

Chapter 5

Toxicity of Halogen, Sulfur and Chlorinated Aromatic Compounds: A Quantitative–Structure– Toxicity–Relationship (QSTR)

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ABSTRACT

In this paper, quantitative–structure–toxicity–relationship (QSTR) models are developed for predicting the toxicity of halogen, sulfur and chlorinated aromatic compounds. Two sets of compounds, containing mainly halogen and sulfur inorganic compounds in the first set and chlorinated aromatic compounds in the second, are investigated for their toxicity level with the aid of the conceptual Density Functional Theory (DFT) method. Both sets are tested with the conventional density functional descriptors and with a newly proposed net electrophilicity descriptor. Associated R^2 , R^2_{CV} and R^2_{adj} values reveal that in the first set, the proposed net electrophilicity descriptor ($\Delta\omega^\pm$) provides the best result, whereas in the second set, electrophilicity index (ω) and a newly proposed descriptor, net electrophilicity index ($\Delta\omega^\pm$) provide a comparable performance. The potential of net electrophilicity index to act as descriptor in development of QSAR model is also discussed.

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INTRODUCTION

Quantitative Structure–Activity Relationship (QSAR), Quantitative Structure–Property Relationship (QSPR) and Quantitative–Structure–Toxicity–relationship (QSTR) studies have seen recent upsurge of interest because of their potential in predicting various activities and properties of complex molecules bypassing the actual experimental observation. These studies rest on the presupposition that the molecular descriptors bear the signature of the molecular structure and hence are capable of providing insights into the molecular activity/reactivity and properties. However, it becomes a daunting task to find out the appropriate molecular descriptors for a given physical/chemical/biological property. Furthermore, one should attempt to use always the simplest molecular descriptors possible, as these usually allow interpreting a QSAR model in a more straightforward way (Lipinski et al., 1997).

Fluorine compounds are the best known as fire suppressants (Linteris et al., 1996), chemical extinguishers (Babushok et al., 1996) and ozone-depleting substances (Holmes et al., 1996). Some of them, such as SF_6 , CHF_3 , CCl_2F_2 , are famous for their high global warming potentials. However, fluorine compounds are cumulative toxins. Industrial emissions of fluorine compounds generate increased concentrations in the atmosphere. “The Clinical Toxicology of Commercial Products, 5th Edition (1984)” gives fluorine compound a toxicity rating of 4 (3 = moderately toxic, 4 = very toxic) (fluorine compound org.uk). SF_6 , CHF_3 and CCl_2F_2 have been used in the semiconductor industry, in chemical vapor deposition (CVD), chemical etching and clearing process (Roth et al., 1995). Typically, gaseous effluents which contained various fluorine compounds emitted during these processes are harmful to workers at semiconductor factories.

It has been observed that the toxicity of aromatic hydrocarbons to aquatic plants is extremely variable, depending on the species, compound,

and environmental conditions. Chlorobenzene is only slightly toxic, but on increasing its substitution leads to an increase of toxicity to algae. The acute toxicity level of chlorobenzenes to invertebrates generally parallels to their toxicity level to aquatic plants. 1,2,4,5-tetrachlorobenzene and pentachlorobenzene seem to be very toxic to fish. Chlorobenzenes have been reported to cause DNA reduction in the diatom *Cyclotella meneghiniana*. Chlorobenzenes have been reported to affect reproduction in *Daphnia magna* and the effect seems to increase with an increase in chlorine content of the chlorobenzene (Ramamoorthy et al., 1997).

Therefore, knowledge of its degree of toxicity along with that of its various derivatives has become essential to maintain environmental safety and security. Experimental determination of toxicity of these compounds is difficult due to time, cost, and the availability of sources. In this regard, theoretical modeling has been developed to explain the toxicity of these chemicals in terms of their structural parameters, e.g., geometric, topological, electronic, quantum chemical (QC), etc. This method is termed as quantitative structure–toxicity relationship (QSTR) study (Hansch et al., 1995). A successful QSTR study can predict the relative toxicity/safety of diverse classes of chemical compounds and at the same time suggests new toxic compounds or drug molecules, avoiding problems related to checking all such species experimentally.

Quantum-chemical descriptors based on density functional theory (DFT) (Parr, 1989; Chattaraj, 2009; Chattaraj et al., 2009) have become quite successful in explaining physico-chemical properties (Giri et al., 2008), biological activities (Parthasarathi et al., 2004), and toxicity (Roy et al., 2006; Padmanabhan et al., 2006) of diverse classes of chemical compounds and drug molecules. Chemical potential (μ) (Parr, 1989), electronegativity (χ) (Parr et al., 1978), chemical hardness (η) (Pearson, 1997), and electrophilicity index (ω) (Parr et al., 1999; Chattaraj et al., 2006; Chattaraj et al., 2007) are some of the global reac-

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