Review

Organotins and quantitative-structure activity/property relationships

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Abstract

Quantitative-structure activity/property relationships as related to organotin chemistry are presented in this review. The descriptors discussed ranged from physicochemical parameters to quantum chemical descriptors. Studies ranged from predicting biotoxicity to estimating chromatographic parameters. It is the intent that the review will provide the present state of knowledge and current trends in this area for a new investigator in this field.
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Contents

1. Introduction

The toxicity of organotins, compounds that contain at least one Sn–C bond, was reported as early as 1886 [1]. It was not until the 1950s that their toxicities were studied systematically [2,3]. The toxicity of organotins has been found to be a function of the number of organic groups attached to the tin atom, as well as to the nature of the organic group. It is well documented that triorganotin compounds, those with three Sn–C bonds, have the highest biocidal activities [4–6]. In addition, the nature of the organic group deter-

mines the species to which the triorganotin is most toxic. For example, trimethyltin compounds are highly toxic to insects and mammals while triphenyl derivatives have high toxicities towards fish, fungi and mollusks [4–6]. In addition, compounds with alkyl groups are, in general, more toxic than compounds with aryl groups [7,8].

Significance of the X group in R_3SnX derivatives has been reported to have minor effects on the biological activity of the compounds [2,9] unless X itself is biologically active or can assist the transport of the molecule to the active site. It has also been shown to be significant if the X group is chelated to the tin atom. An increase in activity is reported for the first two cases while the activity is significantly decreased for chelated molecules [10,11]. The increase in activities

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have been attributed to synergistic effects and/or an increase in the solubility of the molecules, while the decrease in toxicity may be due to the inability of the chelated organotin to bind to the active site [10,11].

Due to their various biocidal properties and numerous applications, there has been an increase in the use of triorganotin compounds. In the past few decades, the production of organotin compounds rose from around 2000 ton in 1960 [12] to more than 35,000 ton in 1985 [13]. This increase is due to the development of new applications for this class of compounds. However, this increase has also raised concerns about the fate of these compounds and their degradation products once they are released into the environment, as well as to the cost of developing new compounds. One way to reduce the number of organotins discharged into the environment and to reduce the cost of developing more effective organotins as biocides is to design more effective compounds. Quantitative structure-activity/quantitative structure-property relationship (QSAR/QSPR) studies appear to be the most reasonable approach to address these problems. QSAR/QSPR are mathematical models that relate some measurable biological activity or physical property in a series of similar compounds to a descriptor or descriptors associated with the molecules.

Quantitative structure-activity relationships are generally used to evaluate and predict the toxicity of chemicals. Reduction in cost in producing an effective chemical or drug has been the drive for QSAR techniques. The cost of testing chemical derivatives is estimated to range from a low of $2500 to a high of $1.5 million depending on the test and time duration [14]. In addition, reducing the number of chemicals released into the environment would also greatly lessen the impact of these hazardous chemicals on the ecosystems.

The primary objective of a QSAR/QSPR study is to develop a regression equation that relates some measurable biological activity or physical property of a set of chemicals to a descriptor or a set of descriptors related to the molecules. A typical QSAR/QSPR plot is shown in Fig. 1. The success of a QSAR/QSPR will depend on the quality of the data set and on the suitability of the descriptor(s) selected. Initial QSAR studies have mainly focused on organic systems, and these types of correlation have been used extensively by the drug industry. However, these types of relationships are also applicable to organometallic molecules. QSAR/QSPR studies as germane to organotin systems will be discussed in this review. This review is written with the purpose of providing the present state of knowledge and current trends in organotin QSAR/QSPR methodologies. The vast majority of QSAR studies in organotin chemistry are linked to their biological behavior, thus this aspect will be discussed first.

2. Results and discussion

2.1. Studies related to toxicities

The Hammett sigma constant and the Taft steric parameter were used in early correlation studies. Hansch et al. later develop an octanol/water partition coefficient parameter (P), which is more closely associated with biological activities, and is one of the more popular and commonly used descriptors in biological QSAR studies [15].

