Toxicity analysis of 33′44′5-pentachloro biphenyl through chemical reactivity and selectivity profiles

R. Parthasarathi, J. Padmanabhan[†], V. Subramanian*, B. Maiti[‡] and P. K. Chattaraj[‡]

Chemical Laboratory, Central Leather Research Institute, Adyar, Chennai 600 020, India
[†]Department of Physics, L.N. Government College, Ponneri 601 204, India
[‡]Department of Chemistry, Indian Institute Technology, Kharagpur 721 302, India

Global reactivity profiles like electronegativity, hardness, polarizabilty, electrophilicity index and local selectivity profiles like condensed Fukui function and regional electrophilic power of 33′44′5-pentachloro biphenyl have been calculated using B3LYP/6-31G* including both Hartree–Fock and density functional theory-based exchange functionals in both gas and solution phases in order to gain 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 of the selected system and the most probable sites of toxicity, viz. Cl_{20}, C_{10} and H_{14}. Planarity and electron affinity are the possible criteria for determining the toxic nature of this biphenyl.

TOXICITY of polychlorinated biphenyls (PCBs) has seen an upsurge of interest in recent years[1–9]. These compounds exhibit toxicity similar to that of polychlorinated dibenzo-*p*-dioxin (PCDD). This information on PCB has prompted several investigators to understand the toxic nature of PCBs and their interaction with cellular components[10]. The origin of toxicity of PCDDs has been attributed to the electron accepting nature in charge transfer complex with a receptor in living cells. Hence electron affinity of PCBs is used as an important quantity in understanding their toxic effects. Recently, Arulmozhiraja *et al.*[11] have made an analysis on structure, potential energy and torsional barrier heights for selected polychlorinated biphenyls. Rotational energy barrier, electron affinity and planarity of various PCBs have been calculated in that study to rationalize the non-toxic nature of ortho-substituted PCBs. Rotational energy barriers of biphenyls (BP) and substituted biphenyls have been calculated using B3LYP/6-311+G* calculations by Grein[12]. There are similar calculations on torsional barrier of BP and PCB using various theoretical calculations ranging from semi-empirical AM1 to conventional Hartree–Fock methods. It is evident from the calculations that the toxicity arises mainly from the electron affinity and inherent nature of the planar geometry of the biphenyls and substituted biphenyls. It is well known in gas phase that BP is twisted (torsional angle between two phenyl rings) with twist angle of about 45°. This twist in BP is usually explained as arising from competition between the repulsion of the ortho hydrogens favouring 90° twists (torsional angle (φ) and the electron delocalization effect preferring a coplanar arrangement[13,14]. In chlorinated BPs, this balance in interactions is still perturbed by the chlorine atoms, which influences the geometrical parameters of BPs, specifically the torsional angle between the phenyl rings. It is evident from the previous theoretical studies that torsional angle is not influenced by the chlorine substituents at the para and meta positions[10,11]. However, torsional angle between two phenyl rings with ortho substitution is nearly 90°. In real life systems, PCBs are known to interact with the cellular components and hence addition and removal of electron during the formation of the complex are very significant events. The electron acceptance as well as electron removal to PCBs lead to changes in the torsional angle φ of PCBs and hence their geometry.

Popular qualitative chemical concepts like electronegativity and hardness have been widely used in understanding various aspects of chemical reactivity[15–19]. Rigorous theoretical basis for these concepts has been provided by 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 (HASB) principle[20], maximum hardness principle (MHP)[21,22], minimum polarizability principle (MPP)[23], etc. Local reactivity descriptors like density, Fukui function, local softness, etc. have been used successfully in the studies of site selectivity in a molecule. It is reported in the earlier study that the rotational freedom of PCBs allows it to orient with any torsional angle in the protein field and provides the pathway for easy interaction with receptors in living cells and hence their toxicity. In this investigation, an attempt has been made to examine how various chemical reactivity and selectivity indices and their associated electronic structure principles manifest themselves when PCBs rotate in the realistic environment so that a proper descriptor can be selected to define toxicity of various compounds.

---

*For correspondence. (e-mail: subuchem@hotmail.com)

Theoretical background

The chemical hardness (η) has been shown to be a useful global index of reactivity in atoms, molecules and clusters[24,25]. 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 $V(r)$.

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

The corresponding global softness is expressed as

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

Using the finite difference method and Koopmans' theorem[25], working equation for the calculation of chemical hardness has been given by

$$\eta = \frac{\text{IP} - \text{EA}}{2}, \qquad (3)$$

where IP and EA are ionization potential and electron affinity of the atom or molecule. If $\varepsilon_{\text{HOMO}}$ and $\varepsilon_{\text{LUMO}}$ are the energies of highest occupied and lowest unoccupied molecular orbitals respectively, then the above equation can be rewritten as

$$\eta = \frac{\varepsilon_{\text{LUMO}} - \varepsilon_{\text{HOMO}}}{2}. \qquad (4)$$

Based on the inverse relationship[26–28], a minimum polarizability principle has been proposed[23] as a companion to MHP. The site selectivity of a chemical system cannot, however, be studied using the global descriptors of reactivity. For this, appropriate local descriptors of selectivity need be defined. An appropriate definition of local softness $s(r)$ is given by[29],

