STRUCTURE-ACTIVITY STUDY OF SOME ALIPHATIC AMINES

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SUMMARY

The QSAR toxicity of 13 primary, 9 secondary, and 8 tertiary aliphatic amines was investigated using the hydrophobicity (logP), the total energy (Etot) and the polarizability (Pol) featuring on differences between Gaussian, non-Gaussian and mixed sets of data. Keywords: QSAR, hydrophobicity, Hansch model.

INTRODUCTION

Amines are organic compounds and functional groups that contain a basic nitrogen atom with a lone pair. Amines are derivatives of ammonia, wherein one or more hydrogen atoms are replaced by organic substitutes such as alkyl and aryl groups [1-3], while Aliphatic amines are considered to be strong organic bases [4]. The production of primary fatty amines (in 1992) with a chain length of C₈ to C₁₈ was about 8,000 tones and, for example the production of octylamine, was like 450-500 tones [5].

About 75 % of the primary fatty amines are used as intermediates for synthesizing ethoxylated fatty amines. These are widely used as cationic, surface-active substances, for example in auxiliary agents for dyeing and textile, as additives for mineral oil and as antistatic agents for plastics [6]. Cyclohexylamine is suspected to have a teratogenic, mutagenic and carcinogenic potential [7]. A mammalian fertility study suggests that
cyclohexylamine targets Sertoli cells in the testes [8]. Alkyl tertiary amines are used as fuel additives; they have similar applications with long chain alkyl amines. Hexamethylenediamine used in the manufacture of nylon-6,6 is prepared by catalytic addition of hydrogen to nitriles [2, 3, 9].

This work likes to model aliphatic amines’ toxicity throughout structural parameters, especially hydrophobicity influence.

**ON HYDROPHOBICITY**

In attempting to correlate the structures of the compounds with their activities, Hansch recognized the importance of the lipophilicity, expressed as the octanol-water partition coefficient, on biological activity [10].

Hydrophobicity represents the tendency of a substance to repel water and to avoid the complete dissolution in water. Being that hydrophobicity is one of the most important physicochemical parameters associated with chemical compounds, several studies have been carried out to understand, evaluate, and predict this parameter [10-17]. The hydrophobic effect can be defined as “the tendency of nonpolar groups to cluster, shielding themselves from contact with an aqueous environment”.

As a result, the partition coefficient P is the quotient of two concentrations and is normally calculated in the form of its logarithm to base 10 (log P), because P ranges from $10^{-4}$ to $10^8$. Log P values are widely used in bio-accumulation studies, in drug absorption and toxicity predictions and, recently, even in biological interactions modeling [18, 19]. With new computational applications and molecular modeling progress and achievements, several methods, capable of predicting log P values for thousand of compounds, have been developed, and can now be classified into five major classes [20]: substitute methods, fragments methods, methods based on atomic contribution and/or surface areas, methods based on molecular properties, and, finally, methods based on solvate-chromic parameters.

**RESULTS AND DISCUSSION**

In Figure 1 were plotted the lethal toxicity dose LD₅₀ (mg/kg), from literature data [21-23], for selected the series of primary, secondary and tertiary aliphatic amines; the molecules included in the “Gaussian or Normal” set have been marked with GS while those considered in the “Non-Gaussian or Non-normal” set were marked as NG.
From the Tables I-III we obtain useful information about the structure parameters in correlation with hydrophobicity and biological activity.

For the stage “trial” (these compounds belongs to a Gaussian-activity set) the minimum of SEE tells us that the model LogP=f(Pol) is predicted as the most reliable one across the LogP models of Table I; it leads with idea that the ionic or electrostatic character of the interaction primary influences the hydrophobicity towards the final stabilization by the steric (energy-optimum configuration) effect.

<table>
<thead>
<tr>
<th>Model Equation</th>
<th>R</th>
<th>SEE</th>
<th>EV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogP=1833.586 + 0.142 E_{tot}</td>
<td>0.2676</td>
<td>2.3704</td>
<td>0.000235</td>
</tr>
<tr>
<td>LogP=-41.6543+0.4225Pol</td>
<td>0.5773</td>
<td>2.0086</td>
<td>0.2821</td>
</tr>
<tr>
<td>LogP= -2158.89 -0.16 E_{tot} + 0.58 Pol</td>
<td>0.6154</td>
<td>2.0181</td>
<td>0.2752</td>
</tr>
<tr>
<td>A= -2.698 -0.0705 LogP</td>
<td>0.8876</td>
<td>0.09004</td>
<td>0.7716</td>
</tr>
<tr>
<td>A= -2.7199 -0.0232LogP -0.0027(LogP)^2</td>
<td>0.8983</td>
<td>0.0894</td>
<td>0.7748</td>
</tr>
</tbody>
</table>
Whenever possible, these relationships have proven useful in describing possible mechanisms of interaction.

Most interesting, the values (R-correlation factor, SEE-standard error of estimation and EV –explained variance) for the stage “test” (the non-Gaussian molecules of Figure 1) furnish the same situation, i.e. the model LogP=f(Pol) is predicted as the most reliable one from hydrophobicity models of the Table II.

It is probably correct to assume that molecular hydrophobicity and/or partitioning properties are responsible for many of the passive distribution properties contributing to observed pharmacokinetics. Both regressions showed that the relationship between hydrophobicity and polarizability of the primary, secondary and tertiary aliphatic amines is significant.

Going to the activity-hydrophobicity analysis, for the amines in „trial” we see the R value for the simple relationship between toxicity and hydrophobicity. Thus, the significant relationship indicates that the toxicity of all aliphatic amines can be best described if the two descriptors (logP and (logP)^2) are included in a multiple-factorial regression model. The toxicity (LD50) of the aliphatic amines could be described best by a bilinear regression model including the hydrophobicity.

Moreover, while the Gaussian A=f(LogP) models provides the highest statistical relevance comparing with Non-Gaussian and Gaussian ∧ Non-Gaussian sets of molecules,
worth noting they are the complements of those NG values in what respect all QSAR models treated.

Finally, note that treating a non-discriminative set of molecule for QSAR analysis, i.e. without distinguishing for normal or non-normal distribution curve of selected population leaves with quite puzzling results, with no clear interpretation and assessments (see Table III).

Conclusion

Throughout a comprehensive hydrophobicity based QSAR analysis for predicting the toxicity it was showed that the whole group of aliphatic amines can not be described by the hydrophobicity \( \log P \) alone while a Hansch regression type provide substantial improvement. However, for a given dataset a satisfactory various regression models combining the hydrophobicity, the total energy \( \text{E}_{\text{tot}} \) and the polarizability \( \text{Pol} \) reveals an interesting complementarities between the Gaussian and Non-Gaussian selected molecular populations, while falling to provide useful information for their mixed normal plus non-normal biological activities. The selected best QSAR model gained out of considered aliphatic amines molecular sets may be further used to predict pesticides’ toxicity.

References

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