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Study of Local Hard−Soft Acid−Base Principle to Multiple-Site Interactions

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In this paper, we have presented a detailed study of a local hard−soft acid−base (HSAB) principle for describing multiple-site interactions between the molecular systems. The local HSAB principle, which has been recently used to study single-site based interactions, can be generalized for the description of multiple-site-based interactions by different ways. We have elaborated these approaches and showed the validity of these models by making a detailed study on model prototype interactions that are relevant to biological molecular interaction processes. We discuss the nature of these approaches and the domain of their applicability.

I. Introduction

Density functional theory (DFT) has evolved into a successful theory for the study of molecular structure, chemical bonding,[1−3] and factors determining the reactivity and selectivity of molecules.[4−6] DFT has also provided the theoretical basis for concepts such as electronic chemical potential, electronegativity, and hardness, collectively known as global reactivity descriptors (GRD).[7−9] These descriptors essentially determine the response of the energy of a system to the change in the number of electrons at fixed external potential. The chemical potential of the two systems determines the flow of electrons. On the other hand, chemical hardness can be seen as a resistance to charge transfer. Furthermore, the local descriptors, like the Fukui function and local softness, relating the change of electron density to the number of electrons and the chemical potential, respectively, have been used to determine the reactive sites of a system.[10,11] The potential applicability of the global and local reactivity descriptors has been analyzed qualitatively by many groups for the description of reactivity and selectivity in molecular reactions.[12−15] At the same time, Pal and co-workers have shown the failure of the Fukui function and local softness to predict intramolecular reactivity trends in several organic carbonyl compounds and subsequently have proposed new reactivity descriptors, relative electrophilicity and nucleophilicity, to explain this trend.[16] Nguyen and co-workers also noticed the failure of Fukui indices in rationalizing the regioselectivity of protonation in the fluoro- and chloro-substituted phenol.[17] More recently, Roy et al. have analyzed the difficulty of obtaining the rank ordering of reactivity in a molecule when these Fukui indices become negative, and they have given procedures to obtain the correct nonnegative Fukui indices.[18] Fuentealba et al. have also discussed the possible existence of negative values of the Fukui indices by computing the Kohn−Sham frontier orbital density.[19] Chattaraj and co-workers have extended the applicability of these descriptors to describe the reactivity of molecular excited states.[20] Using Sanderson's principle of electronegativity equalization, Toro-Labbé et al. have attempted to evaluate the bond energies of the hydrogen bonded complexes.[21]

By using an energy perturbation method within the framework of DFT, Li and Evans have proposed a reactivity scheme[22] and shown that the Fukui function is one of the key concepts in relating the frontier molecular orbital theory and the hard−soft acid−base (HSAB) principle.[7,23] On this same basic ground, Gazquez and Mendez proposed the local HSAB principle, which states that the interaction between two molecules will occur not necessarily through their softest atoms but rather through those atoms of two systems the Fukui functions of which are similar.[24] The local version of this principle was proved by the minimization of the grand canonical potential. The issue and feasibility of the local HSAB principle has been critically studied.[4,25,26] In a recent study,[27] Ponti has described the regioselectivity criteria for cycloaddition reactions where the pair of interacting atoms does not have matching softness. The criteria are deduced from the atomic grand potential variation instead of the grand canonical potential, and it is called as a separate minimization of the grand potential. In his study, it is assumed that the charge-transfer process is the more dominating term than the charge-reshuffling process.

The working equations of local HSAB are based on perturbative theory and use of the descriptors of the reacting systems. The principle applies well to the weakly interacting systems. As such, the interactions, amenable to study by local HSAB principle, are the weak interactions. In a recent study, we have made a critical study on the applicability of local reactive descriptors (LRD) for weak interactions. The equations for local HSAB also include an ad hoc parameter λ, which cannot be computed rigorously. Several studies have used different values for this parameter. We have used theoretical charge transfer as a criterion for the ad hoc parameter, and this yielded reasonably reliable results. Later, our definition of λ has been used by Chatterjee and co-workers to study the reactivity of several cationic sites in dioctahedral clays.[28] However, so far, application of the local HSAB principle has been restricted to molecular interactions where the interaction proceeds through one pair of sites. Local HSAB principle has not been applied to more complicated interactions involving multiple interaction sites of the two systems. In most of the covalent bonded complexes, the interactions proceed via multiple sites, e.g., the weak intra and intermolecular hydrogen bonding (H-bond) interaction in nucleic acids (DNA and RNA) and the peptide linkages in

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proteins and in most of the supra-molecular complexes.[29−31] We have recently made a preliminary study of extending the local HSAB principle to such cases.[32] However, that was restricted to only a very limited class of systems. In the present paper, we attempt to make a detailed study and discuss different ways of extending the local HSAB principle to be applicable to a wider class of weak multiple-site interaction cases. Specifically, we have 2-fold objectives. The local HSAB principle was originally developed for weak single site interactions. One of the specific objectives of this paper is to see how this can be extended to weak interactions based on multiple sites. Because we will still use the theoretical charge-transfer value as the ad hoc parameter λ, our second objective will be to demonstrate how the λ parameter works for multiple interaction cases as well. The feasibility of the development will be established by selecting several intermolecular H-bonded systems. The complexes studied in this present paper are of biological relevance, and several groups have approached the study of molecular interactions through the available theoretical methods.[29−31] The acid amide-model nucleic acid interactions (formamidine) and other H-bonded complexes are also studied. Some other interesting interaction of π-electron cloud with hydrogen and lithium cations is also studied.

The paper is organized as follows. In section II, we give a brief theoretical background of the global and local reactivity descriptors. In section III, we will describe the local HSAB principle for the single-site interactions and then explain how to adopt this to study the interaction through multiple interaction sites. In section IV, the methodology and computational details are presented. In section V, we will present our results for the multiple-site interaction cases and discuss the validity of the proposed models based on the numerical results.

