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Density Functional Theory Studies of Some Barbiturates on Lipophilicity

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Abstract

This paper deals with the evaluation of lipophilicity expressed by $logP_{ow}$ parameter of ten barbiturate derivatives generally used as sedative-hypnotics based on Density Functional Theory (DFT) calculations. All geometry optimizations and frequency calculations have been carried out by using DFT/B3LYP/ 6-311++G (d,p) basis set in gas phase and also in water and n-octanol phases. Gibbs free energies of solvation for studied barbiturates were calculated to predict $logP_{ow}$. The correlation between the calculated $logP_{ow}$ values and available data in literature has been examined. Root mean square error (RMSE), mean square error (MSE), mean absolute deviation (MAD) and mean absolute percentage error (MAPE) statistics were utilized in measuring predictive accuracy (forecast performance) of DFT method used in this study. Accordingly, the reasonable results have been obtained in estimating the partition coefficient of the mentioned ten barbiturate derivatives by DFT/B3LYP/6-311++G (d,p) method. The lipophilicity tendency of the studied barbiturates was interpreted with the help of the calculated quantum chemical descriptors such as HOMO energy (EHOMO), LUMO energy (ELUMO), molecular volume (Vm), electrophilicity index (ω). ELUMO, Vm, and ω descriptors gave reasonable results rather than EHOMO. Also, the 3D molecular lipophilicity potential (MLP) maps that display the accumulative lipophilic contributions of each atom in studied barbiturates were visualized.

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Keywords: DFT; Barbiturate; Solvation free energy; Error analysis.

Bazı Barbitüratların Lipofilikliği Üzerine Yoğunluk Fonksiyonel Teori Çalışmaları

Öz

Bu makale, Yoğunluk Fonksiyonel Teori (YFT) hesaplamalarına dayalı olarak, genellikle sedatif-hipnotik olarak kullanılan on barbitürat türevinin $logP_{ow}$ parametresi ile ifade edilen lipofilikliğinin değerlendirilmesini ele almaktadır. Tüm geometri optimizasyonları ve frekans hesaplamaları, gaz fazında ve ayrıca su ve n-oktanol fazlarında DFT/B3LYP/6-311++G (d,p) temel seti kullanılarak yapılmıştır. $LogP_{ow}$ değerlerini tahmin etmek için, çalışılan barbitüratların Gibbs serbest solvasyon enerjileri hesaplanmıştır. Hesaplanan $logP_{ow}$ değerleri ile literatürdeki mevcut veriler arasındaki korelasyon incelenmiştir. Bu çalışmada kullanılan YFT yönteminin tahmin doğruluğunun (tahmin performansı) ölçülmesinde ortalama karekök hata (RMSE), ortalama kare hata (MSE), ortalama mutlak sapma (MAD) ve ortalama mutlak yüzde hata (MAPE) istatistiklerinden yararlanılmıştır. Buna göre, bahsedilen on barbitürat türevinin dağılım katsayısının DFT/B3LYP/6-311++G (d,p) yöntemi ile tahmin edilmesinde makul sonuçlar elde edilmiştir. İncelenen barbitüratların lipofilisite eğilimi, HOMO enerjisi (EHOMO), LUMO enerjisi (ELUMO), moleküler hacim (Vm), elektrofilik indeks (ω) gibi hesaplanan kuantum kimyasal tanımlayıcılar yardımıyla yorumlanmıştır. ELUMO, Vm ve ω tanımlayıcıları EHOMO değerine kıyasla daha makul sonuçlar vermiştir. Ayrıca, çalışılan barbitüratlarda her bir atomun birikimli lipofilik katkılarını gösteren 3 boyutlu moleküler lipofiliklik potansiyeli (MLP) haritaları görselleştirilmiştir.

Anahtar Kelimeler: YFT; Barbiturat; Solvasyon serbest enerjisi; Hata analizi.

