Computational Biology and Chemistry 76 (2018) 225–231

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/cbac

Research Article

Toxicity of polyhalogenated dibenzo-*p*-furans in the light of nucleic acid bases interaction

Bhumika K. Sharma, Debesh R. Roy*

Materials and Biophysics Group, Department of Applied Physics, S. V. National Institute of Technology, Surat, 395007, India

ARTICLE INFO

Keywords:
QSAR
Polyhalogenated dibenzo-*p*-furans
Density functional theory
NA bases
Charge transfer
Fukui function

ABSTRACT

Quantitative structure-activity relationship (QSAR) investigation utilizing quantum chemical descriptors under density functional theory is performed to predict the toxicity (pEC_{50}) of a series of polyhalogenated dibenzo-*p*-furans (PHDFs). PHDFs are very important concern to the researchers due to their presence and diverse effects in the environment. A successful two parameter QSAR model is developed with a combination of a global descriptor known as charge transfer (ΔN) between toxins and biosystem and a local descriptor as Fukui function (f^{+}_{max}) for maximum nucleophilic attack at the toxin site. A systematic analysis is performed to identify the electron donation/acceptance nature of the considered PHDF compounds with the choice of a model biosystems comprising five different nucleic acid bases, namely Adenine, Thymine, Guanine, Cytosine and Uracil to identify proper ΔN descriptor. Accordingly, PHDFs are found to be electron acceptors with maximum charge transfer from Guanine and therefore, ΔN_G is utilized as the charge transfer parameter for all the toxins in the present work. The selected combination of global and local descriptors (ΔN_G and f^{+}_{max}) are found to predict 93% of the observed toxicity (pEC_{50}) of the PHDFs. The developed QSAR model is tested for two different test sets: PHDFs and polyhalogenated biphenyls (PHBs) with about 90% of prediction of their toxicity values, which confirms the importance of the selected descriptors.

1. Introduction

The quantitative structure-activity relationship (QSAR) is a mathematical modelling/ relationship between biological activity and structural properties of series of homologues molecules. The measured or computed molecular/ structural features of the considered series of molecules can be correlated with their relevant biological activities in a reliable manner with proper validation (Rogers and Hopfinger, 1994; Hansch et al., 1991; Gao et al., 1999; Franke, 1984). It is reported that due to the time, cost and availability of the resources associated with measuring biological activity and toxicity of large number of compounds, it is often very difficult to carry out such experiments. To overcome such situation, QSAR methodology is developed with the utilization of various structural descriptors with scientific relevance. A number of descriptors with various types have been developed by the researches to model QSAR such as electronic descriptor, thermodynamic descriptor, steric parameters, topological descriptors, spatial parameters, quantum chemical descriptor, etc. (Kubinyi, 1995; Estrada and Molina, 2001; Kier and Hall, 1976; Cartier and Rivail, 1987; Chattaraj and Roy, 2007; Chattaraj et al., 2003; Roy et al., 2008, 2006) It is shown in previous studies that a QSAR modelling not only helps in predicting the toxicity/ activity of molecules but also helps in understanding their mechanism of toxicity or bioactivity (Franke, 1984; Estrada and Molina, 2001; Kier and Hall, 1976; Cartier and Rivail, 1987; Roy et al., 2008, 2006; Rappe et al., 1978; Shen et al., 2017; Thakkar et al., 2017; Oksel et al., 2015; Winkler, 2002).

