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QSR Study Between Octanol-Water Partitioning Coefficients, Total Biodegradation of Barbiturates and Randic Index

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Barbiturates are primarily used for insomnia and preoperative sedation. These drugs contain a "balance" of hydrophilic (2,4,6-pyrimidinetrione ring structure) and lipophilic (5,5'-substituents) functionality. Because of these property, the insertion of these compounds in fatty tissue of body has a high importance in medicinal studies. The octanol-water partition coefficient (K_{ow}) is a measure of the equilibrium concentration of a compound between octanol and water that indicates the potential for partitioning in to soil organic matter (*i.e.*, a high K_{ow} indicates a compound which will preferentially partition into soil organic matter rather than water). Biodegradation (TB_d) is another useful and important factors in chemical and biochemical studies. It needs to use the effective and useful mathematical methods for making good concern between several data in chemistry and biochemistry. Graph theory is a sub discipline of mathematics that is closely related to both topology and combinatory concepts. Here, was used Randic index (χ) for molecular description of structure-property relationship studies for the logarithm of calculated octanol-water partitioning coefficients and total biodegradation [log K_{ow} and TB_d (mol/h), respectively] in barbiturate compounds. The Randic index (χ) one of the useful indices for examination of QSAR studies. The interesting results of concerning among log K_{ow}, TB_d and τ_a index for this compounds are presented.

Key Words: Molecular topology, Randic index, Octanol-water partition coefficient, Biodegradation, Barbiturates.

INTRODUCTION

Barbiturates were first introduced for medical use in the early 1900s. More than 2,500 barbiturates have been synthesized and at the height of their popularity, about 50 were marketed for human use. Barbiturates produce a wide spectrum of central nervous system depression, from mild

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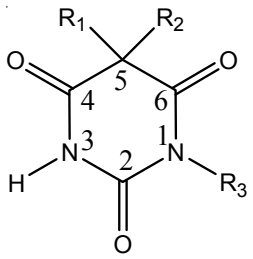
sedation to coma and have been used as sedatives, hypnotics, anesthetics and anticonvulsants. The primary differences among many of these products are how fast they produce an effect and how long those effects last. Barbiturates are classified as ultra-short, short, intermediate and long-acting. The ultrashort-acting barbiturates produce anesthesia within about 1 min after intravenous administration. Barbiturate abusers prefer the short-acting and intermediate-acting barbiturates. After oral administration, the onset of action is from 15 to 40 min and the effects last up to 6 h. These drugs are primarily used for insomnia and preoperative sedation. Veterinarians use pentobarbital for anesthesia and euthanasia. Long-acting barbiturates include phenobarbital (luminal) and mephobarbital (mebaral). Effects of these drugs are realized in about 1 h and last for about 12 h and are used primarily for daytime sedation and the treatment of seizure disorders. Barbiturates contain a "balance" of hydrophilic (2,4,6-pyrimidinetrione ring structure) and lipophilic (5,5'-substituents) functionality. The overall hydrophilic (polar) or lipophilic (non-polar) character of the barbiturates is a function of the hydrophilicity of the pyrimidinetrione ring which is a function of the number of N-substituents and the pKa of the acidic proton(s) and the overall size and structure[1-6] of the two substituents at the 5-position (Fig. 1).



Barbiturates structure

Barbiturates bind to the GABA receptor which ultimately increases GABA-induced Cl-currents. They bind at a site distinct from the BDZ binding site. Barbiturates may also reduce glutamate-induced depolarization by acting as antagonists at AMPA-type receptors. The actions of the barbiturates are described in more detail in the pharmacology notes. General properties of these compounds relatively concern to low lipophilicity and low plasma protein binding[1-6].

The octanol-water partition coefficient (K_{ow}) is a measure of the equilibrium concentration of a compound between octanol and water that indicates the potential for partitioning in to soil organic matter (*i.e.*, a high K_{ow} indicates a compound which will preferentially partition into soil organic matter rather than water). This coefficient is inversely related to

the solubility of a compound in water. The log K_{ow} is used in models to estimate plant and soil invertebrate bioaccumulation factors. The log K_{ow} is commonly used in QSAR studies and drug design, since this property is related to drug absorption, bioavailability, metabolism and toxicity. This parameter is also used in many environmental studies to help in determining the environmental fate of chemicals[7,8]. It has a lot of use in medicine and medicinal chemistry. Biodegradation (TB_d in mol/h)) is another useful and important factors in chemical and biochemical studies[8].

