Quantum-mechanical parameters for the risk assessment of multi-walled carbon-nanotubes: A study using adsorption of probe compounds and its application to biomolecules☆

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ABSTRACT

This work forwards new insights into the risk-assessment of multi-walled carbon-nanotubes (MWCNTs) while analysing the role of quantum-mechanical interactions between the electrons in the adsorption of probe compounds and biomolecules by MWCNTs. For this, the quantitative models are developed using quantum-chemical descriptors and their electron-correlation contribution. The major quantum-chemical factors contributing to the adsorption are found to be mean polarizability, electron-correlation energy, and electron-correlation contribution to the absolute electronegativity and LUMO energy. The proposed models, based on only three quantum-chemical factors, are found to be even more robust and predictive than the previously known five or four factors based linear free-energy and solvation-energy relationships. The proposed models are employed to predict the adsorption of biomolecules including steroid hormones and DNA bases. The steroid hormones are predicted to be strongly adsorbed by the MWCNTs, with the order: hydrocortisone > aldosterone > progesterone > ethinyl-oestradiol > testosterone > oestradiol, whereas the DNA bases are found to be relatively less adsorbed but follow the order as: guanine > adenine > thymine > cytosine > uracil. Besides these, the developed electron-correlation based models predict several insecticides, pesticides, herbicides, fungicides, plasti-cizers and antimicrobial agents in cosmetics, to be strongly adsorbed by the carbon-nanotubes. The present study proposes that the instantaneous inter-electronic interactions may be quite significant in various physico-chemical processes involving MWCNTs, and can be used as a reliable predictor for their risk assessment.

1. Introduction

In recent years, carbon-nanotubes (CNTs) had gained significant popularity in biomedical applications as an efficient drug delivery system, besides having potential applications in the environmental and material sciences (Fabbro et al., 2012; Vashist et al., 2011; Zhu and Xu, 2010). However, CNTs are not free from nanotoxicological effects (Firme and Bandaru, 2010; Zhou et al., 2013). For example, *in-vitro* and *in-vivo* studies, had revealed that the CNTs can have many associated risks like pulmonary inflammation, modification of protein structure, abnormal tissue function, formation of bio-corona, enzymatic degradation, to name a few (Shvedova et al.,

2009; Bhattacharya et al., 2013; Lanone et al., 2013). For the drug delivery, adsorption is the main process for loading a drug onto the CNTs, which can affect not only the pharmacokinetics but also the toxicological behaviour of CNTs (Shvedova et al., 2009; Bhattacharya et al., 2013; Lanone et al., 2013). The large aspect (surface to volume) ratio of CNTs provides a greater surface area for the adsorption besides the nano-needle nature of CNTs making them viable for the biomedical applications. However, CNTs also have large extended π-electron density making them lipophilic and hence, suitable for the adsorption of biomolecules (Lacerda et al., 2007). The strength of such adsorption, however, depends on the molecular interactions between the adsorbate molecule and CNTs.

In the studies so far, the adsorption of molecules (both aliphatic and aromatic) on the CNTs has been characterized by various molecular features of the adsorbate molecules, which though are mainly described through the dispersion forces (Abraham et al., 1999; Xia et al., 2010; Hüffer et al., 2014; Apul et al., 2015; Yu

et al., 2015). Nanomaterials such as CNTs may interact selectively or specifically, for example, during cell penetration, these can interact with the biologically targets like proteins, steroids, fatty acids (Lacerda et al., 2007). But it is quite expensive and time consuming to experimentally investigate the adsorption of such biomolecules; therefore, probe compounds are often used effectively to predict the behaviour of biomolecules towards the nanomaterials (Abraham et al., 1999; Xia et al., 2010). The probe compounds, however, have to be structurally so diverse that the origin of interaction between the biomolecules and the nanomaterial could be appropriately traced out. In the literature, several attempts had already been made to understand and predict the behaviour of biomolecules through probe compounds. For example, Abraham et al. (1999) had proposed a linear free-energy relationship (LFER) through probe compounds for the prediction of brain permeability and skin penetration. In recent years, the descriptors proposed by Abraham et al. (1999) have been analysed in different studies, for example, for predicting the membrane adsorption, sorption by carbon nanomaterials, and lipid-water partition function (Xia et al., 2007; Geisler et al., 2015). Recently, Apul et al. (2013) had reported quantitative structure-activity relationships (QSARs) through a connectivity index to predict the adsorption of organic contaminants by multi-walled CNTs (MWCNTs). Note that most of these studies were carried out mainly using aromatic probe compounds as in the present work, but investigation based on a diverse set of compounds, both aliphatic and aromatic, has also been reported (Hüffer et al., 2014). However, *in-silico* studies can be a good alternative to *in-vitro* and *in-vivo* studies for nanotoxicological risk assessment because the corresponding experiments may require costly infrastructure.

