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Toxicity Analysis of Benzidine Through Chemical Reactivity and Selectivity Profiles: A DFT Approach[#]

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Abstract

Chemical reactivity descriptors based on density functional theory are useful in analyzing the toxicities and in identifying the reactive sites of the molecular systems. In the present investigation the global reactivity profiles such as electronegativity, chemical hardness, polarizability, electrophilicity index and local selectivity profiles like condensed electrophilicity of benzidine are calculated using B3LYP/6–31G* including both Hartree–Fock and density functional theory based exchange functionals (B3LYP) in order to gain deeper insights into the toxic nature of this compound. Both global and local electrophilicity have been found to be adequate in explaining respectively the overall toxicity and the most probable site of reactivity. Interaction between benzidine and nucleic acid (NA) base/selected base pairs and Aryl Hydrocarbon Hydroxylase (AHH) receptors are determined using Parr's formula. The charge transfer involved in the formation of adducts is also qualitatively studied. The results revealed that benzidine acts as an electron–donating agent in their interaction with biomolecules. The planarity and electron affinity are the criteria influencing the toxic nature of benzidine.

Keywords. DFT; toxicity; chemical hardness; chemical potential; philicity; polarizability.

Abbreviations and notations

AHH, Aryl Hydrocarbon Hydroxylase	MHP, Maximum Hardness Principle
DFT, Density Functional Theory	MPP, Minimum Polarizability Principle
FF, Fukui Function	NA, Nucleic Acid
HSAB, Hard –Soft Acid– Base	QSAR, Quantitative structure–activity relationships
MESP, Molecular electrostatic potential	

1 INTRODUCTION

The extended applications of computational chemistry to biodisciplines play an essential role in molecular property based drug design [1–9]. Last decade has witnessed tremendous growth in the development of descriptors for Quantitative Structure Activity–Relationship (QSAR) for various

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systems with a view to develop new molecular materials and de novo drug design. The use of topological descriptors and graph theory in the development of QSAR has gained importance through the seminal contributions of Trinajstić and his group [10]. Although there are numerous studies on the use of quantum chemical descriptors in the development of QSAR, the exploitation of Density Functional Theory based descriptors in the QSAR related studies is scarce. The application of DFT descriptors in the global chemical reactivity and local site selectivity is highly successful [11–16]. In this work an attempt has been made to explore the uses of DFT descriptors to investigate the structure activity relationship in arylamines and in particular toxicity of benzidine.

Aromatic hydrocarbons mainly arylamines and amides come under the class of potentially mutagenic and carcinogenic environmental pollutants. The knowledge of biochemical mechanisms of cancer induction by aromatic hydrocarbons especially arylamines and amides forms the basis of understanding the tumor formation [17]. For this class of organic compounds, the structure activity relationship between aromatic amines and carcinogenic potential has been reviewed in detail [17]. Some studies indicate that benzidine based dyes can be metabolized to benzidine and that human exposure to such dyes is associated with bladder cancer [17]. Epidemiological evidence is currently sufficient to qualitatively establish that benzidine is a bladder carcinogen following occupational exposure. Benzidine must undergo metabolic activation to produce its deleterious effects, probably through binding of oxidized reactive intermediates to nucleic acids (DNA and RNA) and protein target molecules. Currently there is a little that can be done to alter the progression of toxicological events once binding of reactive intermediates to target molecules has occurred. Therefore interfering with metabolic activation of benzidine and the activity of its reactive intermediates seem a more promising approach. Like many other arylamines, benzidine is postulated to require metabolic activation to electrophilic derivatives in order to manifest its carcinogenicity and genotoxicity through covalent bonding with DNA.

Carcinogenic potential of aromatic amines varies considerably with the molecular structures, although the mechanism of metabolic activation, resulting in formation of electrophilic reactants, seems to be common. Rotational energy barrier, electron affinity and planarity of arylamines consisting of two or more conjugated or fused aromatic rings have been considered as significant factors for their reactivity and the toxicity. Defining appropriate descriptors to model reactivity and toxicity of these molecular systems is the key parameter for development of QSAR. Rigorous theoretical basis for the descriptors of global and local reactivity indices have been provided by the conceptual density functional theory. These reactivity indices are better appreciated in terms of the associated electronic structure principles such as electronegativity equalization principle, Hard–Soft Acid–Base (HSAB) principle [18], Maximum Hardness Principle (MHP) [19], Minimum Polarizability Principle (MPP) [20] and generalized philicity [21]. The global reactivity indices such as chemical hardness, chemical potential and electrophilicity are used to understand the chemical reactivity whereas the local quantities such as Fukui functions, local softness and local philicity

indices have been employed to probe site selectivity and the reactivity of molecular systems of size ranging from small organic molecules to reasonably large drug molecules [22]. Recent studies [22] have shown that the results obtained from DFT based reactivity descriptors were in good agreement with experimentally observed quantities, like protonation sites, cycloaddition, aromatic nucleophilic substitution, nucleophilic attack, electronic properties and bond energies of hydrogen bonded complexes etc. Density functional theory based reactivity descriptors has been used to analyze the toxicity and reactivity of dioxins [23]. We have made a systematic attempt to analyze the chemical reactivity and site selectivity of various poly–chlorinated biphenyls by these DFT based reactivity descriptors [24]. Uses of global chemical descriptors in the development of qualitative structure activity and property relationship have also been made to predict the properties of various carbonyl compounds in gas and solution phases [25].