In 1979, Schönfelder et al. developed several QSARs in their studies on the biocidal effects of several triorganotin compounds against the chlorella algae and the *Tetranychus urticae* Koch mite using the methods of Hansch as well as Free and Wilson [16]. Another early organotin study employing the Hansch parameter was by Wong et al. [17]. The authors were able to correlate the degree of toxicity and the hydrophobic characteristics of the toxicant for a series of triorganotins against the alga, *Ankistrodesmus falcatus*. Laughlin et al. used the total surface area (TSA) in addition to the Hansch parameter and found high correlations between these descriptors and the toxicity of a series of di- and triorganotin compounds against the mud crab, *Rhithropanopeus harristii* [18–20]. The results of the regression analyses for the diorganotins yielded correlation coefficient, r^2, ranging from 0.943 to 0.970 and 0.90 to 0.938 for the Hansch and TSA descriptors, respectively. It was further concluded by the authors that the partitioning behavior of the organotins played a major role in the toxicities of the compounds. In addition to $\log P$ values, Vighi and Calamari used electronic (pK_a) and steric (molecular connectivity index) parameters to developed QSARs between the toxicity of a series of organotins and *Daphnia magna* [21,22]. The authors were able to obtain an equation with a high correlation coefficient ($r^2 = 0.98$). This indicated that there is a significant correlation and high predictive capability between the descriptors and the toxicity of the compounds towards the organism.

Similarly, the toxicity for a series of di- and triorganotins was found to correlate well with their hydrophobic characteristics (Hansch π parameters) against two mammalian cell
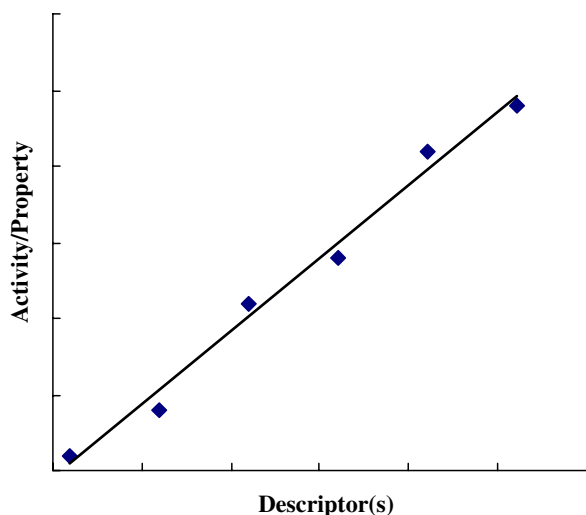
Fig. 1. Typical plot for a QSAR/QSPR study.

lines, i.e., BALB/c mouse fibroblasts 3T3 and neuroblastoma N$_2$A cells [23]. The sequence of the cytotoxicity for the organotins was similar to the earlier studies employing the Hansch parameters as the descriptor [17–21]. In addition to the mammalian cell studies, another study by these same authors using bluegill sunfish (*Lepomis macrochirus*) BF-2 cell lines found that the cytotoxicity of a series of diorganotins was dependent on the hydrophobicity of the diorganotins as expressed by the Hansch π parameters ($r^2 = 0.958$) [24], similar to their mammalian cell line studies [23]. Antitumor activities of organotins have also been evaluated using a QSAR methodology. Using a QSAR approach, Barbieri [25] reported that the toxicity for a series of diorganotin (IV) salts against P388 lymphocytic leukemia in mice can be coupled to the lipophilicity (log$P$) of the organic radicals attached to the tin atom.

The utility of TSA as a descriptor in QSAR studies has been used extensively by Brinckman et al. [18–20] due to its simplicity of calculation. Unlike the Hansch parameter, organotin TSA values are easily calculated since a broad database of bond distances, angles and Van der Waals radii are readily available in the literature. Using these values, Brinckman et al. were able to calculate TSA values for various individual organotin molecules [18–20].

In addition to the earlier study on *R. harristii* [18–20], Brinckman and co-workers were able to obtain a good correlation for a series of triorganotins against *A. falcatus* using additive TSA values [26]. A similar evaluation was found for the uptake of R$_3$SnCl on *Escherichia coli* sphaeroplasts ($r^2 = 0.805$) [26,27]. Using TSA as the descriptor, Eng et al. were able to find a high correlation between a series of di- and triorganotins and several distinct types of organisms [28]. Correlation coefficients, r^2, ranged from 0.85 to 0.98, indicating that the correlations were significant. The study also suggested that the relationship between TSA and toxicity is a function of the hydrophobicity of the organotin compounds rather than on electronic or steric effects. A later study by these authors indicated that TSA was a satisfactory predictor of toxicity for a series of organotins as well as for other metals in Group IVA against the bacteria, *E. coli*, and the alga, *Selenastrum capricornuium*, provided that there are no solubility problems and the toxicity is a function of the hydrophobicity of the organometallic compounds [29]. A study on the inhibitory effects of trimethyl and tributyltin compounds on methanogenic bacteria by Belay et al. [30] revealed that there was an increase in toxicity as the TSA decreased. These results are quite different from the previous results of Laughlin et al. [18–20] and Eng et al. [28]. In addition, the study indicated that the relationships observed with aerobic systems might not be valid for anaerobic systems. A similar trend was observed by Boopathy et al. [31] in their studies of a series of organotin chlorides and sulfates with three methanogenic bacteria. Their data similar to the results of Belay et al. [30], showed that the toxicity decreased with increasing TSA values. Despite scattering, the regression equations had r values ranging from 0.86