1. Introduction

Epilepsy is one of the most common and severe neurological disorders observed as seizures that occur with some symptoms as a result of sudden, abnormal and hyper synchronized discharges of a group of neurons in the central nervous system [1]. A wide variety of treatments to prevent seizure activity options are available. The purpose of the treatment with antiepileptic drugs (AEDs) is to provide the best possible quality of life by not only elimination of seizures or reducing the number of seizures but also avoidance of drug interactions and adverse effects [2]. AEDs are chosen first of all according to clinical success, then tolerability, drug interaction, and ease of use [3-5]. By discovery of phenobarbital, a barbituric acid derivative, many new substances have begun to be used as anticonvulsants in pharmacotherapy [6-7]. Although

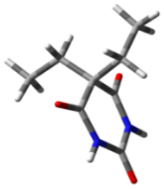
barbituric acid derivatives were initially considered as AEDs due to their anticonvulsive effects, they could be used in very small doses and in mild cases because of their sedative-hypnotic effects. Although barbituric acid itself is not pharmacologically active, 5,5-disubstituted derivatives have been observed to have hypnotic effect. The duration and depth of efficacy of barbiturates varies according to characteristics of substituents. Consequently, the purpose of use in treatment also changes. For instance, long-acting derivatives are used for antiepileptic and hypnotic purposes, while short-acting derivatives are used as injection anesthetics. Due to these features, barbiturates have been included in many Structure-Activity Relationships (SAR), Quantitative Structure-Activity Relationships (QSAR) and also Quantitative Structure-Pharmacokinetic Relationships (QSPkR) studies [8-15].

Computer-aided methods have become a fundamental research tool for scientists from a wide range of fields including biology, physics, chemistry and pharmacology and play a central role in combining theoretical and experimental results. QSAR studies can contribute to the designing new drugs by determining the important interactions that can have an effect on bioactivity, and predicting major parameters such as absorption, hydrophilicity, lipophilicity and toxicity. Among these parameters, the lipophilicity and hydrophilicity have been explored in detail both experimentally and theoretically [16-24]. The capability of a drug to dissolve in a lipid phase when an aqueous phase also exists frequently referred to as lipophilicity. The lipophilicity can be defined numerically by partition coefficient of a molecule in *n*-octanol-water system. The partition coefficient, P is dimensionless, and its logarithm (logP) is often used as the measure of lipophilicity [25]. In medicinal chemistry, logP is an extremely major physicochemical parameter and has private benefit in pharmacology and toxicology [26].

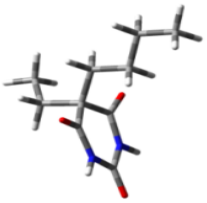
Sedative-hypnotics, despite their different chemical structure, show certain common physicochemical and structural features. All of them contain polar (hydrophilic) groups as well as nonpolar (lipophilic) groups in their structures. Such compounds have dominant lipophilic character. All barbiturates mentioned in this study have two Hydrogen Bonding Donor (HD) and three Hydrogen Bonding Acceptor (HA) sites that influence the pharmacological activity. For barbiturates, maximum effect and pharmacological optimization is achieved by having n-octanol-water partition coefficients around P = 100 (logP = 2) [17]. This property of the compounds is an important criterion in crossing the blood-brain barrier and in their reabsorption.

The main purpose of this study is to explore the efficacy of substitutions at 5 position of barbiturate ring on its lipid solubility based on DFT methods. Thus, DFT calculations for non-ionic forms of ten barbiturate derivatives generally used as sedative-hypnotics have been

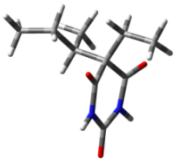
performed. The chemical structures and IUPAC names of studied barbiturates are shown in Fig. 1. Correlations between $\log P_{ow}$ and computed descriptors have been presented.



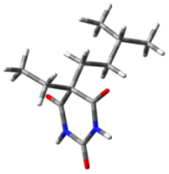
BARBITAL
5,5-Diethyl-1,3-diazinane-2,4,6-trione



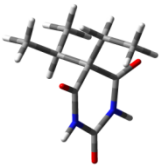
BUTETHAL
5-Butyl-5-ethyl-1,3-diazinane-2,4,6-trione



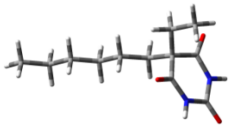
BUTABARBITAL
5-Butan-2-yl-5-ethyl-1,3-diazinane-2,4,6-trione



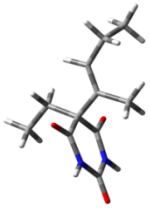
AMOBARBITAL
5-Ethyl-5-(3-methylbutyl)-1,3-diazinane-2,4,6-trione