Biomolecules are the principal targets for the activated derivatives of these arylamines. In particular interaction of these molecules with constituent molecules of AHH receptor and DNA is of special interest. To model their interaction in real life systems, estimation of charge transfer between the biomolecule–benzidine interactions is a significant parameter. Since the reactivity and toxicity of this compound are greatly influenced by the geometry, specifically the rotational angle, the variation in the charge transfer with the rotational angle has also been considered. In this investigation, based on the above–mentioned issues, an attempt has been made to examine how various chemical reactivity and selectivity indices of benzidine and their associated electronic structure principles behave when benzidine interacts with the biomolecules in the realistic environment so as to develop proper descriptor for modeling its reactivity and toxicity.

2 THEORETICAL BACKGROUND

Chemical Hardness (η) has been shown to be a useful global index of reactivity in atoms, molecules and clusters [26,27]. The theoretical definition of chemical hardness has been provided by the density functional theory as the second derivative of electronic energy with respect to the number of electrons N, for a constant external potential $V(\vec{r})$:

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

where E is the total energy, N is the number of electrons of the chemical species and μ is the chemical potential, which is identified as the negative of the electronegativity χ as defined by Iczkowski and Margrave [28]. By applying finite difference approximation to Eq. (1) we get the operational definition for η as:

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

The corresponding global softness is expressed as:

$$S = \frac{1}{2\eta} = \left(\frac{\partial^2 N}{\partial E^2}\right)_{V(\vec{r})} = \left(\frac{\partial N}{\partial \mu}\right)_{V(\vec{r})} \tag{3}$$

Eq. (2) can be rewritten using Koopmans' [27] theorem as:

$$\eta = \frac{\varepsilon_{LUMO} - \varepsilon_{HOMO}}{2} \tag{4}$$

where ε_{HOMO} and ε_{LUMO} are the energies of highest occupied and lowest unoccupied molecular orbitals respectively.

Validation of the maximum hardness principle associated with atoms and molecules and their excited states have been reported recently [29]. It is known that the polarizability is inversely proportional to the third power of hardness [30,31]. Based on this inverse relationship, a minimum polarizability principle has been proposed [20,32] as a companion to MHP. The electric dipole polarizability is a measure of the linear response of the electron density in the presence of an infinitesimal electric field F and it represents a second order variation in energy:

$$\alpha_{a,b} = -\left(\frac{\partial^2 E}{\partial F_a \partial F_b}\right) \quad a,b = x,y,z \tag{5}$$

The polarizability α is calculated as the mean value as given in the following equation:

$$\langle \alpha \rangle = \tfrac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \tag{6}$$

The Fukui Function, which measures the sensitivity of a system's chemical potential to an external perturbation at a particular site, is defined as [33]:

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\delta \mu}{\delta v(\vec{r})}\right)_N \tag{7}$$

Since the above derivatives are discontinuous, three different types of Fukui Function have been defined [34–36]:

$$f^{+}(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}), \text{ for nucleophilic attack} \tag{8a}$$

$$f^{-}(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}), \text{ for electrophilic attack} \tag{8b}$$

$$f^{0}(\vec{r}) = (\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r}))/2, \text{ for radical attack} \tag{8c}$$

Parr et al [37] introduced the global electrophilicity index (ω) in terms of chemical potential and hardness as:

$$\omega = \frac{\mu^2}{2\eta} \tag{9}$$

The local electrophilicity index (ω_k^+) is defined as:

$$\omega_k^+ = \omega f_k^+ \tag{10}$$

where f_k^+ is the electrophilic Fukui function.

Recently Chattaraj *et al*. [21] have proposed a generalized concept of philicity containing electrophilic, nucleophilic and radical reactions. The condensed–to–atom variants for the atomic site k have been written as:

$$\omega_k^\alpha = \omega f_k^\alpha \tag{11}$$

where α = +, – and 0 refer to nucleophilic, electrophilic and radical attacks respectively. The ω_k^α will vary from point to point in a molecule but the sum of any ω_k^α over all atoms is conserved.