to 0.95. A similar negative correlation was reported by Lascourréges et al. [32] in their study involving the toxicity of a series of organotins and three pure strains of sulfate-reducing bacteria isolated from marine sediments. While TSA may be a good indicator of hydrophobicity [28], it may not be a uniform descriptor in predicting organotin toxicity to all organisms [31].

A topological descriptor closely related to the total surface area of a molecule is the molecular volume. Since both of these descriptors are related to the radius of the molecule, Luedke et al. [33] were able to show that both the total surface area and molecular volume of a series of di- and triorganotins can be used as a descriptor in QSAR studies with an equal level of confidence. The authors were able to obtain regression equations with correlation coefficient values between 0.745 and 0.996 for the diorganotins, and 0.634 and 0.989 for the triorganotins in spite of the different types of organisms employed in the study.

Eng et al. [34], in studying Dutch elm disease, reported the toxicities of a series of aryltins against the fungus, *Ceratocystis ulmi*, the causative agent of Dutch elm disease. The results indicated that neither topological nor partitioning effects were important in determining the activity of the triaryltin chlorides. It was found that an equation was obtainable as a function of the Hammett sigma (σ) values of the substituents on the phenyl ring. A plot of the log of $1/C$ versus σ resulted in a curve with the following equation ($r = 0.93$, $n = 9$): $\log 1/C = 2.36 + 0.92\sigma - 1.98\sigma^2$, where C is the inhibitory concentration and σ is the Hammett sigma value.

Huang and Dai [35] proposed a toxicity mechanism for a series of organotins against two green algae based on QSAR equations. The authors reported that the toxicity of the organotins was mainly controlled by the lipophilicity of the compounds with the electronic property playing a minor role. Similarly, Sun et al. [36] indicated that the toxicity of a series of organotin compounds against rotifer *Brachionus plicatilis* was also dependent on the lipophilicity of the compounds, as well as on an electronic property (polarizability) of the atom. The authors further developed a diparametric correlation equation using several physico-chemical and topological parameters as descriptors.

First order molecular connectivity indices have been used as descriptors in QSAR studies [22]. Singh and Sharma [37] reported a linear relationship between the toxicity of trialkyltin acetates and several fungi using the first and third-order connectivity indices of the organotin. Hence, the authors concluded that connectivity indices of the third order, as well as the first, for organotins played a significant role in determining the toxicity of the trialkyltin acetates against these fungi.

In addition to the traditional parameters, other parameters have been used in QSAR studies. Nagase et al. [38] was unable to generate an acceptable QSAR for the toxicities of 29 organotin compounds against the red killifish, *Oryzias latipes*, using log$P$ as the descriptor since the r value for the correlation was 0.328. Thus, the authors concluded that

the toxicities of these organotin compounds against the red killifish were not a function of their hydrophobicity. However, the authors were able to obtain excellent regression equations to predict the toxicities of the organotin compounds using a new descriptor, index value (IV) with r values ranging from 0.857 to 0.907. The index value was a newly created parameter and is a function of the number of phenyl or alkyl groups attached to the tin atom. The authors further developed a triparametric regression equation using the information index and mean information index, both topological descriptors, in addition to the IV parameter. The equation had a high correlation coefficient (0.907), and therefore can be used to predict the toxicity of the organotins. Using these descriptors as well as the molecular connectivity index, Hamasaki et al. were able to develop an acceptable regression QSAR equation ($r = 0.854$) for predicting the hemolytic activities of 27 organotin compounds [39]. The authors further suggested that the hemolytic activity due to the organotins might be related to the lethal factor in the earlier red killifish study. Using molecular descriptors, Schueuermann and Roederer [40] were able to correlate the toxicity of trialkyltins against the fungus, *Botrytis allii* with correlation coefficients up to 0.99. The authors also indicated that other descriptors such as log POW and electronic parameters were not as important in describing the toxicity of the trialkyltins.