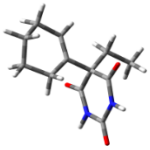
PROBARBITAL
5-Ethyl-5-propan-2-yl-1,3-diazinane-2,4,6-trione



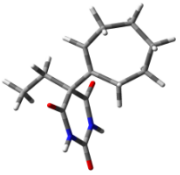
HEXETHAL
5-Ethyl-5-hexyl-1,3-diazinane-2,4,6-trione



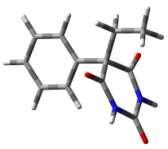
VINBARBITAL
5-Ethyl-5-[(E)-pent-2-en-2-yl]-1,3-diazinane-2,4,6-trione



CYCLOBARBITAL
5-(Cyclohexen-1-yl)-5-ethyl-1,3-diazinane-2,4,6-trione



HEPTABARBITAL
5-(Cyclohepten-1-yl)-5-ethyl-1,3-diazinane-2,4,6-trione



PHENOBARBITAL
5-Ethyl-5-phenyl-1,3-diazinane-2,4,6-trione

Figure 1: The chemical structures and IUPAC names of studied barbiturates

2. Materials and Methods

DFT calculations of the barbiturate derivatives were performed by using Gaussian 09 software package [27]. Also, 3D frontier molecular orbital diagrams were visualized by means of GaussView 5 molecular visualization software [28]. Geometry optimizations of all molecules were completed in vacuum and also in water (ε = 78.36) and n-octanol (ε = 9.863) media by using Becke, three-parameter, Lee-Yang-Parr (B3LYP) method and 6-311++G (d, p) basis set [29, 30]. The effect of the medium dielectric constant was examined by means of self-consistent reaction field (SCRF) theory calculations using the **I**ntegral **E**quation **F**ormalism **P**olarizable **C**ontinuum **M**odel (IEFPCM) for water and n-octanol phases [31-34]. The Gibbs free solvation energies of the studied molecules were calculated with the data obtained from IEFPCM calculation outputs.

As known, in accordance with Koopmans theorem [35], the ionization energy (I) and electron affinity (A) can be described via HOMO and LUMO orbital energies [36, 37] as follows (Eqn.(1) and Eqn. (2)) :

$$I = -E_{HOMO} \tag{1}$$

$$A = -E_{LUMO} \tag{2}$$

In addition, this study includes the calculation of theoretical physicochemical parameters like energy gap (ΔE), chemical softness (S), chemical hardness (η), electronegativity (χ), elec33trophilicity index (ω) and chemical potential (μ). Computational chemists make extensive use of the quantum chemical descriptors proposed by Parr and co-workers [38-42] to predict the chemical behavior of a particular molecule. The relevant formulas are given below (Eqn. (3)-(7)):

$$\mu = \frac{E_{HOMO} + E_{LUMO}}{2} \tag{3}$$

$$\chi = \frac{I+A}{2} \tag{4}$$

$$\eta = \frac{I-A}{2} \tag{5}$$

$$S = \frac{1}{2\eta} \tag{6}$$

$$\omega = \frac{\mu^2}{2\eta} \tag{7}$$

3. Results and Discussion

3.1. Partition coefficient calculations of barbiturates

Thermochemistry is as relevant to solution chemistry as it is for molecules and reactions in the gas phase. An often-desired quantity is the free energy, which can be used to compute the solvation energy of a molecule: the energy going from the gas phase to solution. To get an idea about the relative solubility of a solute in different environment, free energy of solvation can be computed for the same solute with different solvents [43]. In this study, Gibbs free energies of solvation for barbiturates were calculated in water and n-octanol phases by using IEFPCM solvent model mentioned in Materials and Methods section in order to predict logP. The theoretical logP partition coefficient can be estimated according to formula given below (Eqn. (8)) [44].

$$\boldsymbol{LogP_{ow}} = \frac{\Delta G_{water} - \Delta G_{n-octanol}}{2.303RT} \quad (8)$$

In Formula, R and T are the gas constant and temperature, respectively. ΔG_{water} and $\Delta G_{n\text{-}octanol}$ are the free energy differences of compounds in solvent and in gas phase. Results of calculations for solvation free energy and theoretical $LogP_{ow}$ values are shown in Table 1.