Molecular electrostatic potential (MESP) [38] is immensely useful in understanding the reactive sites of the molecule. The electrostatic potential $V(\vec{r})$ is defined as:

$$V(\vec{r}) = \sum \frac{Z_A}{|\vec{r}-\vec{R}_A|} - \int \frac{\rho(\vec{r}')d\vec{r}'}{|\vec{r}-\vec{r}'|} \tag{12}$$

where Z_A is the charges on nucleus A located at $\vec{R}_A$, and $\rho(\vec{r}')$ is the electron density at a point r for the molecule. $V(\vec{r})$ can assume positive as well as negative values and can provide useful information about the electron rich sites.

The global interactions between the constituents of AHH receptors and NA bases/base pairs have been determined using the parameter ΔN, which represents the fractional number of electrons, transferred from a system A to system B, and is represented by [39]:

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} \tag{13}$$

3 COMPUTATIONAL DETAILS

The geometry of benzidine is depicted in Figure 1 along with the atom numbering. The geometry of benzidine is optimized by using Becke's three parameter hybrid density functional, B3LYP/6–31G*, which includes both Hartree–Fock exchange and DFT exchange correlation functionals [40–42]. It is noted from previous studies on similar molecular systems that B3LYP/6–31G* provides comparatively reliable results [24] and hence in the present investigations the same basis set has been used. Above calculations are carried out using GAUSSIAN 98 package [43]. The relative energy of benzidine is calculated as a function of torsional angle ϕ, (rotation through the bond C (atom No. 7)–C (atom No. 3). To calculate the relative energy, the geometry at various ϕ values are optimized at B3LYP/6–31G* level. The relative energy for benzidine is calculated as $\Delta E(\phi) = [E(\phi) - E(\phi=90.0)]$ using the total energies of respective optimized conformations. To select proper electronic descriptor based on DFT, for the possible toxicity of the benzidine, the

various reactivity and selectivity descriptors such as chemical hardness (η) calculated using Eq. (2), chemical potential (μ) defined as: $\mu = -\frac{\varepsilon_{LUMO}+\varepsilon_{HOMO}}{2}$, polarizability ($\alpha$) using Eq. (6), electrophilicity index (ω) using Eq. (9) and the local philic power (ω_k^{α}) using Eq. (11) are calculated for all the rotated conformations. Since, Hirshfeld [44] population scheme (Stockholder Partitioning Scheme) is known to provide non–negative Fukui function (FF) values, it has been used to calculate FF values as implemented in the DMOL [45] package employing BLYP/DND method. For a system of *N* electrons, independent calculations have been made using Hirshfeld scheme on *N*–1, *N* and *N*+1 –electronic systems with the same molecular geometry to get the charges $q_k(N-1)$, $q_k(N)$ and $q_k(N+1)$ for all atoms *k* and these values were substituted in the Eqs. (8a–c) and the corresponding FF values for f_k^+, f_k^- and f_k^0 were obtained and using which ω_k^+, ω_k^- and ω_k^0 are calculated from Eq. (11). MESP of the various rotational angles of the benzidine are analyzed from the geometries generated from G98W calculation used for DMOL[3] [45]. Further the geometries for the nucleic acid bases/base pairs viz., Adenine, Guanine, Cytosine, Thymine, Uracil, ATH, GCWC and the Aryl Hydrocarbon Hydroxylase (AHH) receptors such as histidine (his), phenylalanine (phe) and tryptophan (trp) are optimized using 6–31G* basis set in the framework of B3LYP theory. We have also calculated the amount of charge transfer [39] between benzidine and various bases, viz., adenine (A), guanine (G), thymine (T), cytosine (C), uracil (U) and DNA base pairs GCWC, ATH and AHH receptors by using Eq. (13).

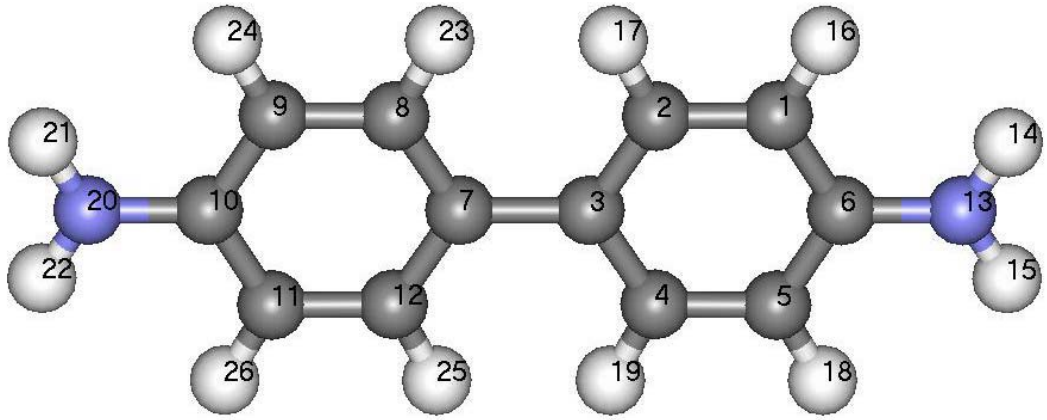

Figure 1. The geometry of benzidine with the atom numbering.