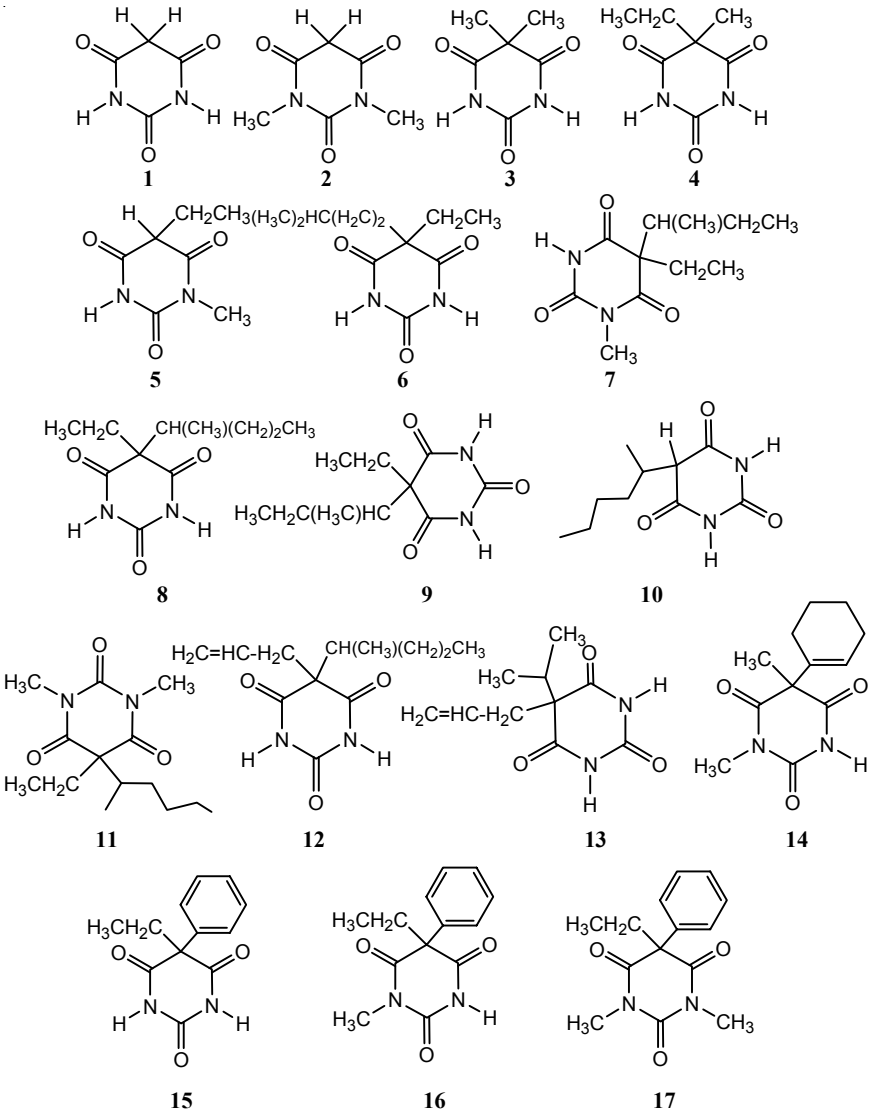


Fig. 1. The Barbiturates **1-17** structures

It needs to use the effective and useful mathematical methods for making good concern between several data of chemical properties, medicinal chemistry and biological activity of chemicals. Graph theory is an attractive field for the exploration of proof techniques in discrete mathematics and its results have applications in many areas of sciences. A graph is a topological concept rather than a geometrical concept of fixed geometry and hence Euclidean metric lengths, angles and three-dimensional spatial configurations have no meaning. Chemists employ various types of names and formulas when they wish to communicate information about chemicals and their structures. For the most part names and formulae have no direct, immediate or explicit mathematical meaning. Graph theory provides many different methods of characterizing chemical structures numerically.

It has been found to be a useful tool in quantitative structure activity relationship (QSAR) and quantitative structure property relationship (QSPR)[9-14]. Numerous studies have been made relating to the above mentioned fields by using what are called topological indices (TI)[14,15].