Table 1: Solvation free energy and $logP_{ow}$ values of studied barbiturates

	ΔG_{solv} (kcal/mol)			**$LogP_{ow(lit)}$**				
	Water (ε=78.39)	Octanol (ε=9.863)	$LogP_{ow}$ (calc.)	Ref. [10]	Ref. [21]	Ref. [8]	Ref. [24]	
Barbital	9.35	8.09	0.92	0.65	0.65	0.68	0.65	0.72
Butethal	9.28	7.94	0.98	1.65	1.89	1.65	1.70	1.78
Butabarbital	8.88	7.61	0.93	1.45	1.69	1.56	1.69	1.66
Amobarbital	9.29	7.97	0.97	1.95	2.07	2.07	2.09	2.19
Probarbital	9.68	8.27	1.04	0.95	-	-	0.95	1.13
Hexethal	9.95	6.73	2.36	2.65	-	-	3.08	2.84
Vinbarbital	10.02	8.44	1.15	-	1.65	-	1.95	1,95
Cyclobarbital	9.73	8.43	0.96	1.20	-	-	1.20	1.24
Heptabarbital	9.88	8.50	1.01	-	-	-	2.03	1.77
Phenobarbital	10.68	9.23	1.06	1.42	1.42	1.42	1.41	1.39

When the values given in the literature are compared with the $logP_{ow}$ values calculated at the 6-311++G (d,p) level of theory, the graph in Fig. 2 appears. Figure 2 shows the relationship between the calculated $logP_{ow}$ values and the values given in different sources. It is understood from these results that the DFT/B3LYP/6-311 ++ G (d, p) theoretical computational method has the power to predict the partition coefficients of the mentioned barbiturates with a ratio of over 50%. Additionally, method performance analysis has been conducted to investigate the compatibility of the DFT/B3LYP/6-311++G (d, p) method with different literatures. Root mean square errors (RMSE), mean square errors (MSE), mean absolute deviations (MAD), and mean absolute percentage errors (MAPE) were calculated [45]. Error analysis results of DFT method used for $logP_{calc.}$ are shown in Table 2. The closer RMSE, MSE, MAD results are to zero, the better the predictive power of the method. Also, the smaller MAPE means the better forecast. Therefore, it can be concluded that the DFT/B3LYP/6-311++G (d, p) method used in this study provides reasonable results in estimating the partition coefficient of the mentioned ten barbiturate derivatives.