Polyhalogenated dibenzo-*p*-furans (PHDFs) and polyhalogented biphenyls (PHBs) are the members of a chemical family known as polyhalogenated aromatic compounds (PHAs) which also includes polyhalogenated dibenzo-*p*-dioxins (PHDDs), naphthalene, azobenzens, azoxybenzene, etc., have a great interest of research because of its extensive presence in environment and their considerable toxicity. These compounds are involved in several contaminations of food products, rivers, land etc. by releasing toxins in environment via air, water and soil (Rappe et al., 1978; Shen et al., 2017). These compounds are the wastes of human industries which are released during the process of combustion, refineries, metallurgy production transformer oils and paints (Shen et al., 2017). It has built up great interest in many investigators to study the physicochemical properties, toxicological nature and to avoid this kind of toxins compound in the environment. PHDFs and PHBs have high affinity against aryl hydrocarbon receptors (AhR). The aryl hydrocarbon receptor (AhR) is a member of the basic

* Corresponding author.
E-mail address: drr@phy.svnit.ac.in (D.R. Roy).

https://doi.org/10.1016/j.compbiolchem.2018.07.004
Received 14 May 2018; Received in revised form 24 June 2018; Accepted 3 July 2018
Available online 09 July 2018

helix-loop-helix (bHLH)/PER-ARNT-SIM (PAS) family of an intra-cellular protein. AhR are used to start the induction process by binding inducer. AhR's are expected to bind with PHAs receptors. The process of induction is mediated by binding to a soluble receptor protein with high affinity for PHAs. Due to the high binding affinity of these PAH compounds with cytosolic Ah receptors drawn a huge attention to the researchers for their detail investigation.

Although few QSAR attempts are taken by the researchers with large number of descriptors (in which many are without any proper justifications) and/or weaker predictive models for the toxic potential of polyhalogenated dibenzo-*p*-furan (PHDFs), a simple and reliable model in terms of less number of descriptors with relevant to the toxic mechanism is still lacking (Arulmozhiraja and Morita, 2004; Tysklind et al., 1994; Jingwen et al., 2002; Chen et al., 2001; Beger and Wilkes, 2001; Krishnan and Safe, 1993). The main goal of the present investigation is to understand and explaining toxicity of a series of polyhalogenated dibenzo-*p*-furan (PHDFs) in the light of global and local quantum descriptors as global descriptor: Charge transfer (ΔN) between toxins and biosystem and local descriptor: Fukui function (f^{+}_{max}) for maximum nucleophilic attack at the toxin site, under density functional theory (DFT) (Parr and Yang, 1989). Since toxicity of PAHs is expected to develop during their direct or indirect interaction with nucleic acid bases (NA) in terms of charge transfer in either direction, we have chosen a model bio-system comprising of five nucleic acid bases as Adenine, Guanine, Cytosine, Thymine and Uracil for the better understanding of relevant biological activity and to develop quantum descriptors addressing the relevant toxicity of considered thirty nine PHAs. The amount of charge transfer (ΔN) between PHDFs and nucleic acid bases are computed for a better understanding of origin of toxicity. The experimental toxicity of PHDFs is reported in terms of the negative of the logarithm of molar concentration of chemical necessary to displace 50% of radiolabled tetrachlorodibenzo-p-dioxin (TCDD) from the Ah receptor (AhR) in rat lever (pEC_{50}) (Johansson et al., 1982; So and Karplus, 1997). The developed two parameter (ΔN and f^{+}_{max}) QSAR model for the PHDFs (*training set*: ID 1–25) is tested/ validated for two different test sets comprising seven compounds each (30% of the training set), viz. PHDFs (*Test Set I*: ID 26–32) and also a different type of PAH compounds: polyhalogenated biphenyls (PHBs) (*Test Set II*: ID 23–39).

2. Theory and Computation

The chemical potential (μ) (Parr and Yang, 1989) and hardness (η) (Parr and Yang, 1989) are defined as the first and second order electronic energy E derivatives as a function of the number of electrons (N), for a fixed external potential v(r) as follows:

$$\mu = \left(\frac{\partial E}{\partial \rho}\right)_{v(r)} \tag{1}$$

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

The chemical potential (μ) expresses the ability of a neutral chemical system to perform physical work, whereas the chemical hardness (η) provides the information that how hard a molecule/compound is. The μ and η can also be expressed in terms of ionization potential (IP) and electron affinity (EA) using a finite difference approach as:

$$\mu = -\frac{IP + EA}{2} \quad \text{and} \quad \eta = \frac{IP - EA}{2} \tag{3}$$

The Koopmans' approximation (Parr and Yang, 1989) expresses the IP and EA in terms of the highest occupied (ϵ_{HOMO}) and the lowest unoccupied (ϵ_{LUMO}) molecular orbital energies as,

$$IP \approx -\epsilon_{HOMO};\ EA \approx -\epsilon_{LUMO} \tag{4}$$

The ionization potential (IP) estimates the energy required to detach an electron from a chemical system, whereas the electron affinity (EA) is an important chemical reactivity parameter which estimates the energy release in a neutral chemical system due to addition of an electron on it.