II. Theoretical Background

II.1. Global and Local Quantities. In DFT, the ground-state energy of an atom or a molecule is written in terms of its electron density ρ(r) as[33]

$$E[\rho] = F[\rho] + \int \mathrm{d}r\, v(r)\, \rho(r) \tag{1}$$

where $v(r)$ is the external potential that includes the nuclear potential and $F[\rho]$ is the universal Hohenberg−Kohn functional composed of the electronic kinetic energy and the electron−electron repulsion. 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.[7−9] The global softness is the inverse of the hardness. The global descriptor of hardness has been known as an indicator of overall stability of the system.[34,35] It has been customary to use a finite difference approximation for the computation of μ and η.[1]

The site-selectivity of a chemical system, cannot, however, be studied using the global descriptors of reactivity. For this, appropriate local descriptors need be defined. An appropriate definition of local softness $s(r)$ is given by[10]

$$s(r) = \left(\frac{\partial\rho(r)}{\partial N}\right)_{v(r)} \left(\frac{\partial N}{\partial\mu}\right)_{v(r)} \tag{2a}$$

$$= f(r)S \tag{2b}$$

such that

$$\int s(r)\, \mathrm{d}r = S \tag{3}$$

where $f(r)$ is defined as the Fukui function.[10] The Fukui function is defined as

$$f(r) = \left(\frac{\partial\rho(r)}{\partial N}\right)_{v} = \left(\frac{\delta\mu}{\delta v(r)}\right)_{N} \tag{4}$$

The second relation of Fukui function can be obtained using the relation that density is the functional derivative of energy with respect to external potential at constant N. The Fukui function describes the sensitivity of the chemical potential of a system to a local external potential. It is obvious that the local softness contains the same information as the Fukui function as well as the additional information about the molecular softness.[36] Using left and right derivatives with respect to the number of electrons, the electrophilic and nucleophilic Fukui function and local softness can be defined. To describe 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 atomic contribution in a molecule. This can be achieved by electronic population analysis. Thus, for an atom x in a molecule, depending upon the type of electron transfer, we have three different types of condensed Fukui function of the atom x:[11]

$$f_{x+} = [\rho_x(N+1) - \rho_x(N)] \text{ for nucleophilic attack} \tag{5a}$$

$$f_{x-} = [\rho_x(N) - \rho_x(N-1)] \text{ for electrophilic attack} \tag{5b}$$

$$f_{x0} = 1/2[\rho_x(N+1) - \rho_x(N-1)] \text{ for radical attack} \tag{5c}$$

where $\rho_x(N)$, $\rho_x(N+1)$ and $\rho_x(N-1)$ denote the gross electronic population of atom x in the neutral molecule, anionic, and cationic systems, respectively. The corresponding condensed local softnesses s_{x+}, s_{x-}, and s_{x0} can be defined. Larger value of the condensed Fukui function of a site x in a molecular system indicates greater reactivity at the particular atomic center x in the molecule.[10] This can determine the behavior of different reactive sites with respect to the hard and soft reagents.

III. Local HSAB Principle:

III.1. Local HSAB Principle for the Single Interacting Site. Using energy as a functional of the number of electrons (N) and the external potential (ϑ), the interaction energy is defined as the difference between the two interacting model systems A and B, and it is given as[1,4,37]

$$\Delta E_{\mathrm{int}} = \frac{-1}{2}\left(\frac{(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^2}{\eta_{\mathrm{A}} + \eta_{\mathrm{B}}}\right)_{\nu} - \frac{1}{2}N_{\mathrm{AB}}{}^2(\eta_{\mathrm{AB}} - \eta_{\mathrm{AB}}{}^*)_{\mu} \tag{6}$$

where η_{AB} and are η_{AB}* the hardness of the complex at the equilibrium and at the isolated state, respectively. For the details of the mathematical part of the derivation for the eq 6, one can refer to the work by Gazquez and Mendez[24,37] and by us.[4] Here, the interaction between systems A and B is assumed to take place in two steps, ΔE_v and ΔE_μ. In the first step, the interaction takes place at constant external potential through the equalization of chemical potential which is referred as ΔE_v.[24] In the second step, A and B evolve toward the equilibrium state through changes in the electron density of the global system produced at constant chemical potential which is referred ΔE_μ. The second step is a manifestation of principle of maximum hardness.[34,35,38] One can relate the difference in the hardness terms present in the second term of the above eq 6 to the softness of system A and B with a proportionality constant (K).[39] Thus, the second term, ΔE_μ, of eq 6 can be now rewritten in terms of the softness of systems A and B as

$$\Delta E_{\mu} = -\frac{1}{2}N_{\mathrm{AB}}{}^{2}K\left(\frac{1}{(S_{\mathrm{A}} + S_{\mathrm{B}})}\right)_{\mu} = -\lambda\ [1/4(\mathrm{S_A} + \mathrm{S_B})]_{\mu} \quad (7)$$

Herein, we introduce an ad hoc term λ as the product of $2N_{\mathrm{AB}}{}^{2}$ and the proportionality constant K. This parameter λ cannot be computed rigorously only through the softness of the molecular complexes. On substituting expression 7 in the eq 6, one can get the global model in terms of the softness parameter of the systems A and B

$$\Delta E_{\mathrm{int}} \approx \frac{-(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^{2}}{2}\left(\frac{S_{\mathrm{A}}S_{\mathrm{B}}}{S_{\mathrm{A}} + S_{\mathrm{B}}}\right)_{v} - \frac{1}{4}\left(\frac{\lambda}{S_{\mathrm{A}} + S_{\mathrm{B}}}\right)_{\mu} \quad (8a)$$