In this study, will be considered the relationship of Randic index, for molecular description of structure-property relationship studies for the logarithm of calculated octanol-water partitioning coefficients and total biodegradation [log K_{ow} and TB_d (mol/h), respectively] in barbiturate compounds (**1-17**).

EXPERIMENTAL

The branching index that was introduced by Randic is defined as the sum of certain bond contributions calculated from the degree of the bonds suppressed molecular graphs. These bond contributions, named C_{ij} are calculated as:

$$C_{ij} = (\delta_i \, \delta_j)^{-0.5} \quad (1)$$

where δ_i is the degree of the vertex representing atom 'i', *i.e.*, the number of bonds incident to this atom. Accordingly, the Randic index is defined as:[9,15,16-18]

$$\chi = \Sigma \, C_{ij} = \Sigma(\delta_i \, \delta_j)^{-0.5} \quad (2)$$

where the summation is carried out over all the bonds of compounds **1-17**. The inverse squared-root of the vertex degree is identified here as a measure of the relative accessible parameter of an atom from the outside. These parameters, which have length units, are proposed to be measured in a new unit called the Randic index (χ). On this basis, the bond contributions to the Randic index are relative areas of bond accessibility from the environment.

Graphs: All graphing operations were performed using the Microsoft Office Excel-2003 program.The data of octanol-water partitioning co-efficients and total biodegradation (log K_{ow} and TB_d, respectively) were calculated by EPI-suit v3.12 package[19].

RESULTS AND DISCUSSION

It was accepted that the organic compounds toxicity properties can be introduced by utilizing the log K_{ow}[20]. The quantitative structural activities and properties relationship results hold true for quite a lot of organic compounds, the most commonly used for test organism, follows this standard pattern[21]. Biodegradation is usually quantified by incubating a chemical compound in presence of a degrader and measuring some factors like oxygen or production of CO_2. The biodegradation QSAR studies demonstrate that microbial biosensors are a viable alternative means of reporting on potential biotransformation. However, a few chemicals are tested and large data sets for different chemicals need for QSAR modeling[22]. This study shows the structural relationship between Randic index (χ), log K_{ow} and total biodegradation (TB_d) for barbiturates (**1-17**). The values of the relative structural coefficients of the barbiturates structures (**1-17**), Randic index (χ) to logarithm of octanol-water partitioning coefficients (log K_{ow}) and calculated total biodegradation (TB_d) in mol/h, data were shown in Table-1. The χ values of compounds **1-17** increase with the increasing the number of branches in the appropriate structures. The Randic index (χ) for barbituric acid (**1**) in respect with the branches of the structure is equal to 2.1216. See eqns. 1 and 2 and the appropriate data extended in Table-1 for other members of these group.

$$\chi = 6[(2 \times 4)^{-0.5}] = 2.1216$$

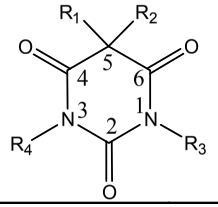
In Figs. 2-4 were shown two dimensional diagrams of the relationship between the values of Randic index, log K_{ow} and TB_d.

The Fig. 2 shows a good linear relationship between the values of log (K_{ow}) *vs.* the Randic indices (χ) for barbiturates (**1-17**). The eqn. 3 is relevant to Fig. 2 and as could see by this equation can extend the linear behaviour of the calculated log K_{ow} and χ for these compounds. The R-squared value (R^2) for this graph is equal to 0.9248.

$$\log (K_{ow}) = 1.0309(\chi) - 3.3924 \quad (3)$$

By this way, eqn. 3 afford a good approximation for calculation of logarithm value of octanol-water partitioning coefficient (log K_{ow}) by the use of Randic index (χ) and directly for the barbiturates. The large values results for solving the first order eqn. 3 are acceptable. For achieving to log K_{ow} can use directly from eqn. 3, in accordance with the structural 'χ' values for these compounds.

