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Single-descriptor based quantum-chemical QSPRs for physico-chemical properties of polychlorinated-dibenzo-*p*-dioxins and -dibenzo-furans (PCDD/Fs): Exploring the role of electron-correlation

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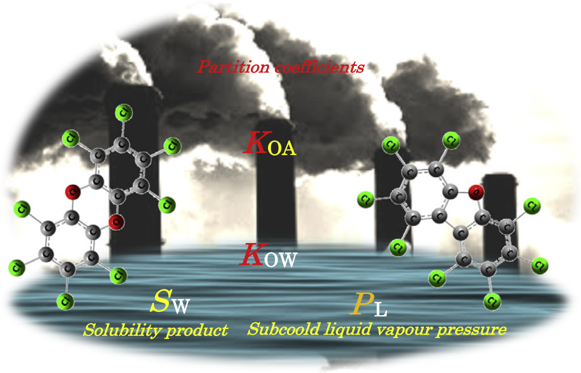
HIGHLIGHTS

- Solubility product, partition coefficients and liquid vapour pressure are modeled.
- Energy and polarizability observed to be best predictors for the properties modeled.
- Dipole moment is found to be a poor descriptor for all the properties assessed.
- Molecular energy is reported as a reliable measure of intra-molecular interactions.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, we propose and analyze single-descriptor based quantitative structure–property relationships (QSPRs) developed using quantum-chemical descriptors and their electron-correlation contribution, for various physico-chemical properties, namely, aqueous solubility, subcooled liquid vapour pressure, *n*-octanol/water and *n*-octanol/air partition coefficients of polychlorinated-dibenzo-*p*-dioxins (PCDDs) and -dibenzo-furans (PCDFs). The predictivity of the developed QSPRs is examined through external validation procedures employing an external prediction set of chemicals not used in the QSPR model development. From the comparison of different models, it is observed that the total energy and the mean polarizability of a molecule are highly significant in determining the predictivity of a QSPR, whereas dipole moment is found to be a poor descriptor in the models developed for all the properties analyzed. Besides these, the electron density based descriptors, namely, absolute electronegativity and electrophilicity index, were also observed to be highly influential in determining the external prediction for partition coefficients.

1. Introduction

An accurate prediction for the physico-chemical properties of persistent organic pollutants (POPs) is highly significant in the determination of fate and transport of these chemicals in the environment. However, an experimental determination of these properties is not only expensive but can also be environmentally unfriendly because of the use of other toxic chemicals and solvents (Rordorf et al., 1986; Shlu et al., 1988; Harner et al., 2000). Therefore, quantitative structure–property relationships (QSPRs) offer a viable route for the prediction of these properties

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(Yang et al., 2006, 2007; Zeng et al., 2012, 2013). However, a QSPR model has to be not only internally robust but should be externally validated, that is, it should be capable of predicting properties of chemicals not used in the development of the model (Chirico and Gramatica, 2011, 2012). Nowadays, for developing a QSPR, quantum-chemical descriptors are routinely employed (Yang et al., 2006, 2007; Zeng et al., 2012, 2013). The accuracy of these descriptors, however, relies on the quantum-mechanical (QM) method used for their computation. Most often employed QM methods are advanced semi-empirical (SE) methods such as RM1 (Rocha et al., 2006), PM6 (Stewart, 2007) along with their previous variants, and *ab initio* methods such as Hartree–Fock (HF) (Jensen, 2007), and density functional theory (DFT) (Jensen, 2007).

The reliability of a quantum-mechanical method, however, depends on the way the instantaneous electron–electron interactions are taken care of by the method (Jensen, 2007). These interactions are commonly referred as electron-correlations (Löwdin, 1995). In our recent studies (Vikas et al., 2013; Vikas and Chayawan, 2014; Reenu and Vikas, 2014), it was observed that the electron-correlations can be highly significant in the prediction of biological and physico-chemical properties of chemicals. For example, during the modeling of mutagenicity for nitrated-polycyclic aromatic hydrocarbons, it was observed that the quantitative model based only on the electron-correlation contribution of quantum-chemical descriptors can be more reliable and externally predictive as compared to the model developed using the complete descriptors (Vikas et al., 2013; Reenu and Vikas, 2014). Similarly, in a study on the supercooled vapor pressure of polychloro-naphthalenes, we had observed that the single-descriptor QSPRs developed using only the electron-correlation contribution to the total energy are highly reliable and externally predictive (Vikas and Chayawan, 2014).