If the interaction between the systems occur through the atom x of A with the molecular system B, one can express the total interaction energy from the local point of view as[4,37]

$$(\Delta E_{\mathrm{int}})_{\mathrm{A}x} = \frac{-(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^{2}}{2}\left(\frac{S_{\mathrm{A}}f_{\mathrm{A}x}S_{\mathrm{B}}}{S_{\mathrm{A}}f_{\mathrm{A}x} + S_{\mathrm{B}}}\right)_{v} - \frac{1}{4}\left(\frac{\lambda}{S_{\mathrm{A}}f_{\mathrm{A}x} + S_{\mathrm{B}}}\right)_{\mu} \quad (8b)$$

where S_{A} and $f_{\mathrm{A}x}$ are the global softness and condensed Fukui function of the atom x in a system A, respectively. We have used the local softness and Fukui functions of isolated systems, and this approximation is justified for weak to moderately weak interactions. The parameter λ has been related to the deviation of total softness of interacting system AB from the sum of the softnesses of individual systems A and B. It has been defined somewhat arbitrarily in the literature.[26,38] In our earlier work,[4] we have related the parameter λ as the change in the electron densities at the interacting site before and after the interaction process. This change will give the effective number of valence electrons that have participated in the interaction process. For the case of predominantly ionic bonding systems, it has been adequately described as an electron-transfer parameter. Thus, an expression for the term λ can be written as the difference of electron densities of the system A before and after the interaction:

$$\lambda_{\mathrm{A}} = \sum_{i=1}^{\mathrm{p}} \rho_{\mathrm{A}i}^{\mathrm{eq}} - \sum_{i=1}^{p} \rho_{\mathrm{A}i}^{0} \quad (9a)$$

Alternately, the term λ can be defined as the difference of electron densities for system B

$$\lambda_{\mathrm{B}} = \sum_{j=1}^{q} \rho_{\mathrm{B}j}^{\mathrm{eq}} - \sum_{j=1}^{q} \rho_{\mathrm{B}j}^{0} \quad (9b)$$

where the first terms of the right-hand side of the eqs 9a and 9b 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 9a and 9b 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 above expression (8b) of interaction energy is derived on the basis of the fact that only one specific atom in the molecule is interacting with the other molecule. In the next subsection, we extend the local HSAB principle to describe simultaneous interaction of many sites of system A with different sites of B.

III.2. Local HSAB Principle for Multiple Interacting Sites. Let us consider the case of multiply bonded systems A and B. The distinctive reactive sites of A and B are designated x, y, z, etc. and k, l, m, etc. respectively. We assume 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. These reactive sites can be located at any part of the systems A and B. To apply local HSAB principle for such cases, we extend formula 8b, and we will now explain the different approaches.

In the simplest version of the model, (localized reactive model, hereafter referred to as LRM-I), we assume that the interaction between the different molecular systems is taking place through the individual reactive atom of the systems A and B. Each reactive atom can be located at the different part of the system, and there is no cooperative between the reacting atoms. Thus, although the reaction proceeds simultaneously through many reaction centers, interaction energy may be calculated in a decoupled manner. Hence, the total interaction energy for the complex AB may be represented as the sum of interactions arising from each part of the interacting atoms of A and B ($x-k$, $y-l$, $z-m$, etc.). Thus, the net interaction is obtained as a logical extension of single-site local HSAB principle to multiple sites by assuming that the interaction occurs in a decoupled manner and the additivity of energy. According to this model, the interaction energy expression is given as

$$\Delta E_{\mathrm{int}} \approx \frac{-(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^{2}}{2}\left(\frac{S_{\mathrm{A}}S_{\mathrm{B}}f_{\mathrm{A}x}f_{\mathrm{B}k}}{S_{\mathrm{A}}f_{\mathrm{A}x} + S_{\mathrm{B}}f_{\mathrm{B}k}} + \frac{S_{\mathrm{A}}S_{\mathrm{B}}f_{\mathrm{A}y}f_{\mathrm{B}l}}{S_{\mathrm{A}}f_{\mathrm{A}y} + S_{\mathrm{B}}f_{\mathrm{B}l}} + \frac{S_{\mathrm{A}}S_{\mathrm{B}}f_{\mathrm{A}z}f_{\mathrm{B}m}}{S_{\mathrm{A}}f_{\mathrm{A}z} + S_{\mathrm{B}}f_{\mathrm{B}m}} + \ldots\right)_{\vartheta} - \frac{\lambda}{4}\left(\frac{1}{S_{\mathrm{A}}f_{\mathrm{A}x} + S_{\mathrm{B}}f_{\mathrm{B}k}} + \frac{1}{S_{\mathrm{A}}f_{\mathrm{A}y} + S_{\mathrm{B}}f_{\mathrm{B}l}} + \frac{1}{S_{\mathrm{A}}f_{\mathrm{A}z} + S_{\mathrm{B}}f_{\mathrm{B}m}} + \ldots\right)_{\mu} \quad (10)$$

Collecting the expression for the interaction between Ax and Bk, Ay and Bl, etc. from the first and the second terms of eq 10, one can write

$$\Delta E_{\mathrm{int}} = \Delta E_{\mathrm{A}x-\mathrm{B}k} + \Delta E_{\mathrm{A}y-\mathrm{B}l} + \Delta E_{\mathrm{A}z-\mathrm{B}m} + \ldots \quad (11)$$

where $\Delta E_{\mathrm{A}x-\mathrm{B}k}$ defines the interaction energy derived from the site Ax and Bk. Considering the definition of the local softness, $s(r) = f(r)S$, a term of the eq 11, e.g., $\Delta E_{\mathrm{A}x-\mathrm{B}k}$ can be rewritten as

$$\Delta E_{\mathrm{A}x-\mathrm{B}k} \approx \frac{-(\mu_{\mathrm{A}} - \mu_{\mathrm{B}})^{2}}{2}\left(\frac{s_{\mathrm{A}x}s_{\mathrm{B}k}}{s_{\mathrm{A}x} + s_{\mathrm{B}k}}\right)_{\nu} - \frac{\lambda}{4}\left(\frac{1}{s_{\mathrm{A}x} + s_{\mathrm{B}k}}\right)_{\mu} \quad (12)$$

Similarly, other terms of eq 11 can be written in terms of local softness of the reacting sites of A and B.