TABLE-1
THE VALUES OF THE RELATIVE STRUCTURAL COEFFICIENTS OF BARBITURATES STRUCTURES **(1-17)**



No.	R_1	R_2	R_3	R_4	Randic indices (χ)	log K_{ow}	$TB_d \times 10^{-5}$ (mol/h)
1	H	H	H	H	2.1216	-1.2488	7.2
2	H	H	CH_3	CH_3	3.0166	-0.8264	5.9
3	CH_3	CH_3	H	H	2.4144	-0.3777	5.9
4	H	H	CH_3	C_2H_5	3.4751	-0.1289	5.4
5	CH_3	H	C_2H_5	H	4.0358	0.6045	5.0
6	$(CH_2)_2CH(CH_3)_2$	C_2H_5	H	H	5.3911	2.0043	4.2
7	$CH(CH_3)CH_2CH_3$	C_2H_5	CH_3	H	4.8266	1.7244	4.1
8	$CH(CH_3)(CH_2)_2CH_3$	C_2H_5	H	H	5.4564	2.0043	4.3
9	$CH(CH_3)CH_2CH_3$	C_2H_5	H	H	4.9564	1.5132	4.4
10	$CH(CH_3)(CH_2)_3CH_3$	H	H	H	4.7188	1.5508	4.4
11	$CH(CH_3)(CH_2)_3CH_3$	C_2H_5	CH_3	CH_3	5.9978	2.9178	4.4
12	CH_2-CH=CH2	$CH(CH_3)(CH_2)_2CH_3$	H	H	5.3152	2.3590	4.0
13	CH_2-CH=CH2	$CH(CH_3)_2$	H	H	4.5277	1.3768	4.4
14		CH_3	CH_3	H	4.3593	1.8548	3.8
15	C_6H_5-	C_2H_5	H	H	4.8025	1.3301	4.0
15	C_6H_5-	C_2H_5	CH_3	H	5.0059	1.5413	3.8
17	C_6H_5-	C_2H_5	CH_3	CH_3	4.8761	1.7525	3.6

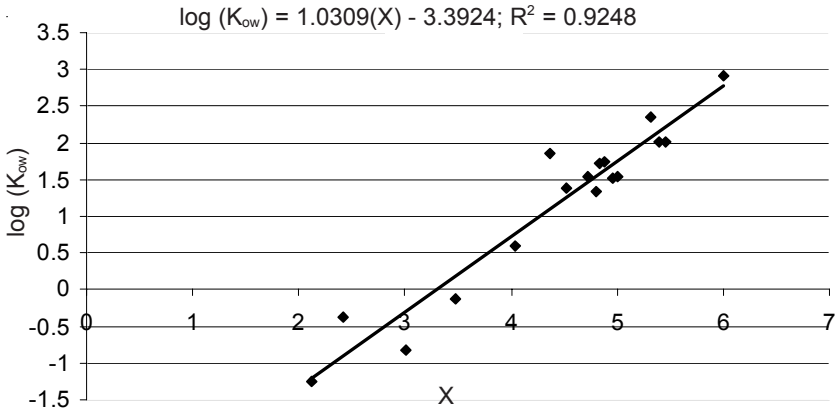


Fig. 2. Linear relationship between the values of log K_{ow} *vs.* the Randic indices (χ) for barbiturate derivatives (**1-17**)

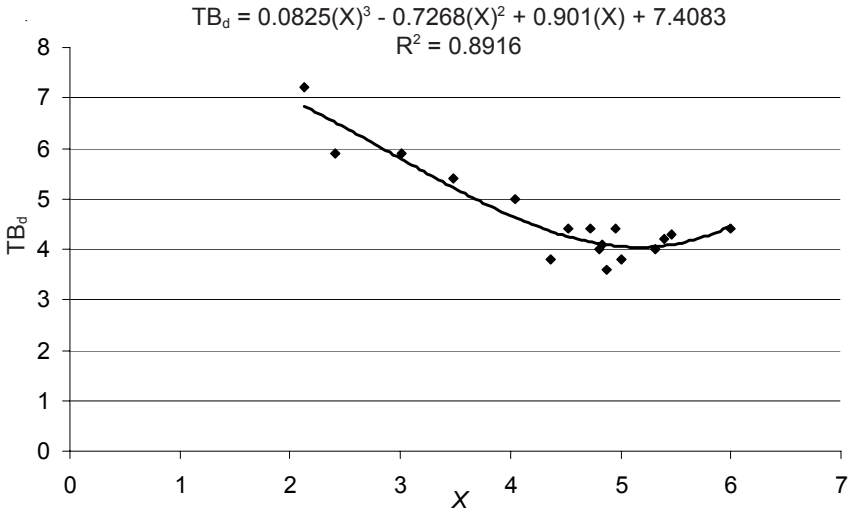


Fig. 3. Curve between values of Randic indices (χ) and calculated total biodegradation (TB_d) for (**1-17**)