$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu}\right)_{v(r)}, \qquad (5)$$

such that

$$\int s(r)\mathrm{d}r = S. \qquad (6)$$

Combining eqs (5) and (6),

$$s(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)}\left(\frac{\partial N}{\partial \mu}\right)_{v(r)} = \left(\frac{\partial \mu}{\partial v(r)}\right)_{N} S = f(r)S, \qquad (7)$$

where $f(r)$ is termed as the Fukui function (FF)[30,31]. To describe the reactivity of an atom in a molecule, it is necessary to condense the values of $f(r)$ around each atomic site into a single value (f_{k}) that characterizes the atomic contribution in a molecule. For an atom k in a molecule, the f_{k} values are defined as[32–34]

$$f_{\text{k}}^{+} = q_{\text{k}}(N+1) - q_{\text{k}}(N) \quad \text{for nucleophilic attack,} \qquad (8a)$$

$$f_{\text{k}}^{-} = q_{\text{k}}(N) - q_{\text{k}}(N-1) \quad \text{for electrophilic attack,} \qquad (8b)$$

$$f_{\text{k}}^{o} = [q_{\text{k}}(N+1) - q_{\text{k}}(N-1)]/2 \quad \text{for radical attack,} \qquad (8c)$$

where q_{k} is the gross electronic population of atom k in the molecule. Parr and Yang have proposed that larger FF values indicate more reactivity. Hence greater the value of the condensed FF, more reactive is the particular atomic center in the molecule.

Local softness contains the same information as the Fukui function $f(r)$ plus additional information about the total molecular softness, which is related to the global reactivity with respect to a reaction partner, as stated in HSAB principle.

$$s_{\text{k}}^{+} = f_{\text{k}}^{+}S, \qquad (9)$$

for a nucleophilic attack, and

$$s_{\text{k}}^{-} = f_{\text{k}}^{-}S \qquad (10)$$

for an electrophilic attack.

Roy *et al.*[35] have suggested that relative local electrophilicity ($s_{\text{k}}^{+}/s_{\text{k}}^{-}$) which is the electrophilicity of any site as compared to its own nucleophilicity provides a reliable trend of the reactivity of a particular site.

Parr *et al.*[36] have introduced another global electrophilicity index ω defined as

$$\omega = \frac{\mu^2}{2\eta}. \qquad (11)$$

According to the definition, ω measures the ability of a molecular species to soak up electrons and is used[37] in understanding the reactivity of the human immunodeficiency virus type 1 (HIV-1) nucleocapsid protein p7 (NCp7) when reacted with a variety of electrophilic agents. Similar to this global quantity, local (regional) electrophilic power[38] can be defined as

$$\omega_{\text{k}} = \omega f_{\text{k}}^{+}. \qquad (12)$$

The site which has the maximum value of the ωf_{k}^{+} can be considered as the active site for the electrophilic attack and this site also coincides with the softest site (nucleophilic) in a molecule and hence the most reactive.

Computational details

The geometry of 33′44′5-pentachloro biphenyl (PCBP) is optimized by using Becke's three parameter hybrid density functional, B3LYP/6-31G*, which includes both Hartree–Fock exchange and DFT exchange functionals[39–41]. Above calculations have been carried out using GAUSSIAN 98 package[42]. The optimized geometries are characterized by harmonic vibrational frequencies, which confirmed that the structure of 33′44′5-PCBP is a minimum on the potential energy surface. The relative energy of 33′44′5-PCBP is calculated as a function of torsional angle (rotation through the bond C_4–C_7). Since the dihedral rotation with 30° increments is made in the selected PCB along the pseudo –C2 axis, we restricted the rotational range between –30 and 210° to avoid repetition. To calculate the relative energy, the geometry at various ϕ values is optimized at B3LYP/6-31G*. The relative energy is computed as $\Delta E(\phi) = [E(\phi) - E(30)]$ using the total energies of respective optimized conformations. To select proper electronic descriptor based on the density functional theory for the toxicity of 33′44′5-PCBP, the various reactivity and selectivity descriptors such as chemical hardness, chemical potential, polarizability, electrophilicity index and the condensed electrophilicity have been calculated for all the rotated conformations. The condensed Fukui function is calculated using the natural population analysis (NPA)[43]. We have also calculated the amount of charge transfer between 33′44′5-PCBP and various bases, viz. adenine (A), guanine (G), thymine (T), cytosine (C), uracil (U) and DNA base pairs GCWC and ATH by applying the formula[44]

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

We have also calculated the electric dipole polarizability, which is a measure of the linear response of the electron density in the presence of infinitesimal electric field F and represents second order variation in energy

$$\alpha_{a,b} = -\left(\frac{\partial^2 E}{\partial F_a \partial F_b}\right) \quad a, b = x, y, z. \tag{14a}$$

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

$$\langle \alpha \rangle = \frac{1}{3}(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}). \tag{14b}$$

Further since Hirschfeld[45] population scheme (Stockholder Partitioning Scheme) is known to provide non-negative Fukui function (FF) values, it has also been used to calculate FF values as implemented in the DMOL^3 package[46] employing BLYP/DN method.