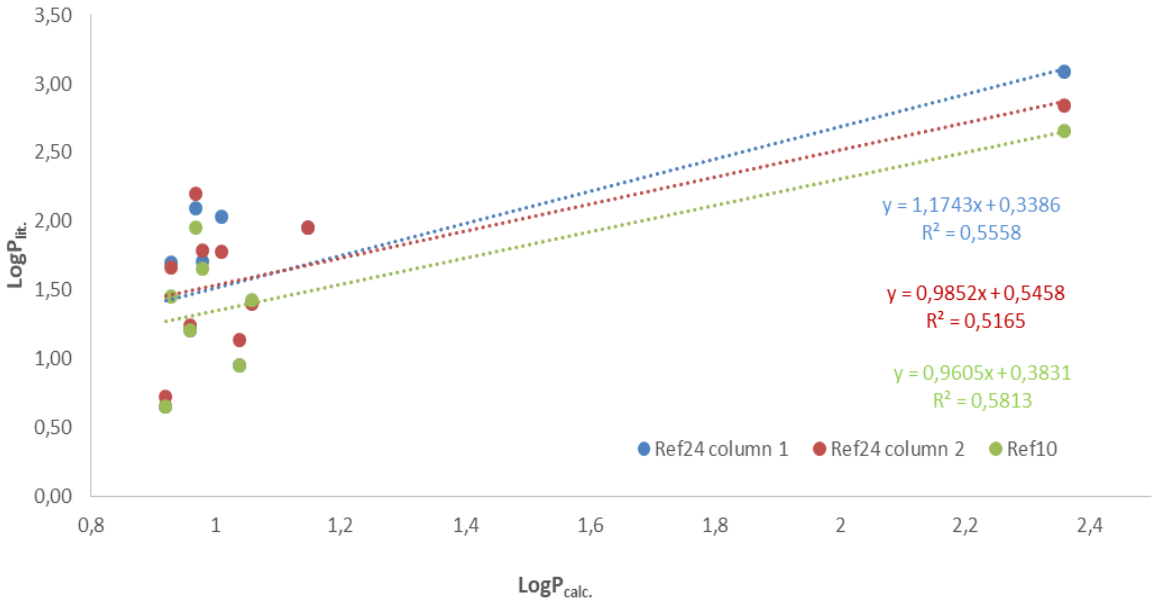


Figure 2: Linear correlations of $logP_{calc.}$ and $logP_{lit.}$ values

Table 2: Error analysis of DFT method used for prediction of $logP_{calc.}$

	RMSE	MSE	MAD	MAPE
Ref. [10]	0.50	0.25	0.43	29.2
Ref. [24] Column 1	0.69	0.48	0.61	35.1
Ref. [24] Column 2	0.66	0.43	0.57	32.8

3.2. HOMO-LUMO analysis of barbiturates

As it is already well known, HOMO and LUMO energy levels are very important in molecular reactivity. EHOMO and ELUMO can describe the hydrogen bond basicity and hydrogen bond acidity of a molecule respectively [46]. Therefore, in this study, frontier molecular orbital energy levels and energy gaps (ΔE) were calculated for barbiturates to investigate the chemical reactivity behaviors. Some physicochemical properties such as Chemical Hardness (η), Softness (S), Electronegativity (χ), Chemical Potential (μ) and Electrophilicity index (ω) were also calculated with the same level of theory. We also carried out calculations in two different solvent media by using IEFPCM solvent model which is the most widely used one to evaluate the solvent effect [34]. The calculated results are listed in Table 3 and Table 4. Figure 3 represents the ΔE values of barbiturates according to changing dielectric media. No sharp increases or decreases in energy gap values were observed on going from gas phase to solvent phase. However, a decrease was observed in ΔE values of barbiturates containing cyclic and unsaturated substituents compared to others. The high energy gap value indicates good stability and low reactivity. The 3D diagrams for HOMO-LUMO energy levels of studied barbiturates are given in Fig. 4. According to Figure 4, while the LUMO locations do not change, it is observed that the HOMO locations change in barbiturates containing cyclic and unsaturated substituents.

Table 3: EHOMO, ELUMO and Energy gap (ΔE=ELUMO-EHOMO) results for studied barbiturates at different dielectric media (in eV)

	Gas			**Water (ε=78.39)**			**Octanol (ε=9.863)**		
	E_{HOMO}	E_{LUMO}	ΔE	E_{HOMO}	E_{LUMO}	ΔE	E_{HOMO}	E_{LUMO}	ΔE
Barbital	-7.735	-1.729	6.005	-7.740	-1.698	6.041	-7.739	-1.706	6.033
Butethal	-7.719	-1.707	6.011	-7.735	-1.690	6.045	-7.734	-1.696	6.037
Butabarbital	-7.683	-1.775	5.907	-7.697	-1.763	5.933	-7.696	-1.769	5.926
Amobarbital	-7.716	-1.703	6.013	-7.734	-1.687	6.046	-7.731	-1.692	6.039
Probarbital	-7.704	-1.707	5.997	-7.728	-1.699	6.029	-7.727	-1.704	6.022
Hexethal	-7.701	-1.792	5.912	-7.713	-1.764	5.948	-7.711	-1.771	5.940
Vinbarbital	-7.072	-1.681	5.391	-7.026	-1.757	5.268	-7.014	-1.746	5.267
Cyclobarbital	-7.008	-1.667	5.340	-6.962	-1.754	5.207	-6.948	-1.742	5.206
Heptabarbital	-6.932	-1.669	5.263	-6.892	-1.750	5.141	-6.880	-1.738	5.141
Phenobarbital	-7.280	-1.759	5.521	-7.271	-1.820	5.451	-7.255	-1.810	5.445

