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Correlation of molecular total surface area with organotin toxicity for biological and physicochemical applications

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There exists a high correlation between molecular total surface area (TSA) values and diorganotin toxicity towards several distinct types of organisms. This correlation was found for N_2a neuroblastoma cells, 3T3 fibroblasts, *Daphnia magna* *Rhithropanopeus harrisii* and *Ankistrodesmus falcatus*. In the case of *Rhithropanopeus harrisii*, a high correlation was also found between TSA and toxicity for triorganotins as well. This study suggests that the relationship between TSA and toxicity is a function of the hydrophobicity of the organotin compounds rather than electronic or steric effects.

Keywords: Organotin, toxicity, total surface area, quantitative structure–activity relationships, molecular topology, N_2a neuroblastoma cells, 3T3 fibroblasts, *Daphnia magna*, *Rhithropanopeus harrisii*, *Ankistrodesmus falcatus*

INTRODUCTION

The use of organotin chemicals has grown significantly in the past 15 years.[1] In fact, there are more commercial uses of organotins than of any other organometallic system.[2] Organotin compounds have a host of industrial, commercial and agricultural applications. The use of organotins in their various applications is dependent on both the nature and number of organic groups associated with the tin atoms; consequently these represent a major industrial class of molecular 'designed' materials. For example, mono- and diorganotins are primarily used as heat and light stabilizers in the manufacture of poly(vinyl chlorides)[3–5] whilst triorganotins have biological activities against various species. Biocidal activities of organotins depend upon the specific nature of the organic group,[2,6] and a broad range are in commercial use. Triphenyltin compounds are currently used as agricultural fungicides[7–9] while tributyltins are used as antifouling agents in marine paints and coatings.[10–12] In addition, various investigators have shown that several classes of organotins possess antitumor activity against P-388 lymphocytic leukemia in mouse cells.[13,14]

The increased production of these chemicals as well as the formulation of new organotin compounds has led to an increased concern about the fate of these compounds and their degradation products as environmental pollutants. Therefore, it is essential to develop procedures to achieve reliable correlations between the toxicities of these compounds and the physicochemical properties of the molecule. This would then allow predictions of toxicities of untested or unstudied molecules, and promote quantitative molecular design prospects for safer industrial and medical applications.

Quantitative structure–activity relationships (QSARs) have long provided a useful technique for estimating biological effects of a molecule based on existing information, such as its lipid–water partitioning coefficients.[15–17] Two of the more common parameters used in QSAR studies are the Hansch and Taft–Hammett parameters.[18,19] However, these additive substituent parameters cannot fully account for geometric

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and/or conformational effects. Thus, a more complete or holistic approach, utilizing the molecule's entire geometrical and/or electronic configuration, is even more attractive.[20]

Presently, a major emphasis in this area of biophysico-organometallic chemistry is being placed on determination of predictions based on molecular structures. The leading topological parameters or predictors include molecular connectivity index,[21–23] branching index,[24] shape parameters[25,26] and total surface area (TSA).[16,17,27–30] The use of total surface areas as a predictor in QSAR studies for organometallic systems was first effectively employed by Brinckman *et al.* for both organoarsenical and organotin systems.[16,17,31] These investigators have found a high correlation between TSAs and toxicities for some organotins[16,17] as well as their chromatographic retention.[16] In order to determine the scope of applying TSAs as a predictor of toxicities for organotin compounds, we have investigated QSARs between toxicities of several species ranging from aquatic organisms to mammalian cells and the TSA values of the toxicants.

EXPERIMENTAL

The SAREA program,[32] suitably modified for the National Bureau of Standards main-frame computer (VAX 11/785), was employed to calculate total surface areas (in Å^2). The details of our procedures have been previously described.[16,17,20] The input data necessary for the TSA calculations, including conventional bond distances, bond angles, and van der Waals radii, are all obtained from the literature. Both holistic molecular calculations[20] and an assembly of molecular TSAs from the addition of mean functional groups and atom TSA values[33] were employed in this study. The term 'holistic' refers to a particular fixed conformation for the complete molecule and does not necessarily imply that the TSA value for the whole molecule is more than the sum of its parts.