4 RESULTS AND DISCUSSION

Relative energy and global chemical reactivity descriptors such as chemical hardness, chemical potential, polarizability and electrophilicity index of benzidine are presented in Table 1. The variation of relative energy and chemical hardness of benzidine are displayed in Figure 2 for various rotational angles.

Table 1: Calculated Relative Energy, Chemical Hardness, Chemical Potential, Polarizability and Electrophilicity Index of Benzidine

Torsional angle (degrees)	Relative Energy [a]	Chemical Hardness [b]	Chemical potential [b]	Polarizabilty [c]	Electrophilicity index [b]
–30	0	2.33	–2.10	151.97	0.95
0	6.59	2.22	–2.13	149.06	1.02
30	0	2.33	–2.10	143.46	0.95
60	4.28	2.48	–2.14	139.07	0.92
90	11.19	2.61	–2.36	143.47	1.07
120	4.28	2.48	–2.14	149.04	0.92
150	0	2.33	–2.10	152.04	0.95
180	6.59	2.22	–2.13	149.04	1.02
210	0	2.33	–2.10	151.97	0.95

[a] in kJ/mol; [b] in eV; [c] in au

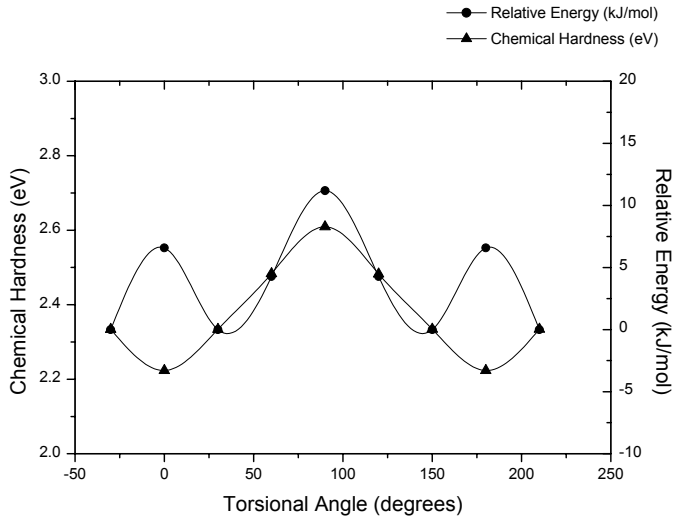

Figure 2. The variation of relative energy (kJ/mole) and chemical hardness (eV) with the torsional angles (degrees) for benzidine.

The most stable conformation corresponds to ϕ = 30° rotated conformation about C–C (about atom Nos. 7 and 3) bond. Minimum global hardness values coincide with the ϕ =180° and 0°, respectively. According to the principle of maximum hardness both these conformations are highly reactive when compared to the twisted conformation as observed in earlier studies [23]. Recent molecular orbital calculation on the structure and vibrational spectra of benzidine confirms the above finding [17]. It is possible to note from the rotational energy barrier, which has a small variation (0 to 11.19 kJ/mol) that this molecule is highly flexible and it can adopt variety of conformations. This rotational freedom allows benzidine to freely interact with the cellular components in the realistic environment and hence their toxic nature. The variation in the rotational energy barrier and polarizability are shown in Figure 3 while those of other global quantities (electronegativity and electrophilicity) are given in Figure 4.

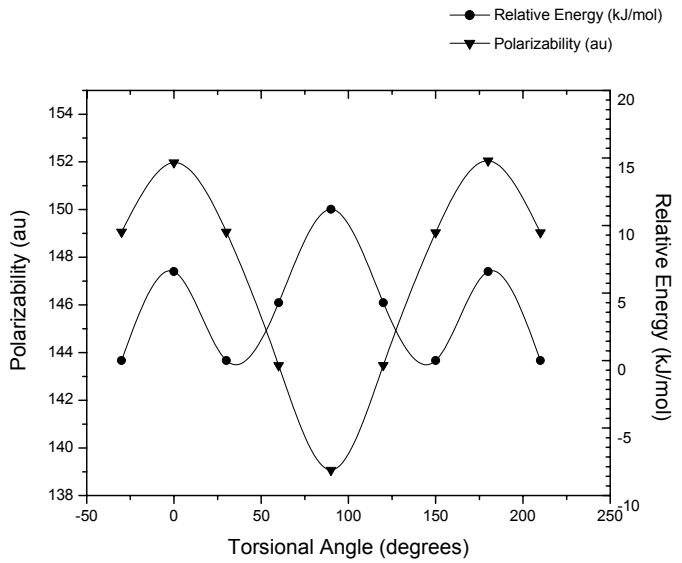

Figure 3. The variation of polarizability and relative energy (kJ/mole) with the torsional angles (degrees) for benzidine.