Recently, Xia et al. (2010, 2011), had utilized the Abraham's LFER in the formulation of a linear solvation energy relationship (LSER) through a biological surface adsorption index (BSAI) approach to predict the adsorption of organic contaminants by MWCNTs, and also for the characterisation of surface adsorption coefficient of carbon nanomaterials and other metal nanomaterials. The LFER proposed by Abraham et al. (1999) to unlock the forces responsible for the adsorption on carbon nanomaterials, can be described as,

$$\text{Log } K = c + r\,R + p\,\pi + a\,A + b\,B + v\,V, \qquad (1)$$

where the various forces to predict the adsorption coefficient (K) are proposed to originate from excess molar refraction (R), polarizability (π) including the effective solute dipolarity, effective hydrogen-bond donating ability or the acidity (A), and effective hydrogen-bond accepting ability or the basicity (B) of the solute besides its characteristic volume (V) (Xia et al., 2010). In Eq. (1), the c, r, p, a, b, v are the regression coefficients in the multi-linear relation corresponding to the aforementioned descriptors. From this five-descriptors based LFER, it can be presumed that the adsorption is mainly governed by the non-covalent interactions. Recently, Saleh et al. (2015) had made an attempt to relate the non-covalent interactions through electrons and energy distributions. Exploring such relations is important not only for relating the classical electrostatic dispersion forces to quantum-mechanical formulations but also for understanding the structural changes occurring in the probe compounds or bio-molecules during interactions with CNTs. Moreover, such studies will also reduce the complexity of Eq. (1), for example, in the experimental determination of the descriptors (Sprunger et al., 2008).

However, to the best of our knowledge, investigations purely based on the quantum-mechanical parameters for developing a quantitative quantum-chemical model for the adsorption of various organic probe compounds on carbon nanomaterials are still unknown. One of the aims of the present work is to propose the

quantum-mechanical descriptors to characterise the adsorption of probe organic compounds by MWCNTs. Recent studies from our research group have found that the dynamic electron-correlation (the instantaneous interactions between the electrons) in a molecule plays a significant role in the origin of biological and physico-chemical properties of molecules (Vikas et al., 2013; Vikas and Chayawan, 2014; 2015; Chayawan and Vikas, 2015; Reenu and Vikas, 2014; 2015a, 2015b, 2016). For example, while developing the quantitative structure-property relationships (QSPRs) for physico-chemical properties such as subcooled vapour pressure, partition coefficients, and aqueous solubility of poly-chloronaphthalenes (PCNs), and polychlorodibenzo-p-dioxin/furans (PCDDs/Fs), it was observed that the quantum-mechanical descriptors based on the intra-molecular electron-correlations significantly improve the internal stability and external predictivity of the QSPR models (Vikas and Chayawan, 2014; 2015; Chayawan and Vikas, 2015). Similarly, the mutagenicity of a set of nitrated-polycyclic hydrocarbons (PAHs) and the toxicity of a diverse set of pollutants were also observed to be significantly dependent on the electron-correlation (Vikas et al., 2013; Reenu and Vikas, 2014; 2015a, 2015b, 2016).

To be specific, the dynamic electron-correlation accounts for the instantaneous interactions between the electrons of same spin (generally referred as quantum-mechanical exchange interactions or Fermi correlation) besides the classical columbic interaction between the electrons, occurring irrespective of their spin, which are often refereed as Coulomb correlation (Jensen, 2007). The *ab-initio* quantum-mechanical methods like Hartree-Fock (HF) takes care of the exchange interactions but ignores the Coulomb correlation, whereas the density functional theory (DFT) can account for the both exchange and correlation interactions through an exchange correlation (XC) functional (Szabo and Ostlund, 1982; Parr and Yang, 1989). In this study, using different quantum-mechanical methods, the effect of electron correlation is investigated for the adsorption of probe organic compounds by MWCNTs while modelling the adsorption in terms of logarithmic of an adsorption coefficient (K_∞) corresponding to an infinite adsorbate concentration, and also in terms of specific surface area adsorption coefficient (K_{SA}) (Apul et al., 2013; Wang et al., 2013). The best proposed models, developed using the methodology described in the following sections, are then deployed to predict the adsorption coefficients for the adsorption of a few biomolecules including DNA bases and steroid hormones. Besides this, predictions are also made for the adsorption for a selected set of pollutants including insecticides, pesticides, herbicides, fungicides, plasticizers, and anti-microbial agents in cosmetics, by the MWCNTs.

2. Methodology

In the present study to analyse the effect of electron correlation, various quantum-mechanical molecular descriptors, for the dataset of compounds listed in supporting information (SI) Table S1, were computed using the HF and DFT methods besides an advanced semi-empirical PM7 method (Stewart, 2013). The descriptors for which the effect of electron correlation was analysed include the total electronic energy (E), energies of highest occupied molecular orbital ($HOMO$) and lowest unoccupied molecular orbital ($LUMO$), dipole moment (d), isotropic (mean) polarizability (α), absolute electronegativity (χ), chemical hardness (η) and electrophilicity index (ω) (for the detailed equations, see Chayawan and Vikas, 2015; Vikas and Chayawan, 2014; 2015; Vikas et al., 2013; Reenu and Vikas, 2014; 2015a, 2015b, 2016). For the DFT computations, one of the widely used B3LYP exchange correlation (XC) functional was employed (Becke, 1993; Lee et al., 1988). The effect of electron-correlation (CORR) on a quantum-mechanical