RESULTS AND DISCUSSION

It has been shown earlier that organotin toxicities are primarily dependent on the hydrophobicity of the tin species[16] and not on their electronic or steric environment.[17] While there is an acceptable correlation coefficient, r^2, found between the toxicities of various diorganotin species and the Hansch π parameter[16] (an index of hydrophobic activity), as seen in Eqn [1]:

$$\ln LC_{50} = -6.13(\sum \pi) + 7.64 \quad r^2 = 0.97 \quad [1]$$

neither the π nor the σ (an index of electronic effects) parameters[16,17] can be considered to be effective correlation indexes. This has been attributed to their inability to distinguish local atom geometries and/or conformation details that probably influence the passage of the organotins from the bulk solvent into the cell.[33] One approach by Kamlet *et al.*[19] to correlate the solubility in, and partition among, human blood, brain, lung, kidney, muscle, and fat tissue is to use a linear solvation energy relationship as seen in Eqn [2]:

$$SP = SP_0 + mV/100 + s\pi^* + b\beta_m + a\alpha_m \quad [2]$$

in which SP represents the solubility properties, $mV/100$ is the cavity term, $s\pi^*$ is the dipolarity/polarizability parameter, $b\beta_m$ is the hydrogen bond-acceptor basicity, and the hydrogen bond-acceptor acidity is indicated by $a\alpha_m$. Although the correlation fit is quite good with r values ranging from 0.995 to 0.921, data values must be available or calculated for all the parameters in Eqn [2]. Thus, an approach that would eliminate the above limitations is by using TSA values as the descriptor. This has been found for solubility of organotins[34] as seen in Eqn [3]:

$$-\log S = 0.0224(TSA) + 0.442 \quad r^2 = 0.992 \quad [3]$$

and for the capacity factor in high-performance liquid chromatography[34] as seen in Eqn [4]:

$$\ln k' = 0.0117(TSA) \quad r^2 = 0.995. \quad [4]$$

Furthermore, total molecular surface area parameters have the advantage of being calculated based on their molecular structures whilst the Hansch and other parameters are empirically based.[18] On the basis of known speciation of organotins, the TSA values for the triorganotin species were calculated based on an established penta-coordinated structure[35] while the diorganotins were computed based on a hexa-coordinated environment.[16]

The correlations between TSA values and the toxicities for diverse types of organisms are shown in Fig. 1. Borenfreund and Babich measured the toxicity of diorganotins to the mammalian 3T3 fibroblasts and N_2a neuroblastoma cells.[36] *Daphnia magna* toxicity values were determined by Vighi and Calamari.[37] The toxicity of tri- and di-organotin compounds to *Rhithropanopeus harrisii* were measured by Laughlin *et al.*[16] The alga *Ankistrodesmus falcatus* toxicity values were found by Wong *et al.*[15] It is evident from this figure that there is a high correlation between the toxicities and the TSAs which is independent of the cell type. This suggests that it is the hydrophobic behavior of the organotin species that governs the toxicity process in all cell types studied. Similar findings have been observed for two aquatic organisms.[33] It can also be seen from Fig. 1 that the toxicity to both procaryotic and eucaryotic organisms from diorganotins varies over a range of two orders of magnitude, whereas the toxicity of the