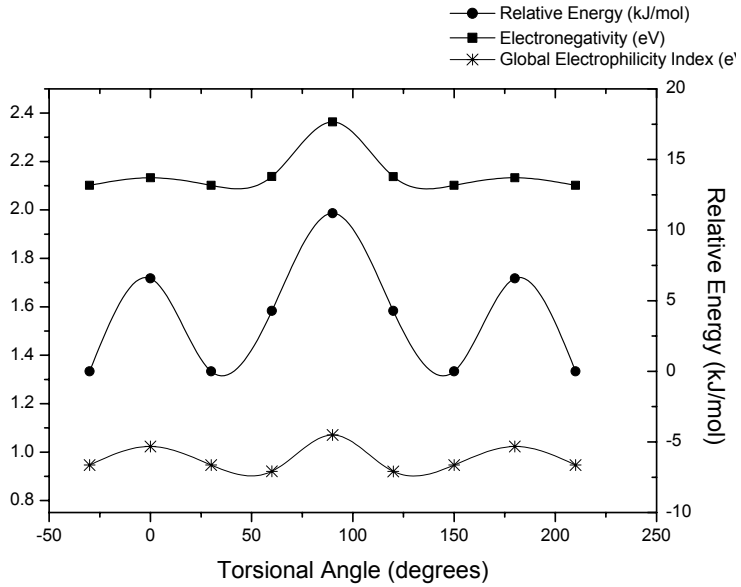

Figure 4. The variation of relative energy (kJ/mole), electronegativity (eV) and global electrophilicity index (eV) with the torsional angles (degrees) for benzidine

The changes in global quantities with rotational angles indicate that there is a violation of maximum hardness principle and minimum Polarizability principle at $\phi = 90°$ conformation and this may be attributed to the toxicity of the arylamines. For the global minimum conformation the hardness is less and polarizability is more compared to the perpendicular conformation and its associated reactivity. Both the MHP and MPP seem to be not operative at the global maximum energy conformation ($\phi = 90°$). We may consider this behaviour as a consequence of the large toxicity of the system vis–a–vis the energetics of rotation augmented by its kinetics.

The site selectivity profiles like condensed local electrophilicity have been used in the earlier studies on PCB to understand their toxicity nature [24]. It can be seen from the previous work that local electrophilicity provides the exact site of attack [21]. A unified philicity concept has also been extended here to analyze the toxicity of benzidine. Due to the symmetry of the selected system, the variations in the philicity (ω_k^+, ω_k^- and ω_k^0) with rotational angle for symmetry atoms are presented in Figures 5–7.

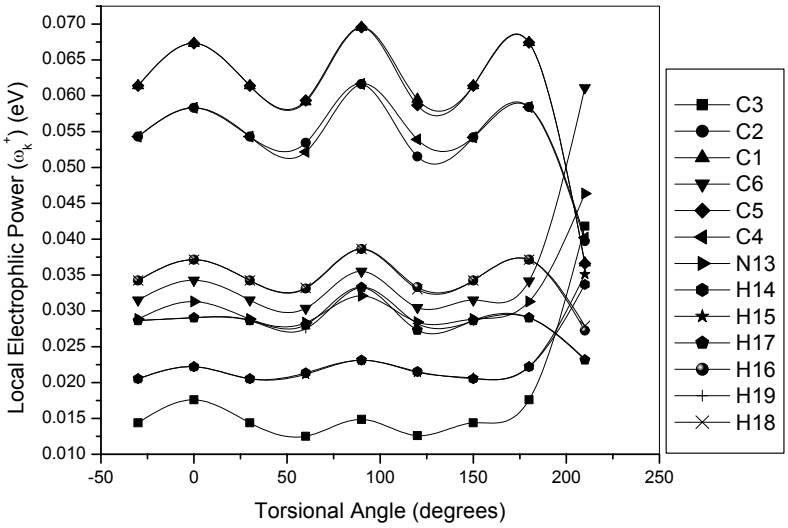

Figure 5. The variation of local philic power ω_k^+ (eV) with the torsional angles (degrees) for benzidine.

