/mol using ΔN_{second} for FRM−FD(4) and ACT−FD(6) complexes, respectively, whereas their N-methyl derivative, i.e., NFRM−FD(5) and NATM−FD(7) complexes, have −2.4116 and −1.4202 kcal/mol for IE values, respectively. A similar trend is observed in IE calculated using other charge transfer

Table 6. ΔE_v, ΔE_μ, and Total Interaction Energy of All the Complexes As Described in the Text, Calculated by the Parameters ΔN_{first} and ΔN_{second} Using the CCSD(T)/6-311G(d,p) Method[c]

	ΔE_v		ΔE_μ		ΔE_{total}		
complex	ΔN_{first}	ΔN_{second}	ΔN_{first}	ΔN_{second}	ΔN_{first}	ΔN_{second}	$\Delta E_{conventional}$
SUC-BUTL(1)	−0.1207	−0.1207	−14.8756	−14.9117	−14.9963	−15.0364	−14.8035
FA-FD(2)	−0.1118	−0.1118	−10.5770	−10.5633	−10.6888	−10.6751	−12.6066
AA-FD(3)	−0.0582	−0.0582	−8.0401	−8.0343	−8.0983	−8.0924	−12.2465
FRM-FD(4)	−0.0012	−0.0012	−1.0755	−1.0754	−1.0767	1.0766	−10.3826
NFRM-FD(5)	−0.0006	−0.0006	−0.9555	−0.9556	−0.9562	−0.9562	−10.1929
ATM-FD(6)	−0.0001	−0.0001	−0.3837	−0.3837	−0.3838	−0.3838	−10.3182
NATM-FD(7)	−0.0018	−0.0018	−1.4382	−1.4382	−1.4400	−1.4400	−10.3338
ACT-HCL(8)	−0.4638	−0.4638	−2.2728	−2.2712	−2.7350	−2.7366	−1.1971
ACT-LICL(9)	−0.9755	−0.9755	−2.6091	−2.6077	−3.5846	−3.5832	−4.0198
BUTY-HCL(10)	−1.2529	−1.2529	−4.3970	−4.3924	−5.6499	−5.6453	−3.0173
BUTY-LICL(11)	−1.8470	−1.8470	−4.4627	−4.4652	−6.3096	−6.3121	−10.8380

[c]Energy values are in kcal/mol. The corresponding values of ΔN_{first} and ΔN_{second} are given in Table 1. LRM (eq 26) and SRM (eq 27) have been used to calculate the IE of the complexes SUC-BUTL(1) to NATM-FD(7) and ACT-HCL(8) to BUTY-LICL(11), respectively.

parameters (ΔN_{first} and λ). As per our expectations, complexes of butylene with HCl and/or LiCl have higher values of IE than the corresponding complexes of acetylene. In an earlier study by Pal and co-workers,[59] ΔN_{first} and λ have been used to calculate the IE of multiple site based interactions. Here we have chosen the same molecules but the calculations are performed with a higher level of theory and bigger basis set, which leads to better results of IE compared to the values reported by Pal and co-workers.[59] As an example, for SUC−BUTL(1) and ACT−HCL(8) complexes, the reported values of ΔN_{first} are 0.099 and 0.079, respectively, and the corresponding IEs are −49.71 and −6.37 kcal/mol, respectively, using the HF/3-21g* level of theory. Our results for the ΔN_{first} and IE are better as compared to the previously reported values by Pal and co-workers. In our study, the CCSD(T)/6-311G(d,p) level of theory gives 0.0415 and 0.0365 values of ΔN_{first} for SUC−BUTL(1) and ACT−HCL(8), respectively, and the IEs are −14.9963 and −2.7350 kcal/mol, respectively. The actual IEs are −8.58 and −1.50 kcal/mol, respectively.[84−87]