Results and discussion

The optimized geometry of 33′44′5-PCBP is depicted in Figure 1 along with the atom numbering. The optimized geometrical parameters of the 33′44′5-PCBP at the B3LYP/6-31G* level of theory are listed (Table 1). The optimized geometry is in close agreement with that of the

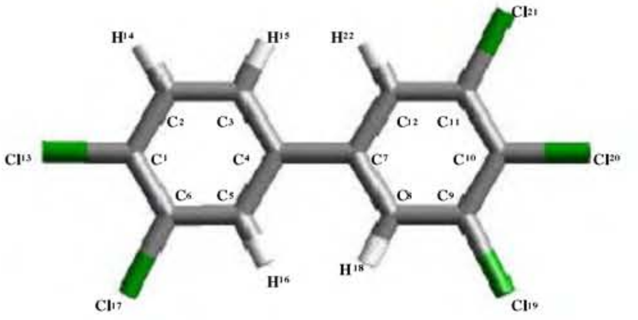

Figure 1. The optimized geometry of 33′44′5-pentachloro biphenyl (PCBP) with the atom numbering.

Table 1. Optimized geometrical parameters of 33′44′5 PCBP at B3LYP/6-31G* level (bond distance-R (Å) and angle-A (deg) with atom numbering

Optimized geometrical parameters of 33′44′5 PCBP at planar orientation	
R(C_4, C_7)	1.515
R(C_7, C_8)	1.403
R(C_7, C_{12})	1.403
R(C_8, C_9)	1.391
R(C_8, H_{18})	1.081
R(C_9, C_{10})	1.403
R(C_9, Cl_{19})	1.747
R(C_{10}, C_{11})	1.403
R(C_{10}, Cl_{20})	1.733
R(C_{11}, C_{12})	1.391
R(C_{11}, Cl_{21})	1.746
R(C_{12}, H_{22})	1.081
A(C_3, C_4, C_7)	121.7
A(C_5, C_4, C_7)	121.2
A(C_4, C_7, C_8)	121.2
A(C_4, C_7, C_{12})	121.5
A(C_8, C_7, C_{12})	117.1
A(C_7, C_8, C_9)	121.4
A(C_7, C_8, H_{18})	121.4
A(C_9, C_8, H_{18})	117.0
A(C_8, C_9, C_{10})	121.2
A(C_8, C_9, Cl_{19})	118.0
A(C_{10}, C_9, Cl_{19})	120.7
A(C_9, C_{10}, C_{11})	117.3
A(C_9, C_{10}, Cl_{20})	121.3
A(C_{11}, C_{10}, Cl_{20})	121.3
A(C_{10}, C_{11}, C_{12})	121.2
A(C_{10}, C_{11}, Cl_{21})	120.6
A(C_{12}, C_{11}, Cl_{21})	118.0
A(C_7, C_{12}, C_{11})	121.5
A(C_7, C_{12}, H_{22})	121.3
A(C_{11}, C_{12}, H_{22})	117.1

previous theoretical results[11] and the small discrepancy in the geometrical parameters may be due to the basis set variation. The relative energy, hardness, chemical potential, polarizability, scaled hardness $(\eta|\mu|^{-1/3})$ and electronegativity[47–51] optimized at B3LYP/6-31G* for the different torsional angle values for the 33′44′5-PCBP are calculated. The relative energy variation for 33′44′5-PCBP with the torsional angle lies between 0 and 9.7 kJ/mol (Figure 2*a*). The minimum energy conformation corresponds to $\phi = 30°$. This small energy variation can be attributed to the flexibility of PCBP. It has been shown that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) which is very flexible is a highly toxic molecule[51]. This gives a strong evidence that 33′44′5-PCBP which is a non-ortho