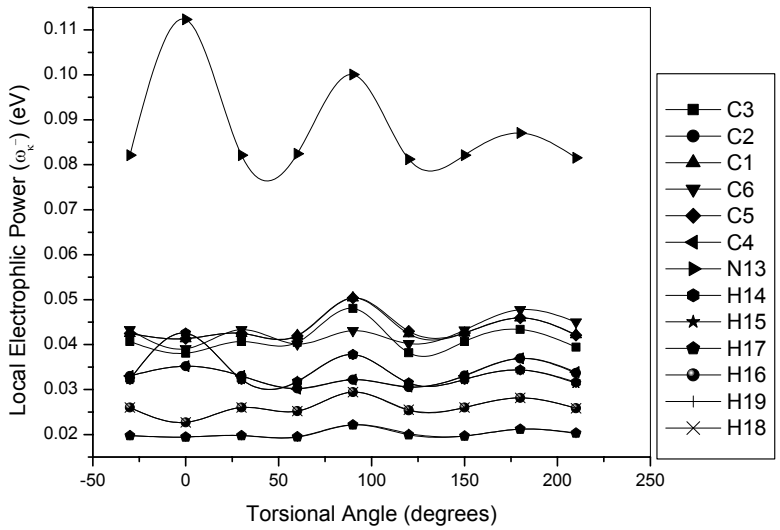

Figure 6. The variation of local philic power ω_k^- (eV) with the torsional angles (degrees) for benzidine.

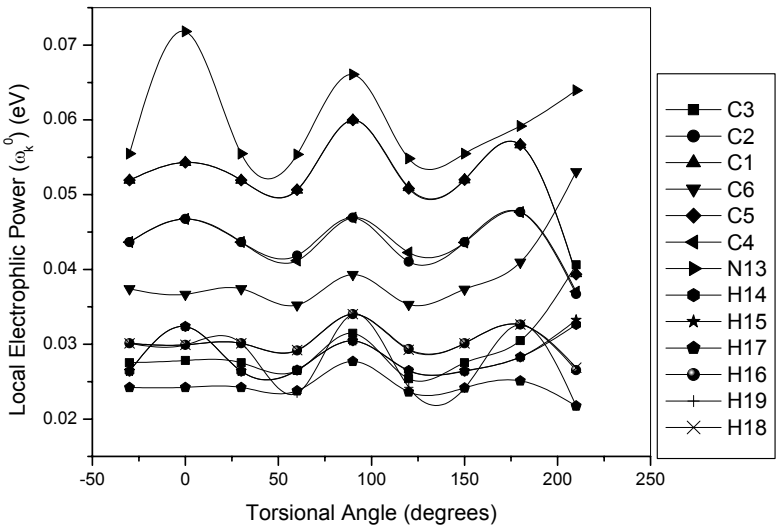

Figure 7. The variation of local philic power ω_k^0 (eV) with the torsional angles (degrees) for benzidine.

The C1, C5 correspond to the sites at which maximum potential for nucleophilic attack is possible whereas the C3 have minimum potential for it. The variations in the ω_k^- profiles reveal that N13 is the possible site with maximum potential for electrophilic attack. The profile of ω_k^0 reveals that N13, H17 has got the maximum and minimum value for the radical attack. The periodic variations in the chemical site selectivity profiles are similar to the changes in the rotational energy barrier and global chemical reactivity descriptors. It is possible to conclude that both local and global quantities have minimum corresponding to the global minimum with respect to the rotational energy barrier.

The local philicity profiles of ω_k^+ show a maximum at perpendicular conformation whereas ω_k^- profiles provide that planar conformation is equally responsible for the toxicity of benzidine. The role of planarity on PCB and its associated toxicity has received much attention. Our recent investigation [24] on planarity and chemical reactivity profiles for various PCB ensures that planarity plays a significant role in the toxic nature of PCB. Since skeletal structures of arylamines are similar to the PCB, the role of planarity is apparent form the reactivity profiles.

We have calculated the amount of charge transfer between Benzidine and the nucleic acid bases/ base pairs viz., Adenine, Guanine, Cytosine, Thymine, Uracil, ATH, GCWC and the Aryl hydrocarbon hydroxylase (AHH) receptors such as his, Phe and Trp by applying Eq. (13). It is seen that the electron transfer for all the bases/ base pairs *viz*., Adenine, Guanine, Cytosine, Thymine, Uracil, ATH, GCWC and the AHH receptors such as His, Phe and Trp is minimum for the ϕ = 90° configuration (Figure 8).

