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QSARs for the aquatic toxicity of aromatic aldehydes from *Tetrahymena* data

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Abstract

The aim of the study was to develop quantitative structure–activity relationships (QSARs) for a large group of 77 aromatic aldehydes tested for acute toxicity to the ciliate *Tetrahymena pyriformis* using mechanistically interpretable descriptors. The resulting QSARs revealed that the 1-octanol/water partition coefficient ($\log K_{ow}$), is the most important descriptor of aldehyde aquatic toxic potency. The model with $\log K_{ow}$ was improved by adding electronic descriptor (the maximum acceptor superdelocalizability in a molecule—A_{max}) based on calculations with the semi-empirical AM1 model. The two descriptors reflect the two main processes responsible for demonstration of acute aquatic toxicity, namely penetration through cell membranes ($\log K_{ow}$) and interaction with the biomacromolecules (A_{max}) into the cells. Results showed that generally the studied group of aldehydes could be modeled by this simple two-descriptor approach. However, the group of 2- and/or 4-hydroxylated aldehydes demonstrates enhanced toxicity compared to the other aldehydes. Transformation to quinone-like structures is proposed as the explanation for this enhanced potency. The 2- and/or 4-hydroxylated aldehydes are modeled successfully by [$\log(1/IGC_{50}) = 0.540(0.038)\ \log K_{ow} + 8.30(2.88)A_{max} - 3.11(0.92)$, $n = 25$, $R^2 = 0.916$, $R^2_{CV} = 0.896$, $s = 0.141$, $F = 120$], while the other aldehydes are modeled by the relationship [$\log(1/IGC_{50}) = 0.583\ (0.034)\log K_{ow} + 9.80(2.62)A_{max} - 4.04\ (0.85)$, $n = 52$, $R^2 = 0.864$, $R^2_{CV} = 0.844$, $s = 0.203$, $F = 156$], which is similar to the general benzene model.
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Keywords: QSAR; Toxicity; Aromatic aldehydes; *Tetrahymena pyriformis*

1. Introduction

As pointed out in the European Union White Paper concerning a future of chemical policy (Anon, 2001) the development of tools able to assess potential hazardous effects of chemicals on living organisms needs to receive attention. To this end, information about the toxicity of industrial organic chemicals to aquatic species is of interest. While experimental testing provides the most reliable data about the effects of chemicals, such testing is time and resource demanding and thus is not deemed suitable for screening of large numbers of potential toxicants. Prediction of toxicity based on quantitative structure–activity relationships (QSARs) has been thought of as an alternative approach (Cronin et al., 2003). In recent years research in this field, especially as it relates to aquatic toxicity has become more

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sophisticated (Bradbury et al., 2003; Comber et al., 2003). QSARs offer the advantages of higher speed and lower costs, especially when compared to experimental testing. One requirement for the recognition of QSARs is to be able to define the chemical space for which the predictions can be done with a given reliability (i.e., the applicability domain). The concept of the domain of applicability is considered crucial for the consideration of a QSAR for regulatory acceptance and is one of the five principles known as "OECD (Organization for Economic Co-operation and Development) Principles for the validation of the (quantitative) structure–activity relationship models for regulatory purposes". Among the many ways for determining the domain of applicability, the understanding of the molecular mechanism of action and description of the structural and functional identifiers of that mechanism is a rational option (Schultz and Cronin, 2003).

Aldehydes are important intermediates in production of a variety of industrial processes (e.g., agrichemicals, pharmaceuticals). In particular, they are important in the flavor and fragrance industry (Prince and Gunson, 1994). Because of their inherent reactivity, these compounds are able to interact with the electron-rich biological macromolecules, in particular proteins and nucleic acids and therefore, have the potential to cause a number of adverse effects.

Excess toxicity of aldehydes to fish (Deneer et al., 1988) is thought to be through specific, irreversible, electrophilic mechanisms (Karabunarliev et al., 1996). Fish acute toxicity syndrome studies conducted by McKim and co-workers demonstrated that the physiological responses observed in rainbow trout (*Oncorhynchus mykiss*) exposed to model aldehydes, including benzaldehyde, is membrane irritation brought on by a concentration–response sloughing of the gill epithelium (McKim et al., 1987). As direct-acting electrophiles aldehydes are also skin-sensitizers (Patlewicz et al., 2001) and genotoxicants (Benigni et al., 2003).

Structure–toxicity studies of aldehydes reveal that hydrophobicity and electro(nucleo)philic reactivity were observed to be mechanistically important to quantifying aquatic toxicity (Karabunarliev et al., 1996; Dimitrov et al., 2003). While some aromatic aldehydes were part of a larger study on *Tetrahymena* toxicity of benzene derivatives (Schultz and Netzeva, 2004), which resulted in the model:

$$\log(1/\mathrm{IGC}_{50}) = 0.545(0.015)\log K_{\mathrm{ow}} + 16.2(0.62)A_{\max} - 5.91(0.20) \quad (1)$$

$n = 384$, $R^2 = 0.859$, $R^2_{\mathrm{CV}} = 0.856$, $s = 0.275$, $F = 1163$, no effort has been made to examine aromatic aldehydes data as a single group.

The aim of this study, therefore, was to develop QSARs for a large group of aromatic aldehydes using hydrophobicity and electrophilicity descriptors that have been shown previously to be relevant in the modeling of aromatic compounds tested for acute aquatic toxicity (Cronin et al., 2001).

2. Methods

2.1. Chemicals

The criteria for selection of chemicals included commercial availability and requirement for presence of an aromatic aldehyde group. The 77 compounds all of which possess an aldehyde moiety connected to an aromatic carbon atom were obtained commercially by Aldrich Chemical Co., Milwaukee, WI, USA; MTM Research Chemicals or Lancaster Synthesis Inc., Windham, NH, USA. The test materials had >95% purity and no further purification was undertaken. Heterocyclic aromatic aldehydes were not selected for these analyses.

2.2. Biological data

Population growth impairment testing with the common ciliate *Tetrahymena pyriformis* (strain GL-C) was conducted following the protocol described by Schultz (1997). This 40-h assay is static in design and uses population density quantified spectrophotometrically at 540 nm as its endpoint. Following identification of concentration range for measured effect, each chemical was tested at minimum three times each using fresh toxicant stock solution. Test replicates consisted of 6–10 different concentrations with duplicates of each concentration. Only replicates with control-absorbency values >0.60 but <0.85 were used in the analyses. In addition, two controls were included; these provided a measure of the acceptability of the assay by indicating the suitability of the medium and conditions as well as a basis for analyzing the data. One control had no toxicant, however, was inoculated with *T. pyriformis*. The other, a blank, had neither toxicant nor inoculum.

The 50% growth inhibitory concentration (IGC_{50}) was ascertained for each aldehyde tested by Probit Analysis of Statistical Analysis System (SAS) software (SAS ver. 6.4, 1998). The aldehyde concentrations were calculated in mM for the QSAR analysis.

2.3. Molecular descriptors

Hydrophobicity was quantified by l-octanol/water partition coefficient ($\log K_{\mathrm{ow}}$) with values being measured or software estimated (ClogP ver. 1.0 for Windows, 1995). Where available, the measured values were preferred than the estimated ones. The distribution coefficient for pH = 7.4 ($\log D_{7.4}$) was also calculated

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