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Externally predictive single-descriptor based QSPRs for physico-chemical properties of polychlorinated-naphthalenes: Exploring relationships of log S_W, log K_{OA}, and log K_{OW} with electron-correlation

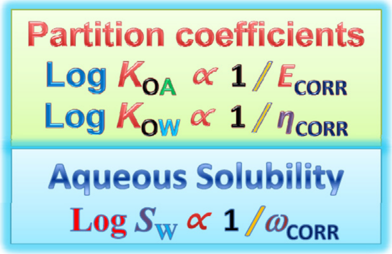
Chayawan, Vikas*

Quantum Chemistry Group, Department of Chemistry & Centre of Advanced Studies in Chemistry, Panjab University, Chandigrah 160014, India

HIGHLIGHTS

- Aqueous solubility and partition coefficient are modelled using single-parameter.
- Electron-correlation observed as a vital predictorof physico-chemical properties.
- For octanol-air partition coefficient, energy and polarizability yield best models.
- Dipole-moment is found to be worst single-descriptor for the properties analysed.

GRAPHICAL ABSTRACT



Partition coefficients

Log $K_{OA} \propto 1/E_{CORR}$

Log $K_{OW} \propto 1/\eta_{CORR}$

Aqueous Solubility

Log $S_W \propto 1/\omega_{CORR}$

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ABSTRACT

Quantitative structure–property relationships (QSPRs), based only on a single-parameter, are proposed for the prediction of physico-chemical properties, namely, aqueous solubility (log S_W), octanol–water partition coefficient (log K_{OW}) and octanol–air partition coefficient (log K_{OA}) of polychloronaphthalenes (PCNs) including all the 75 chloronaphthalene congeners. The QSPR models are developed using molecular descriptors computed through quantum mechanical methods including *ab-initio* as well as advanced semi-empirical methods. The predictivity of the developed models is tested through state-of-the-art external validation procedures employing an external prediction set of compounds. To analyse the role of instantaneous interactions between electrons (the electron-correlation), the models are also compared with those developed using only the electron-correlation contribution of the quantum chemical descriptor. The electron-correlation contribution towards the chemical hardness and the LUMO energy are observed to be the best predictors for octanol–water partition coefficient, whereas for the octanol–air partition coefficient, the total electronic energy and electron-correlation energy are found to be reliable descriptors, in fact, even better than the polarisability. For aqueous solubility of PCNs, the absolute electronegativity is observed to be the best predictor. This work suggests that the electron-correlation contribution of a quantum-chemical descriptor can be used as a reliable indicator for physico-chemical properties, particularly the partition coefficients.

1. Introduction

Polychloronaphthalenes (PCNs) are amongst toxic chemicals, which can cause liver diseases, chloracne, and can also significantly

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* Corresponding author. Tel.: +91 172 2534408; fax: +91 172 2544078.
E-mail address: qlabspu@pu.ac.in (Vikas).

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increase the risk of cancer [1]. PCNs have remained a challenge to the environmentalists because of their prolonged use in the last century, and at present, these are still distributed into the ecosystem as by-products from industries and waste incineration [1,2]. It is important, therefore, to know the fate and distribution of these toxic chemicals in our environment, through predicting their physico-chemical properties. Aqueous solubility ($\log S_W$) and partition coefficients such as octanol–air ($\log K_{OA}$) and octanol–water ($\log K_{OW}$) are important physico-chemical properties that determine the environmental transport and fate of persistent organic pollutants (POPs) like PCNs [3]. Since the experimental determination of these properties can be quite expensive, therefore, quantitative structure-property relationships (QSPRs) are a reliable tool for predicting such properties.

In the existing literature, several QSPR models are available for various physico-chemical properties of PCNs. On the basis of the salvation theory [4–6], Puzyn et al. [7] had modelled the experimental S_W (in μg/dm^3) determined by Opperhuizen et al. [8] for 16 PCNs using "solvent accessible molecular-volume (SAV)" as a descriptor. For modelling $\log K_{OW}$ of PCNs, multi-dimensional QSPRs have been proposed using partial least square (PLS) and principle component regression (PCR) chemometrics [9]. Besides these, Puzyn and Falandysz [10] had also modelled $\log K_{OW}$ through quantum-mechanical, thermodynamic and topological descriptors employing artificial neural network for the model development. For modelling $\log K_{OA}$, the "mean isotropic polarisability" has been deployed as a reliable descriptor in separate studies by Chen et al. [11] and Staikova et al. [12], although the models proposed in the two studies are based on different experimental $\log K_{OA}$ of PCNs determined by Harner and Bidleman [13] and Su et al. [14], respectively. Zhao at el. [15] had modelled $\log K_{OA}$ determined by Harner and Bidleman [13] using "connectivity index" as a descriptor. Besides these, a few models have been proposed by Puzyn et al. [16] based on the experimental values of partition-coefficients taken from different source experiments of Harner and Bidleman [13] and Su et al. [14], though in QSPR modelling, experimental properties from a single source is considered as reliable. Moreover, modelling of this combined experimental partition-coefficient of PCNs has been reported differently using various chemometric techniques, though, all these studies recommended mean polarisability to be the best descriptor for modelling $\log K_{OA}$ of PCNs [10,16–18]. However, it must be noted that QSPR models should not be built using data from different experiments for a given property because different experiments can have varying accuracy and human error, hence, making the proposed models unreliable. Moreover, the proposed models should be externally predictive, that is, the real predictivity of a QSPR model should be tested using an external prediction set of chemicals not employed during the model development [19–20].