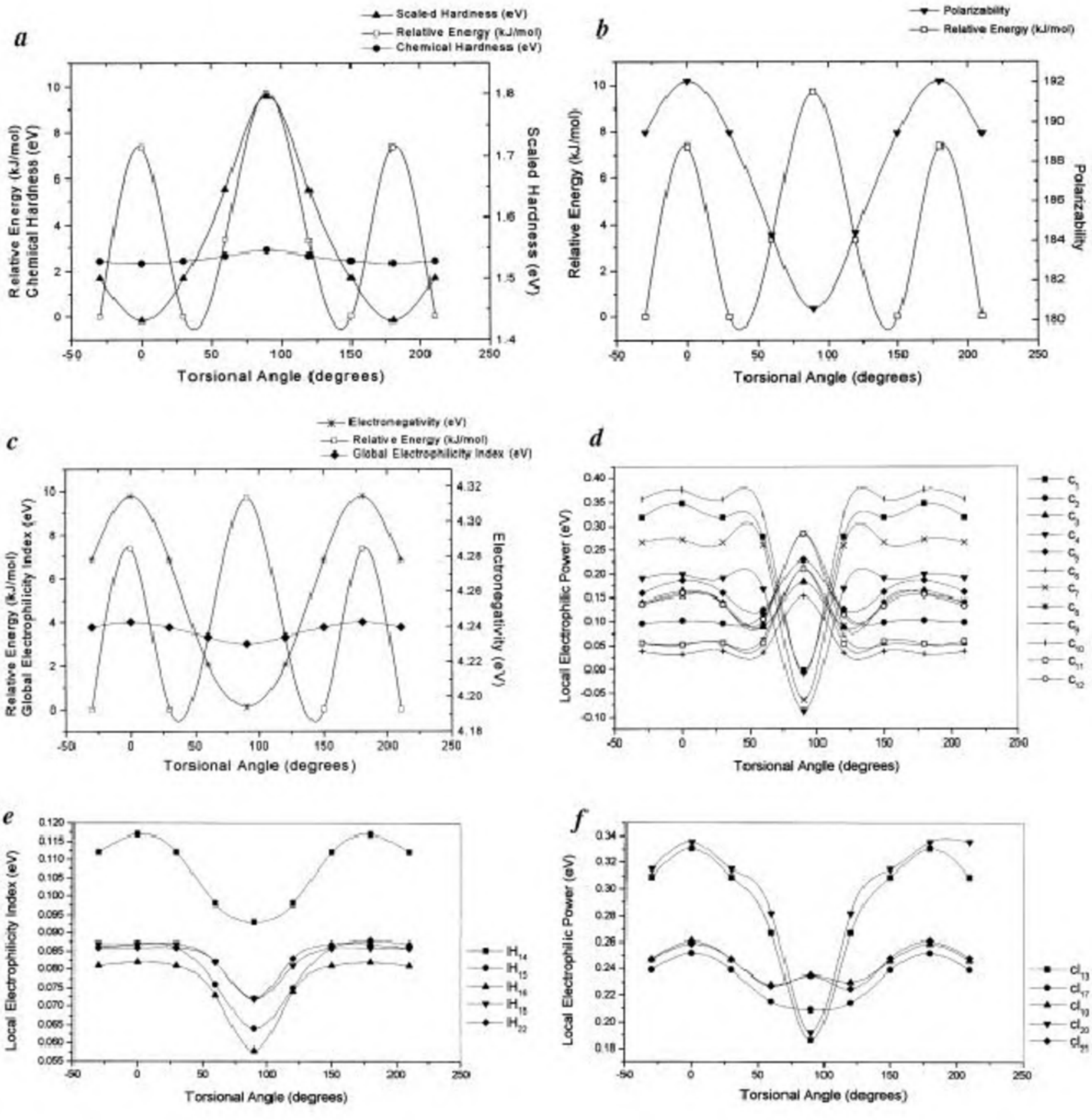

Figure 2. ***a***, The variation of relative energy (kJ/mol), chemical hardness (eV) and scaled hardness (eV) with the torsional angle (degrees) for 33′44′5-PCBP. ***b***, The variation of polarizability and relative energy (kJ/mol) with the torsional angle (degrees) for 33′44′5-PCBP. ***c***, The variation of relative energy (kJ/mol), electronegativity (eV) and global electrophilicity index (eV) with the torsional angle (degrees) for 33′44′5-PCBP. ***d***, The variation of local electrophilic power (eV) with the torsional angle (degrees) for C atoms in 33′44′5-PCBP. ***e***, The variation of local electrophilic power (eV) with the torsional angle (degrees) for H atoms in 33′44′5-PCBP. ***f***, The variation of local electrophilic power (eV) with the torsional angle (degrees) for Cl atoms in 33′44′5-PCBP.