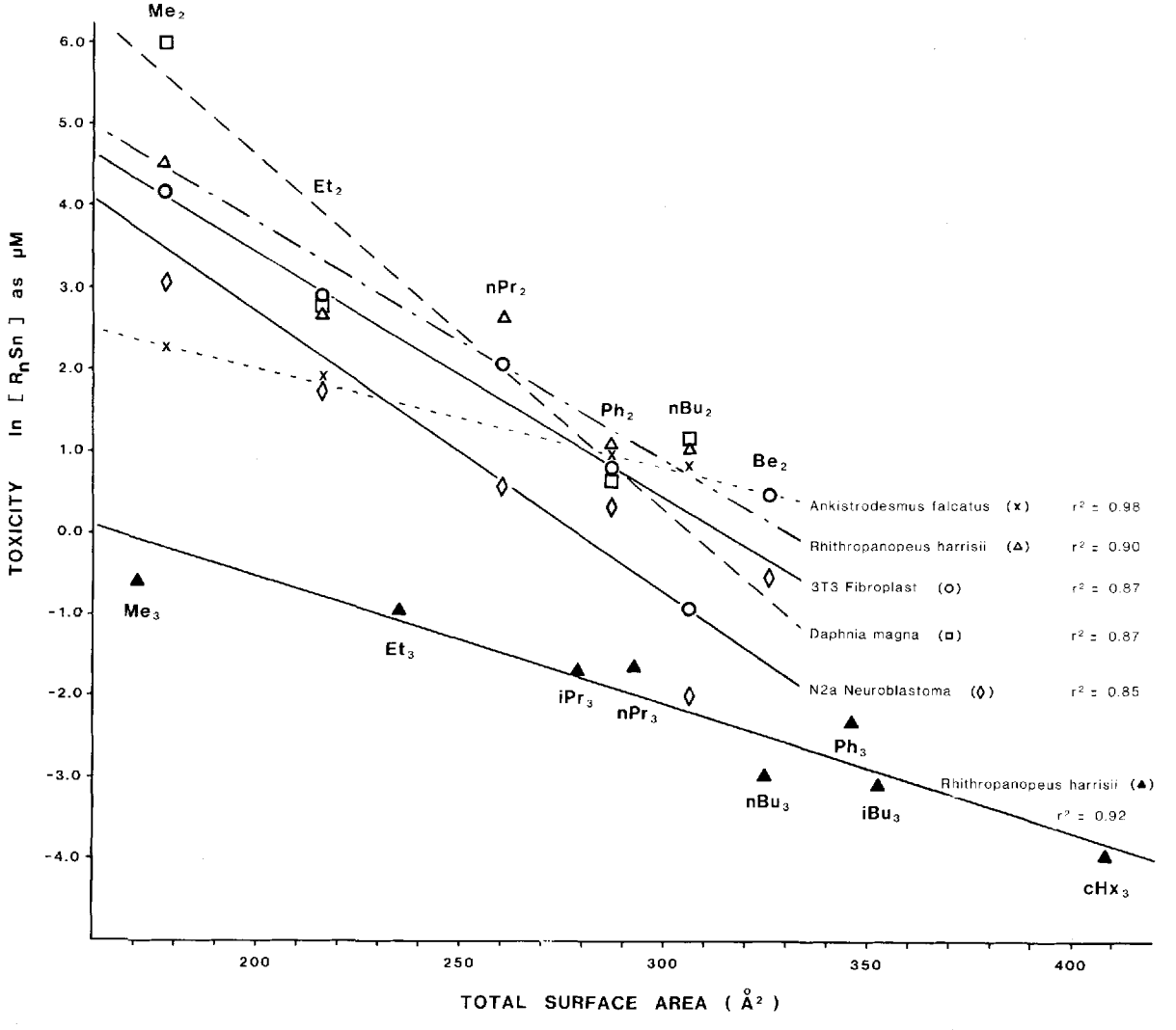

Figure 1 A plot of toxicity LC_{50} in $\mu mol\,dm^{-3}$ versus total surface area ($Å^2$) for N_2a *neuroblastoma cells*,[36] *3T3 fibroblasts*,[36] *Daphnia magna*,[37] *Rhithropanopeus harrisii*,[16] and *Ankistrodesmus falcatus*.[15] The toxicants include: dimethyltin (Me_2), diethyltin (Et_2), di-n-proplytin (nPr_2), diphenyltin (Ph_2), di-n-butyltin (nBu_2), dibenzyltin (Be_2), trimethyltin (Me_3), triethyltin (Et_3), tri-isopropyltin (iPr_3), tri-n-propyltin (nPr_3), tri-isobutyltin (iBu_3), tri-n-butyltin (nBu_3), triphenyltin (Ph_3), and tricyclohexyltin (cHx_3) in which the cations may have been chlorides, bromides, oxides or hydroxides depending upon the study.

triorganotin compounds varies over a range of three to five orders of magnitude depending upon the alkyl substituent. The slopes of the correlations for the diorganotin compounds are all very similar with the exception of *Ankistrodesmus falcatus*, which is less sensitive to the toxicants.

It appears from this study that the total surface area parameter is an excellent predictor of toxicity provided that the toxicity process is primarily a function of hydrophobic activity. Although the present study has been limited to organotin species, this approach of using TSAs as a predictor of toxicity can be readily expanded to include other hydrophobic organometallic compounds[18,29] where suitable structural information exists. This would enable the prediction of toxicity of untested or unstudied, designed molecules bearing a large variety of central metals or metalloid atoms of industrial relevance.

Note Certain commercial products or equipment are mentioned in order to describe adequately experimental procedures. In no case does such identification imply endorsement by the National Bureau of Standards, nor does it imply that the material is necessarily the best available for the purpose.

This work will be included in the dissertation of E.J.T. to be submitted as a partial requirement for the Ph.D. degree from the University of Maryland.

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