Fig. 4 shows a curve for relationship between the values of calculated total biodegradation (TB_d) *vs.* the Randic indices (χ) for compounds **1-17**. The eqn. 4 is relevant to Fig. 4 and can see the non-linear behaviour of the calculated total biodegradation (TB_d) and χ for barbiturates (**1-17**). The equation has three-order structure. The R-squared value (R^2) for this graph shows 0.8916.

$$TB_d = 0.0825(\chi)^3 - 0.7268(\chi)^2 + 0.901(\chi) + 7.4083 \quad (4)$$

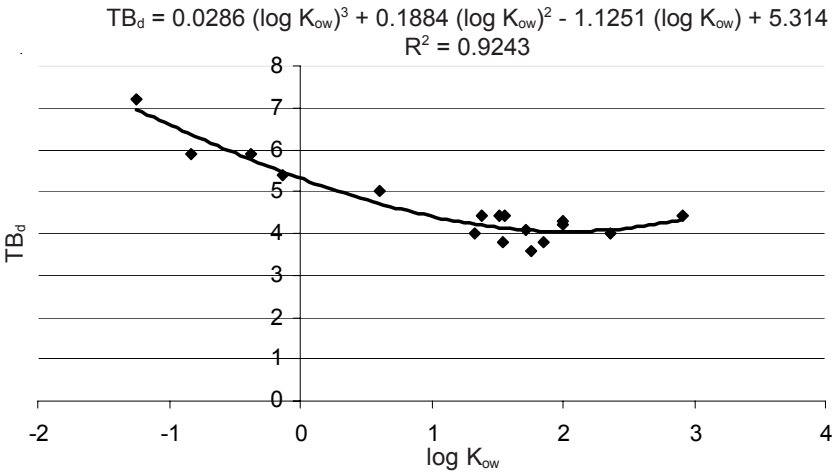


Fig. 4. Plot of the log K_{ow} *vs.* the calculated total biodegradation (TB_d) for barbiturates (**1-17**)

By the use of Randic indices (χ) for **1-17** in the eqn. 4 can achieve to an approximation for total biodegradation (TB_d). All values of TB_d should multiply to 10^{-5} for achieving to calculated total biodegradation in mol/h for the compounds.

A plot of the log (K_{ow}) *vs.* the calculated total biodegradation (TB_d) for barbiturates (**1-17**) was demonstrated in Fig. 5. The equation of this relationship has three-order structure and introduced by eqn. 5. The R-squared value (R^2) for this graph is equal to 0.9243.

$$TB_d = 0.0286 (\log K_{ow})^3 + 0.1884 (\log K_{ow})^2 - 1.1251 (\log K_{ow}) + 5.314 \quad (5)$$

It seems that two methods were achieved for TB_d calculation of barbiturates (**1-17**). One of these two models, is calculation of Randic indices (χ) for these important compounds by the use of eqn. 4. The second method is the measurement of log K_{ow} by the use of (χ) in eqn. 3, then utilize the result in eqn. 5. In respect with the R-squared value (R^2) for these graphs it is obvious that the second model much better for this relationship. Determination of log K_{ow} and TB_d for the barbiturates as an important class of medicinal compounds have highly importance and the models that were demonstrated here show simple methods for this matter.

Conclusion

Graph theory has been found to be an effective tool in QSAR and QSPR. Topological indices (TIs) contain valuable structural information as evidenced by the success of their widespread applications in QSAR. One of the useful indices for examination of structure-property relationship is Randic index. The toxicity property of organic compounds can be

predicted on the basis of the log K_{ow}. The biodegradation QSAR studies demonstrate that microbial biosensors are a viable alternative means of reporting on potential biotransformation. In this study, was considered the relationship of Randic indeices, logarithm of calculated octanol-water partitioning coefficients and total biodegradation (log K_{ow} and TB_d (mol/h), respectively) with each other for barbiturates. Randic indices (χ) show a good differences between the values of logK_{ow} and TB_d as two important factors in chemical and biochemical studies in these compounds.

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