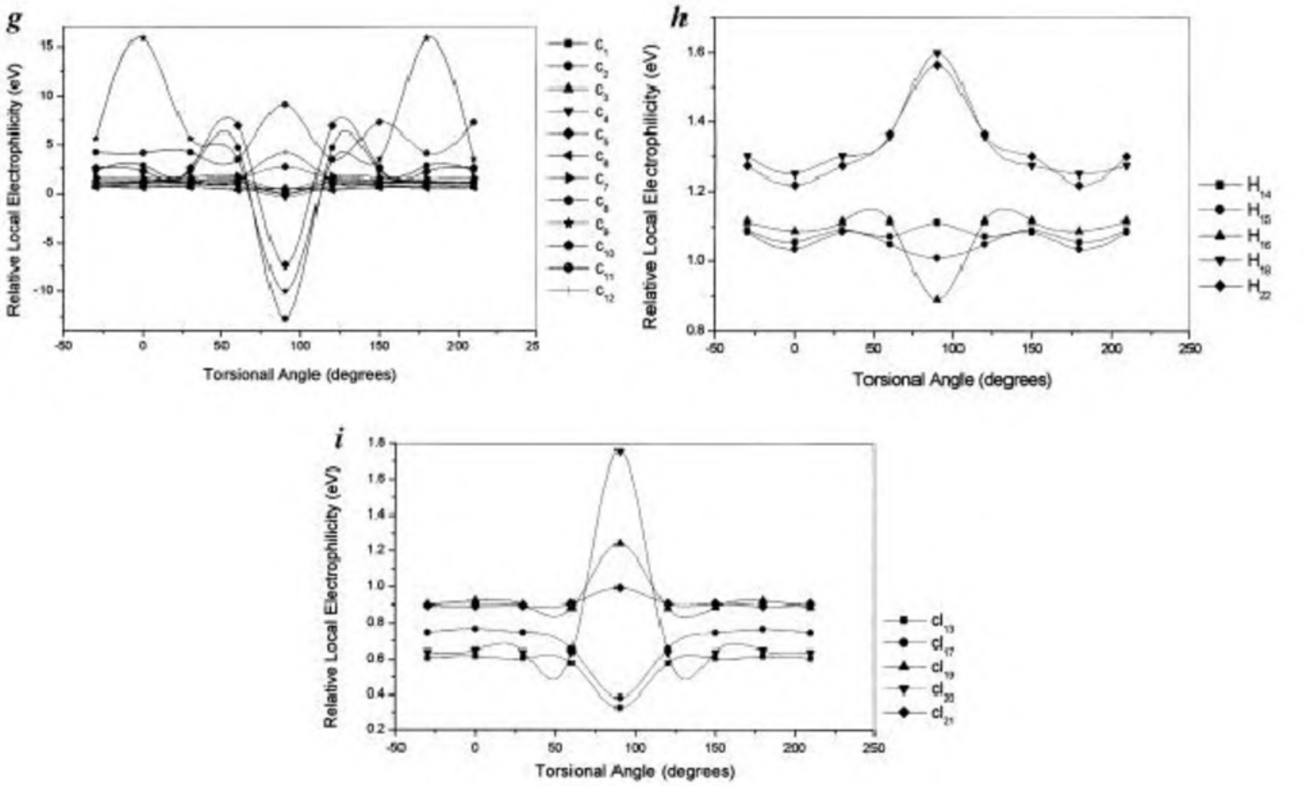

Figure 2. *g*, The variation of relative local electrophilicity (eV) with the torsional angle (degrees) for C atoms in 33′44′5-PCBP. ***h***, The variation of relative local electrophilicity (eV) with the torsional angle (degrees) for H atoms in 33′44′5-PCBP. ***i***, The variation of relative local electrophilicity (eV) with the torsional angle (degrees) for Cl atoms in 33′44′5-PCBP.

Table 2. Calculated density functional descriptors for 33445 PCBP using BLYP/DN method

Torsional angle (degrees)	Hardness*	Chemical potential*	Electrophilicity index*
–30	1.755	–4.467	5.685
0	1.663	–4.513	6.124
30	1.755	–4.467	5.685
60	1.947	–4.397	4.965
90	2.103	–4.390	4.582
120	1.946	–4.397	4.968
150	1.756	–4.467	5.682
180	1.661	–4.513	6.131
210	1.756	–4.467	5.682

*in eV.

substituted PCB must be a toxic molecule. Further, the flexibility and hence, the rotational freedom of PCBs gives greater chances for it to orient with any torsional angle in a protein field and provides ways and means for easy interaction with receptor in living cells which ultimately leads to their higher toxicity. Arulmozhiraja *et al.*[11] have made a systematic investigation on this topic by computing structure, potential energy surface and rotational barrier. In the present study we have made detailed analysis on the toxicity of the selected PCBP by considering all important DFT based reactivity descriptors including local electrophilic power and relative local electrophilicity index to select proper descriptor to develop quantitative structure activity relationship. Calculations have also been carried out in both gas and solvent media for different rotational conformations of the selected PCB. These calculations provide more clear insights into the toxicity and chemical reactivity profiles of PCBP. Results from a BLYP/DN calculation are presented (Table 2), which mimics the trends provided by calculations using B3LYP method (Figure 2*a*, *c*).

The changes in the rotational energy barrier and chemical hardness for 33′44′5-PCBP are depicted in the same figure (Figure 2*a*). Previous studies have shown that for equi-chemical potential samples, maximum hardness can be related to stability of the system[52,53]. It is found that the minimum global hardness values coincide with the two local maxima in the energy profile at ($\phi = 0°$ and 180°) indicating the MHP since these seem to be two of the most reactive conformations. Scaled hardness also exhibits similar profile (Figure 2*a*). The plot of rotational energy barrier and polarizability (Figure 2*b*) reveals that $\phi = 180°$ and 0° are the two structures having high polarizability and hence these conformations are highly reactive. So the MPP also supports the decisive role played by the planarity of the PCBs. Both the MHP and MPP

Table 3. Calculated charge transfer between 33′44′5 PCBP and bases/base pairs

Torsional angle (degrees)	Adenine	Guanine	Thymine	Cytosine	Uracil	GCWC	ATH
–30	0.107	0.132	0.037	0.076	0.023	0.139	0.102
0	0.113	0.138	0.042	0.081	0.027	0.146	0.108
30	0.107	0.132	0.037	0.076	0.023	0.139	0.102
60	0.097	0.121	0.030	0.067	0.017	0.126	0.092
90	0.091	0.114	0.027	0.062	0.014	0.117	0.086
120	0.097	0.121	0.030	0.067	0.017	0.126	0.092
150	0.107	0.132	0.037	0.076	0.023	0.139	0.102
180	0.113	0.138	0.042	0.081	0.027	0.146	0.108
210	0.107	0.132	0.037	0.076	0.023	0.139	0.102

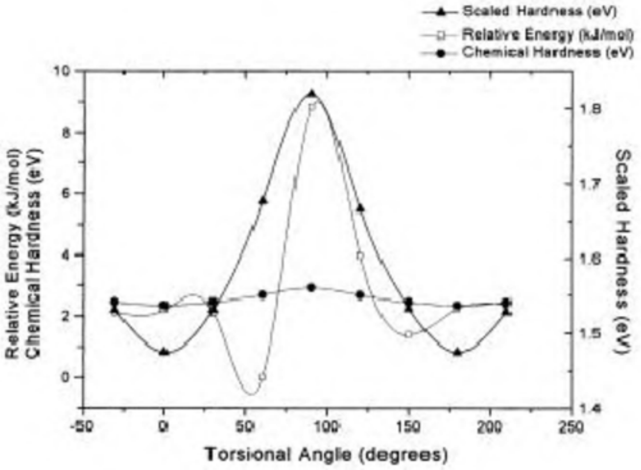

Figure 3. The variation of relative energy (kJ/mol), chemical hardness (eV) and scaled hardness (eV) with the torsional angle (degrees) for 33′44′5-PCBP in the solution phase.