One can generalize eqs 10 or 12 in the cases where the reacting sites consist of a group of atoms. This can arise because of the participation of neighboring atoms in the reaction site or the proximity of the two or more reacting sites, such that they may constitute one reacting site. In such cases, cooperative effects are strong. Let us now consider, the new reacting sites x, y, z, etc. of A which are located at different parts of the system but each of which contains a group of cooperative atoms in the reaction. Let us denote the group of atoms of the reacting site x and y as x_1, x_2, x_3, etc. and y_1, y_2, y_3, etc., respectively. Similarly, for the system B, one can denote the localized sets of the reacting atoms as k, l, m, etc. Each of these sites contain the connected set of atoms which can be called cooperative. Thus, site k contains cooperative atoms k_1, k_2, k_3, etc., and the site l contains a set of atoms l_1, l_2, l_3, etc. For such a general case, one can still write eq 10 in terms of the reacting sites, as before. Equation 11 formally holds. In this case, however, the softness of all of the atoms can be added to define the total softness of the reacting site. This can be called group softness,[6a] and using the group softness of the cooperating atoms in a site, each term $\Delta E_{\mathrm{A}x-\mathrm{B}k}$ can generally be written as

$$\Delta E_{\mathrm{A}x-\mathrm{B}k} \approx \frac{-(\mu_\mathrm{A}-\mu_\mathrm{B})^2}{2}\left[\frac{(\sum_{i=1}^{n} s_{\mathrm{A}x_i})(\sum_{j=1}^{m} s_{\mathrm{B}kj})}{\sum_{i=1}^{n} s_{\mathrm{A}x_i} + \sum_{j=1}^{m} s_{\mathrm{B}k_j}}\right]_\nu - \frac{\lambda}{4}\left[\frac{1}{\sum_{i=1}^{n} s_{\mathrm{A}x_i} + \sum_{j=1}^{m} s_{\mathrm{B}k_j}}\right]_\mu \quad (13)$$

where there are n participating atoms x_1, x_2, x_3, ..., x_n, etc. in the site Ax, and similarly, there are m atoms k_1, k_2, k_3, ..., k_m in the site Bk. One can say that the softness of these cooperative atoms is smeared in the site. ΔE_{int} is sum of all such site interactions $\Delta E_{\mathrm{A}x-\mathrm{B}k}$, $\Delta E_{\mathrm{A}y-\mathrm{B}l}$, $\Delta E_{\mathrm{A}z-\mathrm{B}m}$, etc. Depending on the number of sites and the group of atoms in a site, one can define a different interaction pattern between two systems A and B. We will refer this mode as LRM-II. In the limit that each site contains only one atom this model reduces to the previous model LRM-I. On the other hand, the other limit is the global HSAB, where there is only one site in each system A and B and all atoms are cooperative. In such a limit, there is only one term in the eq 10, and this term now involves the group softness of all atoms, which is the global softness of the systems. LRM-II actually defines all other intermediate interactions between the limit of the fully local (LRM-I) and the global model.

IV. Methodology and Computational Details

Ab initio Hartree−Fock (HF) quantum chemical calculations and density functional calculations (DFT) were performed to examine the validity of the different approaches. The molecular geometries were completely optimized at the HF level using the split-valence basis sets, 3-21G(d,p) and 6-31G(d,p), without any symmetry constraints. The restricted HF method has been used for the energy calculations of the neutral and for the corresponding anionic and cationic systems, and the restricted open shell HF method has been performed. The condensed Fukui function and local softness for each reactive atom were calculated via eqs 5a and 5b using Mulliken population analysis.[40] The ab initio calculations were performed using the GAMESS[41] system of programs on an IRIX-6.2 silicon graphics work station. The DFT calculations were performed using the deMon program,[42] and the energy of the systems was calculated using the three-parameter hybrid functional of Becke[43] and the Lee, Yang, and Parr correlation potential[44] (B3LYP). The optimized geometries obtained from HF/6-31G(d,p) are used in the DFT energy calculations. The basis sets used for C, N, and O are (5,2;5,2) auxiliary and (6311/311/1) orbital basis sets (equivalent to the DZV-P basis set). For H and Li, (5,1;5,1) and (5,2;5,2) auxiliary and (41/1) and (621/1*/1+) orbital basis sets were employed, respectively. Additional auxiliary basis sets are employed to describe the charge density and exchange-correlation potential. The use of the auxiliary basis set improves the numerical efficiency and the accuracy in the calculation of the total energies of the systems. During the iterative steps, the charge density is fitted analytically, and the potential exchange correlation is fitted numerically on FINE grid composed 32 radial shells. The parameter λ was calculated using eqs 9a and 9b, through the 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, $\Delta E = \mathrm{E}_{\mathrm{AB}} - (\mathrm{E}_\mathrm{A} + \mathrm{E}_\mathrm{B})$.

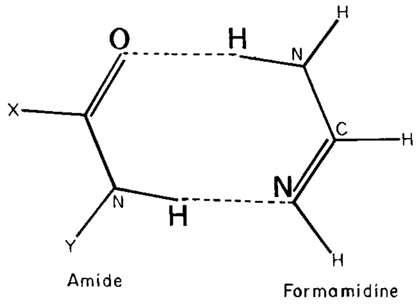

Figure 1. Multiple interactions between acid amide and formamidine. The bold and big letters are the reactive atoms, where X = −H, −CH$_3$, and −CH$_2$═CH, refer to formamide, acetamide, and acrylamide, respectively and in all cases Y is H. In the case of *N*-methyl derivatives, Y is CH$_3$.