As we mentioned earlier, the interaction energy is proportional to the charge transfer parameter (ad hoc term) and vice versa. For the SUC−BUTL(1) complex, values of ΔN_{first} and ΔN_{second} (Table 1) are higher by 0.00789 au compared to λ. As a result of this, the computed IE through ΔN_{first} and ΔN_{second} are higher by ≈2.5 kcal/mol than IE obtained from λ. On the contrary, the FA−FD(2) complex has considerably lower values of both ΔN compared to λ, leading to lower IE when ΔN (ΔN_{first} and ΔN_{second}) is used as the ad hoc parameter instead of λ. It should be mentioned here that the IE of complexes calculated by semiquantitative local HSAB theory are less than the conventional method (Tables 4−6). It could be due to the limited accuracy in the computation of charge transfer parameters and the reactivity descriptors. However, we have observed a qualitative trend in our approach, which makes it useful to study the multiple sites based interacting systems. Figure 3 show the deviation (maximum, average and minimum) of IE calculated through local HSAB principle using three ad hoc parameters from the conventional method. Deviations are observed in this sequence, i.e., DFT > MP2 > CCSD(T). It implies CCSD(T) produce best result of IE for multiple site based interaction among all three methods.
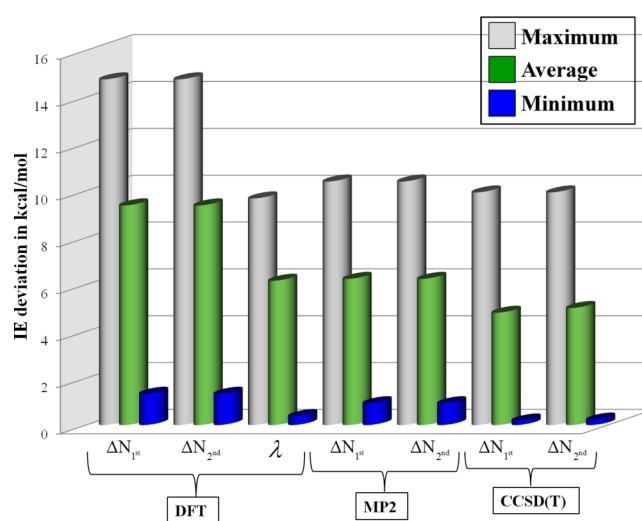

Figure 3. Maximum, average, and minimum deviation of interaction energy calculated through local HSAB (eqs 26 and 27) and conventional methods (eq 29).

5. CONCLUSION

In this work, we have calculated the hydrogen bonding interaction energy of various complexes using the local HSAB principle. We have derived ΔN_{second} and applied it as an ad hoc parameter in the calculation of the IE. Two different ad hoc charge transfer parameters (ΔN_{first} and λ) are also used to calculate the IE, and additionally, the advantage of using ΔN_{first} and ΔN_{second} over λ is highlighted. It is very hard to obtain theoretical information (optimized structure) due to complexity in the interaction in a biological environment. Therefore, to study this kind of interaction, higher order approximations of ΔN should be investigated. To compute ΔN (ΔN_{first} or ΔN_{second}), it is sufficient to have the information of only the reacting species, which is a tremendous advantage over λ where the actual structure of the supermolecule (complex product) is necessary. However, we have observed in our study using all the three methods, viz. DFT, MP2, and CCSD(T), ΔN_{second} does not improve the IE as compared to the ΔN_{first}, which is good enough to study the weak interactions. It must be mentioned here that among all three methods, CCSD(T), the most correlated method gives the minimum deviation of IE calculated through local HSAB and conventional method. Hence, higher correlated

methods should be the choice to deal with multiple site based weak interactions.

The local HSAB principle is based on the second-order perturbation method and the descriptors of the isolated reactants. Both the approximations make this model applicable only to weak interacting systems. In the case of weak interacting molecules, the influence of one monomer on another is comparatively less. Hence, the formula of local HSAB interaction energy more accurately describes the interaction process. On the other hand, the influence of one molecule on the other in the case of strong interactions can be high and in addition, higher orders of perturbation term can become more predominant when the equation is derived using the perturbation method. Therefore, one can modify the local HSAB formula by adding the higher orders of perturbation terms and use for various strong interaction cases.

■ APPENDIX

Evaluation of γ

For a given function $f(x)$, the derivative function is defined as

$$\frac{df(x)}{dx} = \lim_{\Delta x \to 0} \left(\frac{f\left(x + \frac{\Delta x}{2}\right) - f\left(x - \frac{\Delta x}{2}\right)}{\Delta x} \right) \tag{A}$$

Let, $(df(x)/dx) = f'(x)$, $(d^2f(x)/dx^2) = f''(x)$, and $(d^3f(x)/dx^3) = f'''(x)$. Hence,

$$f''(x) = \lim_{\Delta x \to 0} \left(\frac{f'\left(x + \frac{\Delta x}{2}\right) - f'\left(x - \frac{\Delta x}{2}\right)}{\Delta x} \right) \tag{B}$$

Similarly,

$$f'''(x) = \lim_{\Delta x \to 0} \left(\frac{f''\left(x + \frac{\Delta x}{2}\right) - f''\left(x - \frac{\Delta x}{2}\right)}{\Delta x} \right) \tag{C}$$

Taking the value of $\Delta x = 1$ and comparing eqs A, B, and C finally we have

$$f''' = \frac{1}{2}[f(x + 2) - 2f(x + 1) + 2f(x - 1) - f(x - 2)] \tag{D}$$

Therefore we can write

$$\gamma = \frac{1}{6}\left(\frac{d^3E}{dN^3}\right)$$
$$= \frac{1}{12}[E(N + 2) - 2E(N + 1) + 2E(N - 1) - E(N - 2)] \tag{E}$$

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The value of second-order approximation of ΔN (ΔN_{second}) obtained from eq 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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