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 plot of rotational energy barrier and the global electrophilicity index (ω) with torsional angle (Figure 2*c*) shows high electrophilicity value for the conformations $\phi = 180°$ and 0°. It is evident from the electrophilicity profile that $\phi = 90°$ conformation has very high value for ΔE but a low value for ω

A generalized concept of philicity is introduced through a resolution of identity, encompassing electrophilic, nucleophilic and radical attack[54]. The use of this local quantity has been analysed in this investigation. Since this local quantity contains information about all the global and local quantities, these descriptors are expected to provide more clear information about chemical reactivity and selectivity. The local electrophilicity profiles (ωf_k^+) using NPA as a function of torsional angle for the C, H and Cl atoms are calculated respectively (Figures 2*d–f*). It is found that Cl_{20} centre is more toxic than other Cl centres for all conformations except $\phi = 90°$. Also to note that Cl_{20} centre has got higher local electrophilic power (ω_k) values for all conformation compared to other Cl centres showing it as a pronounced toxic site. Reactivity of C_{10} and H_{14} centres also shows high ω_k values compared to other C, H centres for most of the conformations. The relative local electrophilicity (s_k^+/s_k^-) were calculated at C, H and Cl atomic sites for various rotational conformations of PCBP (Figure 2*g–i*). The relative local electrophilicity profiles of Cl suggest that Cl_{19} centre is more toxic than other Cl centres for all conformations except $\phi = 90°$ for which enhanced reactivity of Cl_{20} is observed. C_9 and H_{18} centres also describes high s_k^+/s_k^- values compared to other C, H centres for all conformations except for $\phi = 90°$ and 210°. In general the comparison of the results from the profiles of local electrophilicity power and relative local electrophilicity indices indicate that site corresponding to maximum (minimum) local electrophilicity does not correspond to the site having maximum (minimum) relative local electrophilicity. However the results from relative local electrophilicity do not alter the trends observed from the local electrophilicity profiles. We have also calculated the amount of charge transfer between 33′44′5-PCB and various bases, viz. A, G, T, C, U and DNA base pairs GCWC, ATH by using equation 13 (Table 3). A qualitative estimation of the charge transfer in the interaction of the selected PCB and the DNA base/base pairs is obtained from the values of ΔN. It is known that electron flows from the less electronegative system to more electronegative system and our results (Table 3) clearly shows the electron accepting nature of PCB for all the conformations though the amount of transfer varies for different conformations. We find that planar geometry allows maximum electron transfer for all the considered base and base pairs.

The values of the relative energy, hardness, chemical potential, scaled hardness and electronegativity in solvent phase for different torsional angle values are obtained using polarizable continuum model. The variation of rotational energy with the torsional angle (Figure 3) shows that the minimum energy conformation has shifted to $\phi = 60°$ and relative energy variation is between 0 and 8.83 kJ/mol. We see that the presence of implicit solvent environment around 33′44′5-PCBP reduces its maximum relative energy values from 9.7 kJ/mol to 8.83 kJ/mol. Hence this molecule has more toxic potential in the solvent environment. The other global and local profiles are similar to those observed for gas phase calculations.

Summary

The chemical reactivity descriptors analysis and the possible toxicity effects on 33′44′5-PCBP is analysed by optimizing at B3LYP/6-31G* and the solvation effects on the system are also reported. Further Hirshfeld population analysis is performed to get non-negative Fukui function values. 33′44′5-PCBP has a very small rotational energy barrier, is highly flexible so that it changes its conformation while moving in biological system, interacting readily, exhibiting its toxic characteristics. Solvation technique also provide similar information but for the shift in minimum energy conformation. Semilocal (regional) electrophilic power of the individual atom and possible active reactive sites has been reported. The ΔN calculation for determining electron transfer between 33′44′5-PCBP and bases/selected base pairs has been reported showing clearly the electron accepting nature of PCBP.