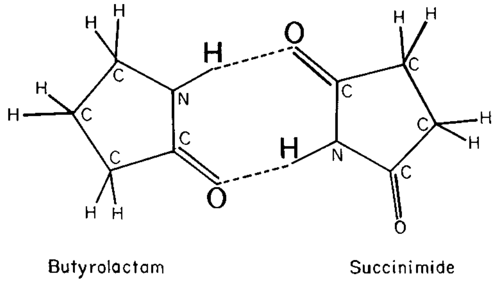

Figure 2. Multiple interactions between butyrolactam and succinimide.

V. Results and Discussions

The interactions of amides and their derivatives with nucleic acid−bases are very essential for understanding most of the biological processes.[29−31] These interactions are largely determined by the multiple inter- and intramolecular H bonds. Hence, the knowledge of the specific multiple interactions are very essential. We have considered prototype molecular systems such as the complexes of formamide, acetamide, acrylamide, formic acid, and acetic acid with the formamidine molecule as a simple nucleic acid−base model. The amide−formamidine complexes have been studied in the past[45−47] and represent the important model complexes having many features similar to the actual nucleic acid base pairs. These complexes have essentially two types of H-bonding (Figure 1), namely, (a) C═O group in amide and acid with formamidine H−N group and (b) amide N−H and acid O−H with formamidine N−C. The multiple interactions between butyrolactam and succinimide[48] are also considered in this present study (Figure 2). In addition to these polar group H-bonding interactions, the multiply bonded π-electron system with electrophilic species are also studied (Figure 3). These types of complexes include the complexes of acetylene and butylene with HCl and LiCl molecules.[49] Here, the cations H and Li are allowed to interact with two carbon atoms of the alkyne system that are connected by the π-electron cloud.

The global and local properties, chemical potential, hardness, and condensed local softness for all systems, are tabulated in Table 1 and Table 2. In genreal, the chemical potential of amide

TABLE 1: Global Properties of the Systems, Chemical Potential, and Hardness (Values Are Given in Atomic Units)

	chemical potential			hardness		
	HF			HF		
system	3-21G(d,p)	6-31G(d,p)	DFT[a]	3-21G(d,p)	6-31G(d,p)	DFT
formamide (FOR)	−0.072	−0.063	−0.160	0.246	0.265	0.215
N-met formamide (NFOR)	−0.070	−0.078	−0.151	0.237	0.239	0.200
acetamide (ACT)	−0.063	−0.056	−0.154	0.237	0.254	0.202
N-met acetamide (NACT)	−0.060	−0.047	−0.145	0.231	0.254	0.190
acrylamide (AL)	−0.102	−0.107	−0.152	0.198	0.202	0.198
N-met acrylamide (NAL)	−0.098	0.104	−0.148	0.192	0.195	0.185
formic Acid (FORMIC)	−0.113	−0.113	−0.174	0.258	0.261	0.240
acetic Acid (ACETIC)	−0.099	−0.099	−0.168	0.247	0.151	0.219
formamidine (F1)	−0.055	−0.049	−0.140	0.247	0.259	0.196
butyrolactam (LACT)	−0.063	−0.067	−0.146	0.231	0.234	0.191
succnimide (SUC)	−0.106	−0.107	−0.140	0.226	0.232	0.203
acetylene (ACET)	−0.087	−0.082	−0.176	0.288	0.279	0.236
butylene (BUTY)	−0.056	−0.057	−0.102	0.266	0.258	0.239
HCl (HCL)	−0.133	−0.138	−0.178	0.300	0.293	0.288
LiCl (LICL)	−0.170	−0.168	−0.186	0.155	0.158	0.176

[a] RHF/6-31G(d,p)//B3LYP/DZVP.

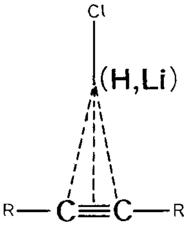

Figure 3. Multiple interactions between acetylene, butylene, and X^+ cations, where X^+ = H and Li; R = H and CH_3 refer to acetylene and butylene, respectively.

TABLE 2: Condensed Local Softness of the Reactive Atoms (Values Are Given in Atomic Units) S_x^+ and S_x^- Are Calculated for H, Li, O, N, and C for the Different Systems, Respectively

	reactive atoms		local softness					
			HF/3-21G(d,p)		HF/6-31G(d,p)		DFT	
system	A	B	A	B	A	B	A	B
FOR	H	O	0.229	0.844	0.490	0.958	0.126	1.112
NFOR	H	O	0.199	0.850	0.186	1.035	0.106	0.829
ACT	H	O	0.211	0.849	0.389	0.977	0.338	1.131
NACT	H	O	0.181	0.842	0.246	0.949	0.351	0.892
AL	H	O	0.305	0.965	0.299	1.177	0.127	0.772
NAL	H	O	0.164	0.977	0.156	1.204	0.098	0.696
FORMIC	H	O	0.195	0.844	0.173	0.994	0.447	1.013
ACETIC	H	O	0.180	0.844	0.159	1.001	0.493	1.022
F1	H	N	0.199	0.508	0.448	0.606	0.485	0.825
LACT	H	O	0.192	0.831	0.133	1.005	0.692	0.652
SUC	C	O	0.159	0.244	0.139	0.221	0.165	0.663
ACET	C	C	0.577	0.577	0.615	0.615	0.773	0.833
BUTY	C	C	0.498	0.498	0.532	0.531	0.446	0.443
HCL	H		0.104		1.190		1.490	
LICL	Li		2.911		2.809		2.503	