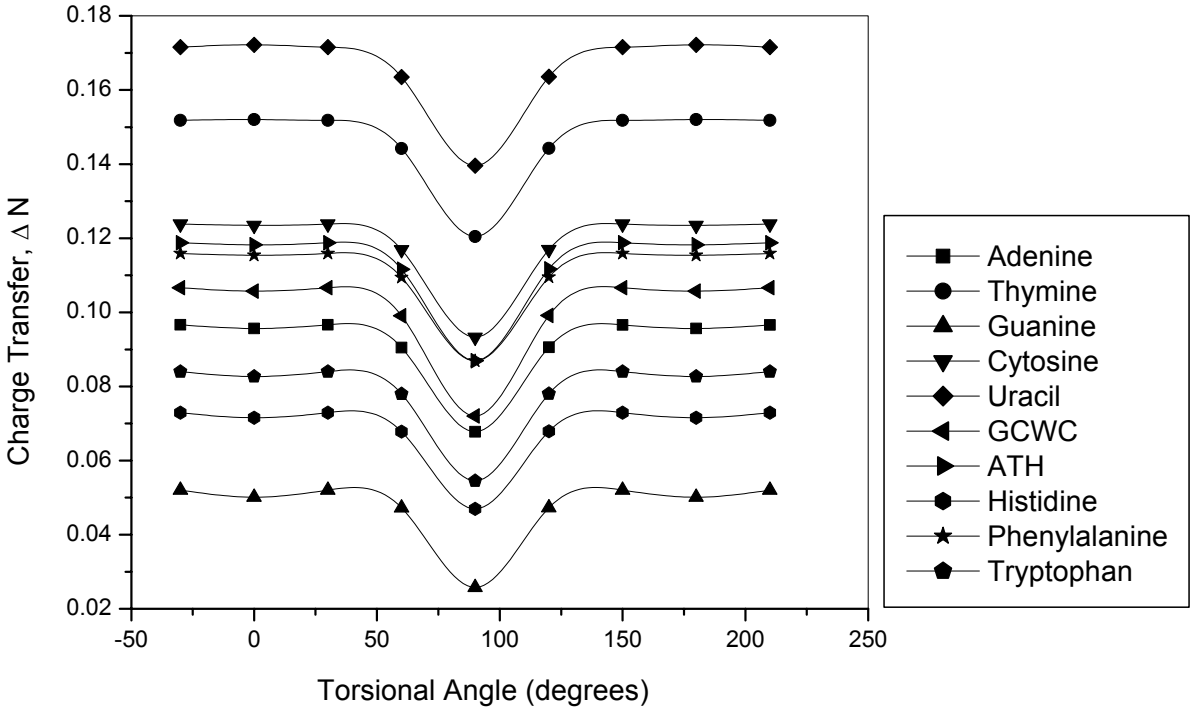

Figure 8. Charge Transfer between benzidine with various torsional angles (degrees) and ATH receptors and NA Bases/Base Pairs

Among the bases uracil and guanine have the maximum and minimum values for ΔN respectively, whereas for the selected base pairs ATH has the maximum value for ΔN for all conformations. If two systems X and Y are brought together, as in a reaction they must form a single system with the constant values of chemical potential. The negative chemical potential can be called the absolute electronegativity and there is always a transfer of electrons from less electronegative system to more electronegative system. The ΔN calculation for determining electron transfer between selected benzidine and bases/selected base pairs, AHH receptors are reported showing clearly the electron donating nature of benzidine. Table 2 reports the global reactivity descriptors (η and μ) for these bases/ base pairs *viz*., Adenine, Guanine, Cytosine, Thymine, Uracil, ATH, GCWC and the AHH receptors such as His, Phe and Trp for completeness.

Table 2. Calculated chemical hardness and chemical potential of the AHH receptors and NA bases/selected base pairs

Bases/Base pairs	Chemical Hardness [a]	Chemical potential [a]
Uracil	3.20	–2.91
Histidine	2.99	–3.34
Phenylalanine	2.62	–2.93
Tryptophan	2.85	–3.10
Adenine	2.89	–3.69
Thymine	2.92	–2.65
Guanine	2.79	–3.37
Cytosine	2.96	–3.92
GCWC	2.02	–3.03
ATH	2.53	–3.26