(Parr and Pearson (1983)) derived an expression to measure the amount of charge transfer ΔN from a molecule A towards B as follows:

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} = \frac{\chi_A - \chi_B}{2(\eta_A + \eta_B)} \tag{5}$$

It is important to note that the electronegativity difference drives the electron transfer whereas the hardness sum provides a resistance to it. Therefore both χ and η are to be considered in analyzing these processes. In the present study, the PHDFs and PHBs are chosen to be system (***A***) whereas the model biomolecules (NA bases) are considered to be system (***B***). It may also be noted that (Maynard et al. (1998)) have shown that the reaction rates from the fluorescence decay studies on the HIV-1 nucleocapsid protein p7 (NCP 7) interacting with several electrophilic agents correlate strongly with the square of the chemical potential divided by its chemical hardness (μ^2/η), which formed a strong foundation for a successful QSAR descriptor known as electrophilicity index (Chattaraj and Roy, 2007) which measures the energy lowering due to maximal transfer of electron between a donor and an acceptor.

The Fukui function (FF) (Fukui, 1987, 1975) is known to be one of the widely used local reactivity descriptors in modelling chemical reactivity and site selectivity. Fukui function (FF) is defined as (Fukui, 1987, 1975):

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

such that $\int f(r)\, dr = 1$.

The slope of $\rho(r)$ vs. N curve in Eq. (6) is discontinuous at integral N, which provides three types of Fukui functions which account for nucleophilic, electrophilic and radical attacks respectively, at a particular reaction site. The condensed Fukui functions have been proposed by (Yang and Mortier (1986)), considering a finite difference method as:

$$f_k^{+} = q_k(N+1) - q_k(N) \text{ [for nucleophilic attack]} \tag{7a}$$

$$f_k^{-} = q_k(N) - q_k(N-1) \text{ [for electrophilic attack]} \tag{7b}$$

$$f_k^{o} = [q_k(N+1) - q_k(N-1)]/2 \text{ [for radical attack]} \tag{7c}$$

where q_k is the electronic population of atom k in a molecule. A large value of f^{+}, f^{-} or f^{0} at any site indicates the probability of respective attacks at that site corresponding to a large change in chemical potential.

The geometry of all the thirty nine compounds: thirty two PHDFs (*Training set*:ID 1-25and *Test Set I*:ID 26–32) and seven PHBs (*Test Set II: ID 33-39*), as well as all the NA acid bases are optimized at the B3LYP (Becke's three-parameter hybrid exchange (Becke, 1993) and LYP correlation functional (Lee et al., 1988)) level of theory with a large all-electron basis set 6-31G + [*d*,*p*]. The Fukui function is calculated using Eqs. (7a)–(7c) and charge transfer by Eq. (5). All the necessary atomic charges are computed using Mulliken Population Analysis (MPA) (Mulliken, 1955) scheme. The actual calculations are carried out utilizing the GAUSSIAN 09 (Frisch et al., 2009) suits of program. The two-parameter (with global ΔN and local f_k) QSAR model is developed using least square error estimation method to predict the toxicity values of considered PHDFs.

3. Results and discussion

The structure of a large number of thirty nine polyhalogenated aromatic compounds (PHAs) are optimized at the B3LYP|6-31 + G(*d*,*p*) level. Table 1 shows the structure of all the 25 training set compounds (PHDFs) as well as both the test sets (7 PHDFs and 7 PHBs). Asystematic