and acid systems differs marginally, in the range of ±0.002−0.018 au. The chemical potential values for the acetylene, butylene, HCl, and LiCl differ considerably. However, it should be noted that the hardness values of all complexes are quite different from each other. The values of the chemical potential calculated by the HF method through 3-21G(d,p) and 6-31G(d,p) basis sets do not vary much. When it is compared with the DFT values, HF values are lesser than the DFT values. In the case of the hardness values, HF values are considerably higher than the DFT values except for the case of LiCl. The effect of methylation at the amide NH_2 group on the chemical potential, hardness, and condensed local softness values of carbonyl oxygen and the hydrogen atoms is significant. It actually reduces the value of the GRD and LRD of the reactive oxygen and hydrogen atoms. Because the methyl group is an electron-donating group, the positive charge on the reactive amide hydrogen atom is reduced. Hence, the reactivity of methylated systems will be considerably reduced, and the corresponding interaction energy values are expected to be less than those of unsubstituted amide complexes.

We will now turn to the problem of obtaining the value of the parameter λ. In our earlier study,[4] we have calculated this parameter for the case of gaseous molecular interaction on the zeolite surface by considering the two reacting atom charge density alone. There, the change in electron density was observed only at the interacting site, and hence, the approximation introduced in defining the parameter λ indeed gave a correct description of the molecular interaction. In this present study, however, the interactions occur through multiple sites, and hence, total change in electron density at all interaction sites should be included. It is simpler to use the total electron transfer from A to B or vice versa. It will be close to the sum of the change in number of electrons at all sites, and it would include the effects of the surrounding atoms. This fact will specifically make a difference in determining the parameter λ for the cases of rigid ionic and covalent complexes. It also emphasizes the importance of the dynamical movement of electrons in weakly held covalent bonded complexes, in determining the stability of the complexes. On examining the value of λ from the Table 3, it can be seen that the λ value is considerably decreased by methylating at the $-NH_2$ group, for the amide complexes. In case of LiCl interaction with acetylene and butylene complexes, the value of λ is almost five times greater than that of HCl complexes. This observation is consistent with our earlier discussion on the values GRD and LRD of amide and other complexes.

Let us now examine the interaction energy values obtained by models that are described in section III.2. We will first consider the case of amide−fomamidine, acid−formamidine, and butyrolactam−succinimide complexes. In amides, the reactive atoms are carbonyl oxygen and the $-NH_2$ hydrogen atom and these reactive atoms are not directly connected to each other. Similarly, the reactive atoms present in formamidine molecule are also not connected to each other (see Figure 1). Although there is a nonbonded interaction (through inductive effect) between the reactive atoms present in the systems, the reactivity of each atom will be locally dominant in nature. This suggests that the reactive atoms in the amide complexes can be

TABLE 3: Value of Parameter λ for the Multiply Bonded Complexes (Values Are in Atomic Unit, the Abbreviations Are Given in Table 1)

	value of the parameter λ			
	HF			ΔN_{CT} [a]
system	3-21G(d,p)	6-31G(d,p)	DFT	HF/3-21G(d,p)
FOR−F1 **1**	0.013	0.007	0.005	0.036
NFOR−F1 **2**	0.012	0.006	0.018	0.033
ACT-F1 **3**	0.009	0.005	0.012	0.017
NACT-F1 **4**	0.008	0.002	0.023	0.012
AL-F1 **5**	0.011	0.007	0.024	0.106
NAL-F1 **6**	0.009	0.003	0.022	0.099
FORMIC−F1 **7**	0.043	0.029	0.041	0.115
ACETIC−F1 **8**	0.038	0.025	0.038	0.090
LACT-SUC **9**	0.222	0.013	0.017	0.099
ACET-HCL **10**	0.022	0.026	0.237	0.079
BUTY−HCL **11**	0.025	0.025	0.037	0.137
ACET-LICL **12**	0.098	0.164	0.170	0.188
BUTY-LICL **13**	0.089	0.180	0.231	0.274

[a] ΔN_{CT} is computed through the expression, $(\mu_A - \mu_B)/(\eta_A + \eta_B)$.

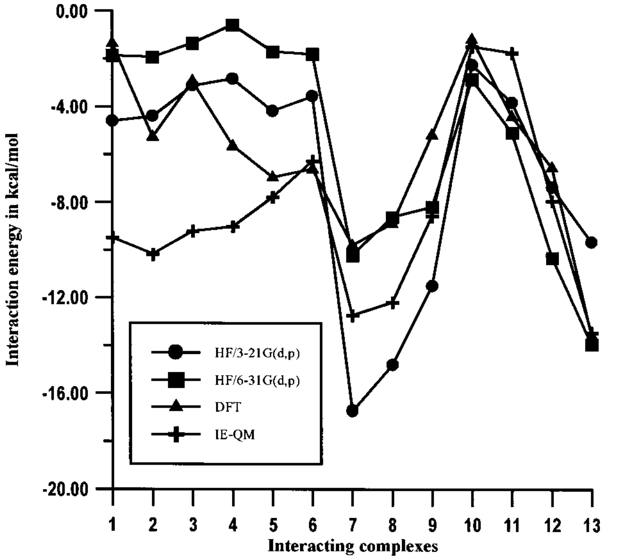

Figure 4. Total interaction energy of the hydrogen bonded complexes, calculated through LRM-I and LRM-II. IE-QM is the interaction energy calculated by other theoretical methods: the BSSE uncorrected ΔE, the difference between the complex and monomer energies, $\Delta E = E_{AB} - (E_A - E_B)$, calculated through DFT method, as described in the text. The number in the *X* axis refers to the corresponding interacting complex given in Table 3.

considered as localized atoms, and they can interact specifically with other molecule where each type of interaction is not much influenced by other reactive atoms. In such a case, the interaction energy can be considered as the sum of interactions arising from each pair of reactive atoms, and thus, LRM-I should give reasonable energy values for the amide−formamidine complexes. The same argument holds true for the interaction between butyrolactam−succinimide and acid−formamidine complexes. In Figure 4, the interaction energy calculated by LRM-I eq 10 is shown for all of the complexes. This is compared with the interaction energy calculated by the conventional method through the difference between the complex and monomer energies from the DFT calculations as described in the section IV.