[a] in eV

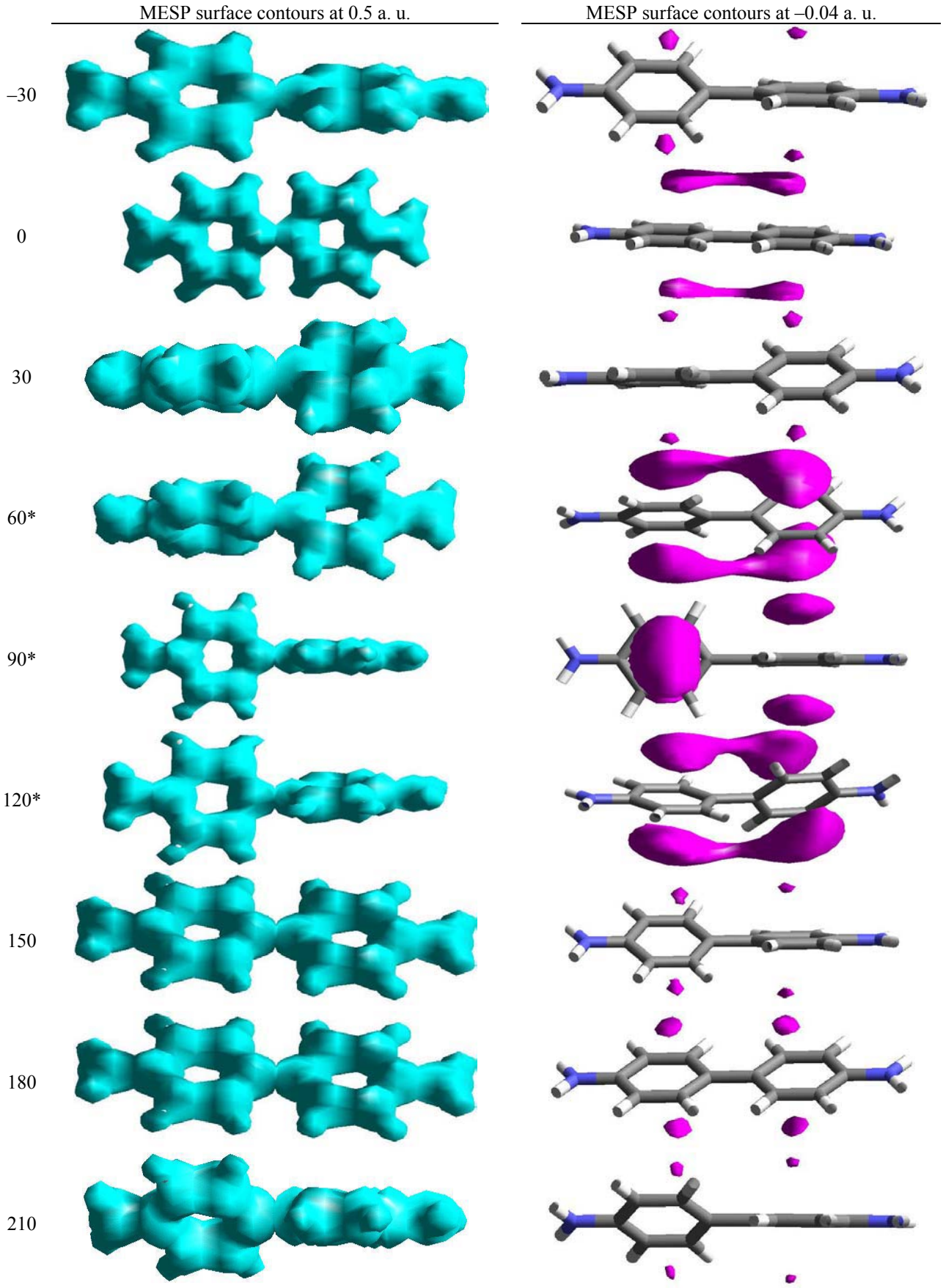

Figure 9. The molecular electrostatic potential surfaces for various conformations of benzidine.

The electrostatic potential $V(\vec{r})$ created in the space around a molecule by its nuclei and electrons has recently become a well–established tool to understand the chemical reactivity of the molecule. The molecular electrostatic potential provides necessary information about the reactive sites. The molecular electrostatic potential surfaces for various conformations of benzidine are shown in Figure 9 (entries marked with * have MESP surface contours at –0.03 a. u.).

The MESP contours over aromatic region reveal interesting features. The most negative MESP regions of all the benzidine conformers ranges from –0.0410 to –0.0388 au. The negative MESP contours of all the conformers of the benzidine molecule have been found above and below the aromatic ring. These electrostatic potential features play a key role while interacting with the biomolecules. The benzidine molecule can interact through π stacking interaction as well as intercalation between the major and minor groove of DNA. With protein molecules, the positively charged amino acids can interact with the benzidine in addition to the π–OH and π–NH_3 types of interactions. The MESP features reveal that with the rotation, the intrinsic reactivity of the molecules changes and hence its reactivity and toxicity in the presence of biomolecules. These trends are in accordance with the global reactivity descriptors such as chemical hardness and electrophilicity.

5 CONCLUSIONS

DFT based chemical reactivity descriptor analysis has provided valuable information about the reactive sites for various types of attacks and orientations for a selected arylamine system namely, benzidine. It has been found that relatively low barrier energy has provided greater flexibility to the selected system, thereby allowing it to orient itself in any desired conformation in the biological system leading to its toxic characteristics. The MESP surface of benzidine reveals the site of attack and also provides clues for the role of electrostatic interactions involved in the reactivity. Further the charge transfer between benzidine and nucleic acid bases/base pairs, AHH receptors has clearly revealed the electron donating nature of benzidine.

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