In the present work, we develop and analyze single-descriptor QSPR models based on quantum-chemical descriptors as well as their electron-correlation contribution, for predicting aqueous solubility ($\log S_W$) of polychlorinated-dibenzo-*p*-dioxins (PCDDs) and -dibenzo-furans (PCDFs) which are also classified as environmental endocrine disruptors (Yang et al., 2006, 2007; Ruelle and Kesselring, 1997). Besides this, the predictivity of quantum-chemical QSPRs for environmentally-important physico-chemical properties, namely, subcooled liquid vapour pressure ($\log P_L$) (Zeng et al., 2013; Xiao and Wania, 2003), *n*-octanol/water partition coefficient ($\log K_{OW}$) (Ruelle, 2000; Yang et al., 2007; Zeng et al., 2012) and *n*-octanol/air partition coefficient ($\log K_{OA}$) of PCDDs Harner et al., 2000; Xiao and Wania, 2003; Zeng et al., 2013, is also analyzed. In the literature, several QSPR models for these properties of PCDDs and PCDFs are already available (Yang et al., 2006, 2007; Zeng et al., 2012, 2013). The models reported are mainly based on quantum-chemical descriptors such as mean polarizability, dipole moment, partial atomic charge, molecular volume, energy of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) (Yang et al., 2006, 2007; Zeng et al., 2012, 2013). These descriptors are mainly computed through DFT that takes care of electron-correlation through an exchange–correlation (XC) functional (Jensen, 2007). However, in our recent studies (Vikas et al., 2013; Vikas and Chayawan, 2014; Reenu and Vikas, 2014), the descriptors computed using computationally inexpensive advanced SE methods such as RM1, PM6, and PM7 (Stewart, 2013), are also found to be as reliable as those computed using *ab initio* methods like DFT as had also been observed in a previous study (Puzyn et al., 2008). The single-descriptor QSPR models developed here for physico-chemical properties of PCDD/Fs are based on quantum-chemical descriptors computed through advanced SE and *ab initio* methods. The models based on a single-descriptor are not only convenient but are also readily understandable.

2. Computational

Various quantum-chemical descriptors employed includes the total energy of the molecule (E), energies of HOMO and LUMO (E_{HOMO} and E_{LUMO}), mean polarizability (α), dipole moment (d), and electron-density based descriptors, namely, absolute electronegativity (χ), chemical hardness (η) and electrophilicity index (ω) (Vikas et al., 2013; Vikas and Chayawan, 2014; Reenu and Vikas, 2014). These descriptor were computed through advanced SE methods, namely, RM1 and PM7 (Stewart, 2013), and also through *ab initio* methods, namely, HF and DFT employing a 6-311G++(d,p) basis set (Jensen, 2007). The geometry of each of the 24 PCDDs and PCDFs (listed in supporting information Tables S1) was first optimized at a chosen level of the theory, which was followed by harmonic frequency analysis at the same level of the theory to verify that the final geometry obtained for the molecule is truly optimized and is a global minimum. All the advanced SE quantum-mechanical calculations were performed using MOPAC2012 quantum-chemistry program (Stewart, 2012), whereas for HF and DFT computations, Gaussian 03 suite of quantum-chemistry package was utilized (Frisch et al., 2004). Further, for the computations using DFT method, a widely used hybrid XC functional, B3LYP, was employed (Becke, 1993). Finally, the electron-correlation contribution (CORR) of the quantum-chemical descriptor is determined using,

$$D_{CORR}^{B3LYP} = D_{DFT}^{B3LYP} - D_{HF}, \quad (1)$$

where D is one of the descriptors, namely, E, E_{HOMO}, E_{LUMO}, d, α, χ, η, and ω, computed using HF and DFT method employing B3LYP functional. All the computed descriptors corresponds to the structure which has been verified to be a global minima at HF/6-311++G(d,p) and DFT/B3LYP/6-311++G(d,p) levels of the theory. The computational economy of these CORR descriptors is relatively much higher than that of the DFT alone, since optimization of HF geometries can consume same or even more computational-time than that using the DFT (Vikas et al., 2013; Vikas and Chayawan, 2014; Reenu and Vikas, 2014). However, the electron-correlation contribution to the correlation-energy (E_{CORR}) can also be directly obtained from the XC energy in DFT computations, provided if a standalone exchange- and correlation functional is employed, however, with less accuracy than that obtained employing hybrid XC functionals which are known to yield highly reliable geometries. Though Eq. (1) only approximately estimates the electron-correlation contribution, however, it is computationally far more economical compared to highly advanced quantum-mechanical methods such as full-configuration interaction and coupled cluster approaches which are in fact practically not feasible for a fairly sized molecule encountered in environmental chemistry (Vikas et al., 2013; Vikas and Chayawan, 2014; Reenu and Vikas, 2014). Using the computed quantum-chemical descriptors aforementioned, single-descriptor QSPR models were developed as described in the next section.

3. Model development and validation

For a reliable calibration of a QSPR model, the experimentally measured values of a physico-chemical property should be taken from the same experiment and as far as possible from the same source. In the present work, the models were developed using known experimental values available for $\log S_W$ of 20 PCDDs (Ruelle and Kesselring, 1997), $\log K_{OW}$ of 17 PCDDs (Yang et al., 2007), $\log K_{OA}$ of 11 PCDDs (Harner et al., 2000), and $\log P_L$ of 15 PCDDs (Mackay et al., 1992; Zeng et al., 2013). These values, provided in the supporting information Tables S2–S5, are mainly determined using the generator-column method employing high-performance liquid chromatography and gas chromatography