We will now consider the second set of complexes arising because of the interaction of acetylene and butylene with H^+ and Li^+ cations. The reactive atoms in the alkynes are the two adjacent carbon atoms that are directly connected to each other by triple bond, as shown in Figure 3. In such cases, the reactivity of the two carbon atoms will be mixed or smeared up and the individual effect of each reactive atom will be lost. Hence, the straightforward assignment of the reactivity of the atoms in the system is not possible. The reactivity of such complexes will predominantly arise from the group of the directly connected C atoms. Hence, the generalized model with the group softness (LRM-II, eq 13) should describe the interaction pattern for these types of complexes. Evidently, one can see from Figure 4 that the interaction energy obtained through LRM-II is very realistic and there is a good agreement between the values obtained by other theoretical results and by the present approach. This clearly indicates the relevant influence of the nearest reactive atoms on the interaction energy of the alkyne−HCl and LiCl complexes. It is gratifying to note that the interaction energy of LiCl with these triply bonded systems is significantly greater than that of HCl complexes. It is known that the lithium affinity toward the electron rich systems is greater than that of other cations, and hence, the interaction energy is expected to be greater than that of other cations. In general, one can see that, although the GRD and LRD of methylated systems are significantly different from the unmethylated systems, the calculated interaction energy of these complexes from the present approach differs marginally in the range of 1−2 kcal/mol. It is also in agreement with other theoretical results.

As seen in Figure 4, the interaction energy of these complexes is less compared to the literature values in the order of a few kilocalories. It could be due to the limited accuracy in the calculation of the parameter λ as well as the reactivity descriptors. The value obtained by HF/6-31G(d,p) basis set is less compared to that of other values. Nevertheless, such variation in the estimated interaction energy values is very systematic and consistent with the available data. The accuracy of the calculation can be improved by choosing a much larger size basis set and including the correlation effects. On comparing the interaction energy calculated by HF and DFT at the 6-31G(d,p) basis set, it can be seen that HF theory tends to underestimate the interaction energy for most of the complexes, and when the correlation is introduced, the values are improved considerably and close to the other available theoretical results. One can see a reliable agreement between the interaction energy obtained by LRM-I and the conventional method, for the formic and acetic acid−formamidine complexes. LRM-I gives the values as −9.82 and −8.89 kcal/mol, and the actual values are −12.74 and −12.20 kcal/mol.[45−47] In case of the amide−formamidine complexes, HF/3-21G(d,p) and DFT values are comparable with the actual values, and there is a difference between the values obtained by LRM-I and the actual values. For the butyrolactum−succinimide complex, LRM-I predicts the interaction energy values evaluated by LRM-I through HF/3-21G(d,p), HF/6-31G(d,p), and DFT as −11.51, +8.19, −5.19 kcal/mol, respectively, and these values are in comparable with the actual interaction energy, −8.58 kcal/mol. In case of the ACET-HCL, BUTY−HCL, ACET-LICL, and BUTY-LICL interaction cases, the actual interaction energy values are −1.5, −1.77, −7.95, and −13.45 kcal/mol, respectively. The values obtained by LRM-II are very close to these values at all levels. For the ACET-HCL complex, for example, the LRM-II predicts the interaction values as −2.28, −2.87, and −1.20 kcal/mol evaluated at 3-21G(d,p), 6-31G(d,p), and DFT methods, respectively, and for the case of ACET-LICL, the values are −7.38, −10.33, and −6.56 kcal/mol. Similarly, one can also see the agreement for BUTY−HCL and BUTY-LICL cases.

A closer inspection on the contribution of the energy terms to the total interaction energy calculated by HF/3-21G(d,p)

TABLE 4: ΔE_v, ΔE_μ, and Total Interaction Energies of All Complexes as Described in the Text, Calculated by the Parameters λ and ΔN Using the HF/3-21G(d,p) Method[a]

	ΔE_v		ΔE_μ		ΔE_{tot}	
system	λ	ΔN	λ	ΔN	λ	ΔN
FOR−F1	−0.06	−0.06	−4.55	−12.96	−4.61	−13.02
NFOR−F1	−0.05	−0.06	−4.37	−12.10	−4.43	−12.16
ACT-F1	−0.01	−0.01	−3.12	−6.30	−3.13	−6.31
NACT-F1	−0.01	−0.01	−2.84	−4.45	−2.85	−4.46
AL-F1	−0.49	−0.49	−3.71	−34.60	−4.20	−35.09
NAL-F1	−0.34	−0.34	−3.24	−36.22	−3.58	−36.56
FORMIC−F1	−0.63	−0.63	−16.11	−42.85	−16.74	−43.49
ACETIC−F1	−0.36	−0.36	14.45	−34.00	−14.81	−34.36
LACT-SUC	−0.41	−0.41	−11.09	−49.30	−11.50	−49.71
ACET-HCL	−0.74	−0.74	−1.55	−5.64	−2.29	−6.37
BUTY−HCL	−1.92	−1.91	−1.94	−10.52	−3.86	−12.43
ACET-LICL	−3.60	−3.60	−3.78	−7.26	−7.38	−10.86
BUTY-LICL	−6.09	−6.09	−3.60	−10.89	−9.69	−16.99

[a] Energy values are in kcal/mol. The corresponding values of λ and ΔN are given in the Table 3. LRM-I and LRM-II have been used to calculate the interaction energy for the complexes, FOR−F1 to LACT-SUC, and ACET-HCL to BUTY-LICL, respectively.

methods (Table 4) reveals that the most important component of the interaction energy arises from the ΔE_μ term. It also emphasizes that this term alone can explain the nature and stability of the complexes, and it provides a driving force for the formation of the complexes. Hence, the charge redistribution process at constant chemical potential can be considered as a decisive modulating factor in determining the strength of the H-bonded and other types of complexes that have been considered in this present study. The effect of the strong directional character and relative arrangement of atoms in the actual interaction is introduced by the factor λ as defined in the eqs 9a or 9b.