For developing externally predictive quantitative models for the biological activities and physico-chemical properties, the molecular descriptors computed using quantum-mechanical methods are generally found to be highly reliable [21–25]. These molecular descriptors include the energy of highest occupied molecular orbital (HOMO), energy of the lowest unoccupied molecular orbital (LUMO), mean polarisability, and density functional theory (DFT) based descriptors *viz.*, absolute electronegativity, chemical hardness and electrophilicity index [26–28]. All these descriptors can be computed quite accurately using *ab-initio* quantum mechanical methods like Hartree–Fock (HF) method [29–32] and DFT, as well as using advanced semi-empirical (SE) methods such as RM1 [33] and PM7 [34]. Besides the above molecular descriptors, our recent studies [21–25] had revealed that the total electronic energy (E) of a molecule, and electron-correlation contribution to the energy (E_{CORR}) and to the aforementioned molecular descriptors can be highly significant in the quantitative modelling of biological activities [21–23] and physico-chemical properties [24–25]. The electron-correlation contribution of a molecular descriptor represents instantaneous electrostatic interactions between the electrons in a molecule. In our previous studies predicting supercooled vapour pressure ($\log P_L$) of PCNs [24], and $\log P_L$, $\log S_W$, $\log K_{OA}$, $\log K_{OW}$ of polychlorinated-dibenzo-*p*-dioxins (PCDDs) and -dibenzo-furans (PCDFs) [25], we observed that these inter-electronic interactions can be even more reliable than the molecular polarisability. Similarly, in another studies modelling mutagenicity of nitrated polycyclic aromatic hydrocarbons (nitro-PAHs), we found that the electron-correlation plays a significant role in the expression of biological activities [21–23]. Following these, the main aim of this work is to explore relationships of electron-correlation with physico-chemical properties of PCNs, and to compare the external prediction capability of the single-descriptor QSPRs developed using electron-correlation contribution in the present work with those available in the literature.

2. Theoretical and computational methodology

The changes in the molecular behaviour to the environment are manifested through the changes in the molecular structure. The fundamental molecular descriptors, which characterize a molecule and its structure, are total energy (E), energy of HOMO (E_{HOMO}) and LUMO (E_{LUMO}), dipole-moment (d), mean polarisability (α) to name a few. Similarly, the chemical potential (μ) of a molecule is a significant indicator of molecular behaviour. The widely used DFT descriptors such as absolute electronegativity (χ), chemical hardness (η) and electrophilicity index (ω) can be formulated using the chemical potential as [26–28],

$$\left.\begin{aligned} \chi &= -\left(\frac{\partial E}{\partial N}\right)_{v(\mathbf{r})} = -\mu, \\ \eta &= \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{v(\mathbf{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{v(\mathbf{r})}, \\ \omega &= \frac{\mu^2}{2\eta}, \end{aligned}\right\} \tag{1}$$

where N is total number of electrons in a molecule and $v(r)$ is the external potential in terms of electronic coordinates (r). The electronegativity and chemical hardness are related, respectively, to E_{HOMO} and E_{LUMO} as,

$$\chi = -\frac{E_{HOMO} + E_{LUMO}}{2}, \text{and} \eta = (E_{LUMO} - E_{HOMO}). \tag{2}$$

For the computations of aforementioned descriptors, the structures of all 75 chloronaphthalene congeners, listed in Table 1, were optimized at the *ab-initio* level of HF and DFT using 6-311++G(d, p) Gaussian basis set including polarisation as well as diffuse functions, and also at the advanced SE levels employing PM7 and RM1 Hamiltonian. For the DFT computations, a widely used hybrid exchange correlation (XC) functional, B3LYP [35], was employed. All the optimized geometries were further subjected to harmonic vibrational frequency and Raman analysis to check whether the optimized structure corresponds to true minima, and to obtain molecular polarisability, respectively. The HF and DFT computations were performed using GAUSSIAN 03 [36] quantum mechanical software whereas calculations using advanced SE methods were performed with MOPAC 2012 [37] software along with GABEDIT [38] graphical user interface.

It should be noted that though HF method effectively takes care of quantum-mechanical exchange interactions between electrons, it ignores a significant part of the instantaneous electron–electron interactions (the electron-correlations) [29–32]. On the contrary,