A three-dimensional descriptor, WHIM (Weighted Holistic Invariant Molecular), was able to predict the toxicities of organotins against *D. magna* [41]. WHIM is a tridimensional molecular descriptor that describes the whole molecular structure of the molecule in terms of size, shape, symmetry and atom distribution. Quantum chemical descriptors have also been used in QSAR studies [42]. The toxicity of organotin compounds on *D. magna* and two green algae was found to correlate with quantum descriptors such as core–core repulsion energy, energy of the lowest unoccupied molecular orbital, total energy, etc.

With the rapid advances in current computer technology, the calculations of various descriptors for molecules are now commonplace. In recent years, QSAR software has become commercially available or has been incorporated into parent programs. Using SYBYL [43], Samuel et al. [44] were able to generate comparative molecular field analysis (COMFA) models to predict the cytotoxicities of a series of dibenzyltin (IV) derivatives against two human cancer cell lines, MCF-7, a mammary carcinoma, and WiDr, a colon carcinoma. Recently, Eng et al. [45–47], using the QSARIS program [48], generated acceptable regression equations with r^2 values ranging from 0.78 to 0.82 for the toxicities of several series of triorganotin compounds against the *Anopheles stephensi* mosquito larvae. In all cases, the cross-validation of the training set indicated that the constructed model could be used to predict the value of the toxicity. One advantage of using a commercial program for QSAR studies is that the program contains many descriptors and is able to generate QSARs rapidly, allowing the chemist to focus on the chemistry at hand.

2.2. Studies related to physicochemical properties

QSARs are most commonly used to predict biological activities; however, they are also frequently used to estimate physicochemical properties, in which case they are referred to as QSPR. In general, solution properties of sparingly soluble molecules are best estimated by QSPRs studies [49], thus hydrocarbon and heterorganic systems are commonly studied.

Using TSA as the descriptor, Brinckman et al. [26] correlated the solubility data taken from the literature for a series of tetraalkyl derivatives of Group IVA elements. A good correlation was obtainable even though the range of solubilities was large.

In addition, Brinckman et al. were able to obtain QSPR correlations between the chromatographic retention indices or capacity factors ($\ln k'$) for a series of mixed tetraorganotins using the Hansch π values as the descriptor [49]. A similar correlation was also obtained using TSA values calculated from a fragment method [26]. In both cases, the authors reported two excellent linear correlations for the two classes of organotins. The flexible alkyl groups exhibited far greater retentivity in the C_{18} reverse bonded-phase column than the more rigid planar phenyl substituents.

A later study by Tierney et al. [50] found significant linear correlations between the TSA values for a series of organotins and the natural logarithms of the capacity factor ($\ln K'$) for both fluxional and rigid organotin systems, as defined by summed carbon hybridization. Tie lines could be drawn between the two systems. The use of these column-dependent tie lines allowed the prediction of unreported compounds with mixed ligands. In addition, the data suggested that the quantitative hybridization summary determined the fluxionality of the organic moieties and, consequently, the solvophobic properties.

Reversed-phase high-performance liquid chromatograph (HPLC) studies using a C_{18} bonded-phase column indicated that there was a linear correlation between the number of tin atoms and the logarithm of the retention time for a series of organopolytins [51]. These types of linear relationships are important from both a theoretical and analytical standpoint. The generated QSPRs may assist in identifying unknown compounds as well as in explaining retention mechanisms [51].

In addition to chromatographic parameters such as retention times and capacity factors, QSPRs have been used to predict other properties. For example, acceptable correlations have been observed between molecular connectivity indices and the molar refractivity of 47 organotins [52].

3. Summary

The diverse studies discussed herein clearly show the importance of QSAR/QSPR studies as related to organotin chemistry. With the increased use of organotin compounds,

it is necessary to determine the impact that these compounds might have on the various ecosystems before they are released into the environment, as well as to design more effective compounds. With limited available resources, QSAR/QSPR models may satisfy both segments of the problem. It can provide the necessary information pertaining to environmental impact as well as the impetus for designing new molecules. Additionally, QSPR correlations may also assist in obtaining estimates of various physicochemical properties of organotins.

Acknowledgement

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