The definition of the parameter λ is ambiguous, and several approximate definitions have been used in the literature.[3b,c,26] Gazquez et al. and Geerlings et al. have used different values of λ (1.0 and 0.5) depending on the systems studied in the literature.[3b,c,26] As described earlier, we have defined the parameter λ as the number of electrons that have been transferred from one system to another system and it can be computed through eqs 9a or 9b. An alternative way to compute this quantity is by using only the descriptors of individual systems A and B, i.e., $\Delta N = (\mu_A - \mu_B)/(\eta_A + \eta_B)$. We have also computed λ as ΔN in this work. To illustrate this, we have computed ΔN values for all of the complexes in HF/3-21 G(d,p) basis, which are presented in the Table 3. The interaction energy calculated using ΔN as well as λ, computed through eqs 9a or 9b are presented in the Figure 5, and these are compared with the available theoretical values. One can see from Figure 5 that the interaction energies calculated via eqs 9a or 9b are much more accurate than the one obtained using ΔN. This is possibly due to the fact that the parameter λ, being the total charge transfer, includes the influence of molecular environment. If one computes the interaction energy through ΔN, this influence will be missed considerably. However, one can still get a qualitatively correct trend of interaction energies using the expression of ΔN. The evaluation of parameter λ, being an electron-transfer variable, involves the calculation of the electronic population of the complex molecule. Although the calculation of the complex cannot be eliminated in the local HSAB principle, the principle provides a different route to the calculation of interaction energy based on softnesses of the reacting systems A and B, compared to the traditional way of obtaining the ΔE_{int} as the difference of energies of the complex and the reacting systems. The present approach allows one to study the change of interactions in terms of the hardness/softness parameters.

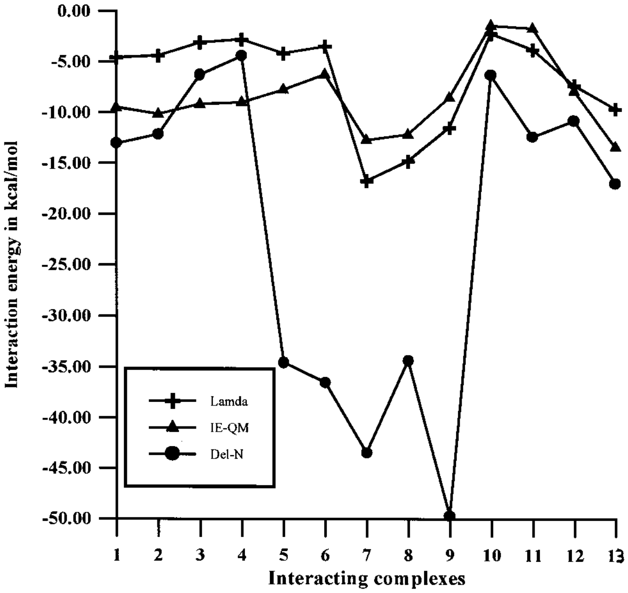

Figure 5. Total interaction energy of all the complexes obtained through the parameter λ and ΔN and the actual interaction energy (IE-QM). The number in the X axis refers to the corresponding interacting complex given in Table 3.

VI. Conclusion

In this work, we have attempted to study the local HSAB principle to complex multiple-site-based interactions, and accordingly, we have followed different approaches. Each of these approaches has its domain of applicability. To study the feasibility of these approaches, we have considered model prototype molecular interactions. We have explained the general interaction pattern that is observed in most of the molecular complexes. Because of the topological nature of the complexes, one can have a variety of complexes, which can be categorized broadly in certain distinguishable ways. In certain cases, the molecular systems may contain the interacting atoms that are directly connected to each other, and the reactivity of these kinds of systems are solely determined by the set of such reactive atoms. Here, the molecular association is effectively taking place with the additive cooperative effects being due to the other reactive atoms. It should be noted that the major dominating interacting forces in these complexes are due to the atoms that are directly involved in the interaction process. In such cases, as detailed in the earlier part of our discussion for the directly connected reactive atoms, a general model LRM-II taking into account cooperative or connected atoms in a site should predict the stability of the complexes correctly. In cases where the reaction takes place through separated atoms, the net interaction will be the sum of such individual interactions that are present in the complex. LRM-I can be used to describe these types of interactions between the complexes. However, if the interaction occurs predominantly through one pair of sites, calculation of interaction energy though single site formula would suffice. In some cases, the molecular interactions can also occur with all atoms that are present in the molecular systems. In such a case, the general LRM-II reduces to the global HSAB model, which is the correct choice for such interactions. Thus, one can treat various types of specific multiple-site interactions within the framework of the local HSAB principle.

Let us also note the limitations of the local HSAB principle to the study of these interactions. Because the basic working equations are derived from the second order perturbative methods and use the descriptors of isolated reactants, these models are applicable only to weakly interacting complexes. In the case of weak interacting molecules, the influence of one monomer reactant on another reactant molecule will be comparatively less, and the formula of local HSAB interaction energy more accurately describes the interaction process. For the strong interaction cases, the influence of one molecule on the other can be high, and in addition, other higher order perturbation terms can become more predominant. Therefore, by consistently following the models, one can handle various weak intermolecular interactions.

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