1. Safe, S. H., Polychlorinated biphenyls (PCBs): Environment impact, biochemical and toxic responses, and implications for risk assessment. *Crit. Rev. Toxicol.*, 1994, **24**, 87–149.
2. Van den Berg, M. *et al.*, Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.*, 1998, **106**, 775–792.
3. Oakley, G. G., Devanaboyina, U. S., Robertson, L. W. and Gupta, R. C., Oxidative DNA damage induced by activation of polychlorinated biphenyls (PCBs): Implications for PCB-induced oxidative stress in breast cancer. *Chem. Res. Toxicol.*, 1996, **9**, 1285–1292.
4. Erickson, M. D., In *Analytical Chemistry of PCBs*, Butterworth Publishers, Boston, 1986.
5. Silberhorn, E. M., Glauert, H. P. and Robertson, L. W., Carcinogenicity of polyhalogenated biphenyls: PCBs and PBBs. *CRC Crit. Rev. Toxicol.*, 1990, **20**, 439–496.
6. Wolff, M. S., Toniolo, P. G., Lee, E. W., Rivera, M. and Dubin, N., Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.*, 1993, **85**, 648–652.
7. Krieger, N., Wolff, M. S., Hiatt, R. A., Rivera, M., Vogelman, J. and Orentreich, N., Breast cancer and serum organochlorines: A prospective study among white, black, and Asian women. *J. Natl. Cancer Inst.*, 1994, **86**, 589–599.
8. Wassermann, M., Nogueira, D. P., Tomatis, L., Mirra, A. P., Shibata, H., Arie, G., Cucos, S. and Issermann, D., Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. *Bull. Environ. Contam. Toxicol.*, 1976, **15**, 478–484.
9. Falck, F., Ricci, A., Wolff, M. S., Godbold, J. and Deckers, P., Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health*, 1992, **47**, 143–146.
10. Miller, G., Sontum, S. and Crosby, D. G., Electron-acceptor properties of chlorinated dibenzo-*p*-dioxins. *Bull. Environ. Contam. Toxicol.*, 1977, **18**, 611–616.
11. Arulmozhiraja, S., Selvin, P. C. and Fujii, T., Structures, potential energy curves, and torsional barrier heights for selected polychlorinated biphenyls: A density functional theory study. *J. Phys. Chem.*, 2002, **A106**, 1765–1769.
12. Grein, F., Twist angles and rotational energy barriers of biphenyl and substituted biphenyls. *J. Phys. Chem.*, 2002, **A106**, 3823–3827.
13. Almenningen, A., Bastiansen, O., Cyvin, L. and Samdal, S., Structure and barrier of internal rotation of biphenyl derivatives in the gaseous state; Part 1. The molecular structure and normal coordinate analysis of normal biphenyl and pedeuterated biphenyl. *J. Mol. Struct.*, 1985, **128**, 59–76.
14. Bastiansen, O. and Samdal, S., Structure and barrier of internal rotation of biphenyl derivatives in the gaseous state; Part 4. Barrier of internal rotation in biphenyl, perdeuterated biphenyl and seven non-*ortho*-substituted halogen derivatives. *J. Mol. Struct.*, 1985, **128**, 115–125.
15. Klopman, G., Chemical reactivity and the concept of charge and frontier controlled reactions. *J. Am. Chem. Soc.*, 1968, **90**, 223–234.
16. Perez, P., Aizman, A. and Contreras, R., Comparison between experimental and theoretical scales of electrophilicity based on reactivity indexes. *J. Phys. Chem.*, 2002, **A106**, 3964–3966.
17. Chattaraj, P. K. and Maiti, B., Chemical reactivity dynamics and quantum chaos in highly excited hydrogen atoms in an external field: A quantum potential approach. *Int. J. Mol. Sci.*, 2002, **3**, 338–359.
18. Chandrakumar, K. R. S. and Pal, S., The concept of density functional theory based descriptors and its relation with the reactivity of molecular systems: A semi-quantitative study. *Int. J. Mol. Sci.*, 2002, **3**, 324–337
19. Roy, R. K., Pal, S. and Hirao, K., On non-negativity of Fukui function indices. *J. Chem. Phys.*, 1999, **110**, 8236–8245.
20. Pearson, R. G., Hard and soft acids and bases – the evolution of a chemical concept. *Coord. Chem. Rev.*, 1990, **100**, 403–425.
21. Parr, R. G. and Chattaraj, P. K., Principle of maximum hardness. *J. Am. Chem. Soc.*, 1991, **113**, 1854–1855.
22. Chattaraj, P. K., Liu, G. H. and Parr, R. G., The maximum hardness principle in the Gyftopoulos–Hatsopoulos three-level model for an atomic or molecular species and its positive and negative ions. *Chem. Phys. Lett.*, 1995, **237**, 171–176.
23. Chattaraj, P. K. and Sengupta, S., Popular electronic structure principles in a dynamical context. *J. Phys. Chem.*, 1996, **100**, 16126–16130.
24. Pearson, R. G., In *Chemical Hardness – Applications from Molecules to Solids*, VCH-Wiley, Weinheim, 1997.
25. Parr, R. G. and Yang, W., In *Density Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, 1989.
26. Chattaraj, P. K. and Poddar, A., A density functional treatment of chemical reactivity and the associated electronic structure principles in the excited electronic states. *J. Phys. Chem.*, 1998, **A102**, 9944–9948.
27. Fuentealba, P., Exchange energy functional from a Pauli correlation factor model. *J. Mol. Struct.* (*Theochem.*), 1993, **287**, 35–38.
28. Ghanty, T. K. and Ghosh, S. K., Correlation between hardness, polarizability, and size of atoms, molecules, and clusters. *J. Phys. Chem.*, 1993, **97**, 4951–4953.
29. Yang, W. and Parr, R. G., Hardness, softness and the Fukui function in the electronic theory of metals and catalysis. *Proc. Natl. Acad. Sci. USA*, 1985, **82**, 6723–6726.
30. Parr, R. G. and Yang, W., Density functional approach to the frontier-electron theory of chemical reactivity. *J. Am. Chem. Soc.*, 1984, **106**, 4049–4050.
31. Fukui, K., Role of frontier orbitals in chemical reactions. *Science*, 1987, **218**, 747.
32. Yang, W. and Mortier, W. J., The use of global and local molecular parameters for the analysis of the gas-phase basicity of amines. *J. Am. Chem. Soc.*, 1986, **108**, 5708–5711.

33. Lee, C., Yang, W. and Parr, R. G., Local softness and chemical reactivity in the molecules CO, SCN^- and H_2CO. *J. Mol. Struct.* (*Theochem.*), 1988, **163**, 305–313.
34. Cioslowski, J., Martinov, M. and Mixon, S. T., Atomic Fukui indexes from the topological theory of atoms in molecules applied to Hartree–Fock and correlated electron densities. *J. Phys. Chem.*, 1993, **97**, 10948–10951.
35. Roy, R. K., Krishnamurti, S., Geerlings, P. and Pal, S., Local softness and hardness based reactivity descriptors for predicting intra- and intermolecular reactivity sequences: Carbonyl compounds. *J. Phys. Chem.*, 1998, **A102**, 3746–3755.
36. Parr, R. G., Szentpaly, L. V. and Liu, S., Electrophilicity index. *J. Am. Chem. Soc.*, 1999, **121**, 1922–1924.
37. Maynard, A. T., Huang, M., Rice, W. G. and Covell, D. G., Reactivity of the HIV-1 nucleocapsid protein p7 zinc finger domains from the perspective of density functional theory. *Proc. Natl. Acad. Sci. USA*, 1998, **95**, 11578–11583.
38. Domingo, L. R., Aurell, M. J., Perez, P. and Contreras, R., Quantitative characterization of the local electrophilicity of organic molecules. Understanding the regioselectivity on Diels–Alder reactions. *J. Phys. Chem.*, 2002, **A106**, 6871–6875.
39. Becke, A. D., Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev.*, 1998, **A38**, 3098–3100.
40. Lee, C., Yang, W. and Parr, R. G., Development of the Colle–Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev.*, 1988, **B37**, 785–789.
41. Hariharan, P. C. and Pople, J. A., The influence of polarization functions on molecular orbital hydrogenation energies. *Theor. Chim. Acta*, 1973, **28**, 213–222.
42. Frisch, M. J. *et al.*, *Gaussian 98*, Revision A.7, Gaussian, Inc, Pittsburgh, PA, 1998.
43. Reed, A. E., Curtiss, L. A. and Weinhold, F., Intermolecular interactions from a natural bond orbital, donor–acceptor viewpoint. *Chem. Rev.*, 1998, **88**, 899–926.
44. Parr, R. G. and Pearson, R. G., Absolute hardness: companion parameter to absolute electronegativity. *J. Am. Chem. Soc.*, 1983, **105**, 7512–7516.
45. Hershfeld, F. L., Bonded-atom fragments for describing molecular charge densities. *Theor. Chim. Acta*, 1977, **44**, 129.
46. $DMOL^3$, Accelrys. Inc, San Diego, California, USA.
47. Chattaraj, P. K., Nath, S. and Sannigrahi, A. B., Hardness, chemical potential, and valency profiles of molecules under internal rotations. *J. Phys. Chem.*, 1994, **A98**, 9143–9145.
48. Chattaraj, P. K., Fuentealba, P., Jaque, P. and Toro-Labbè, A., Validity of the minimum polarizability principle in molecular vibrations and internal rotations: An *ab initio* SCF study. *J. Phys. Chem.*, 1999, **A103**, 9307–9312.
49. Chattaraj, P. K., Pèrez, P., Zevallos, J. and Toro-Labbè, A., *Ab initio* SCF and DFT studies on solvent effect on intramolecular rearrangement reactions. *J. Phys. Chem.*, 2001, **A105**, 4272–4283.
50. Ghanty, T. K. and Ghosh, S. K., Hardness and polarizability profiles for intramolecular proton transfer in water dimer radical cation. *J. Phys. Chem.*, 2002, **A106**, 4200–4204.
51. Arulmozhiraja, S., Fujii, T. and Sato, G., Density functional theory-based descriptors for dioxins. *Mol. Phys.*, 2002, **100**, 423–431.
52. Pal, S., Vaval, N. and Roy, R., Principle of maximum hardness: An accurate *ab initio* study. *J. Phys. Chem.*, 1993, **97**, 4404–4406.
53. Makov, G., Chemical hardness in density functional theory. *J. Phys. Chem.*, 1995, **99**, 9337–9339.
54. Chattaraj, P. K., Maiti, B. and Sarkar, U., Philicity: A Unified treatment of chemical reactivity and selectivity. *J. Phys. Chem.*, 2003, **A107**, 4973–4975.

ACKNOWLEDGMENTS. We thank CSIR, New Delhi for financial assistance, Dr T. Ramasami, Director, CLRI, for his interest and encouragement.

Received 14 May 2003; revised accepted 18 October 2003