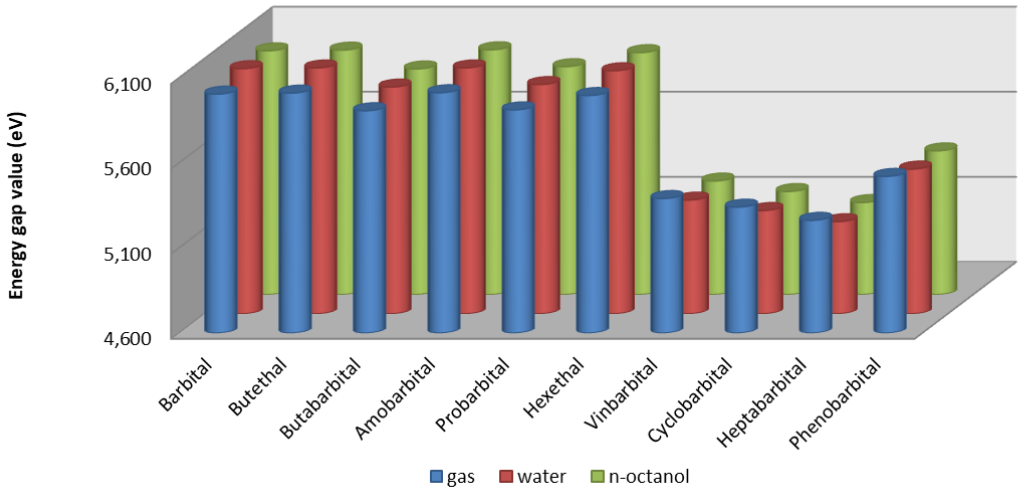


Figure 3: ΔE values of barbiturates according to changing dielectric media

Table 4: Calculated quantum chemical descriptors of studied barbiturates

	Compound	Chemical Hardness (η) (eV)	Softness (S) (eV^{-1})	Chemical Potantial (μ) (eV)	Electronegativity (χ) (eV)	Electrophilicity index (ω) (eV)
gas	Barbital	3.00265	0.16652	-4.73247	4.73247	3.72942
	Butethal	3.00564	0.16635	-4.71342	4.71342	3.69577
	Butabarbital	2.95380	0.16927	-4.72934	4.72934	3.78608
	Amobarbital	3.00673	0.16629	-4.71016	4.71016	3.68932
	Probarbital	2.99870	0.16674	-4.70622	4.70622	3.69302
	Hexethal	2.95639	0.16913	-4.74853	4.74853	3.81352
	Vinbarbital	2.69570	0.18548	-4.37709	4.37709	3.55361
	Cyclobarbital	2.67025	0.18725	-4.33804	4.33804	3.52375
	Heptabarbital	2.63162	0.19000	-4.30077	4.30077	3.51430
	Phenobarbital	2.76074	0.18111	-4.51995	4.51995	3.70008
water	Barbital	3.02088	0.16551	-4.71968	4.71968	3.68690
	Butethal	3.02292	0.16540	-4.71301	4.71301	3.67401
	Butabarbital	2.96672	0.16854	-4.73056	4.73056	3.77154
	Amobarbital	3.02319	0.16539	-4.71111	4.71111	3.67072
	Probarbital	3.01475	0.16585	-4.71410	4.71410	3.68567
	Hexethal	2.97421	0.16811	-4.73914	4.73914	3.77570
	Vinbarbital	2.63447	0.18979	-4.39233	4.39233	3.66156
	Cyclobarbital	2.60373	0.19203	-4.35832	4.35832	3.64764
	Heptabarbital	2.57094	0.19448	-4.32172	4.32172	3.63238
	Phenobarbital	2.72563	0.18344	-4.54580	4.54580	3.79074
n-octanol	Barbital	3.01666	0.16575	-4.72281	4.72281	3.69696
	Butethal	3.01870	0.16563	-4.71533	4.71533	3.68277
	Butabarbital	2.96346	0.16872	-4.73274	4.73274	3.77917
	Amobarbital	3.01979	0.16557	-4.71179	4.71179	3.67591
	Probarbital	3.01135	0.16604	-4.71587	4.71587	3.69260
	Hexethal	2.97013	0.16834	-4.74186	4.74186	3.78523
	Vinbarbital	2.63379	0.18984	-4.38049	4.38049	3.64279
	Cyclobarbital	2.60304	0.19208	-4.34539	4.34539	3.62699
	Heptabarbital	2.57066	0.19450	-4.30947	4.30947	3.61221
	Phenobarbital	2.72264	0.18365	-4.53301	4.53301	3.77357

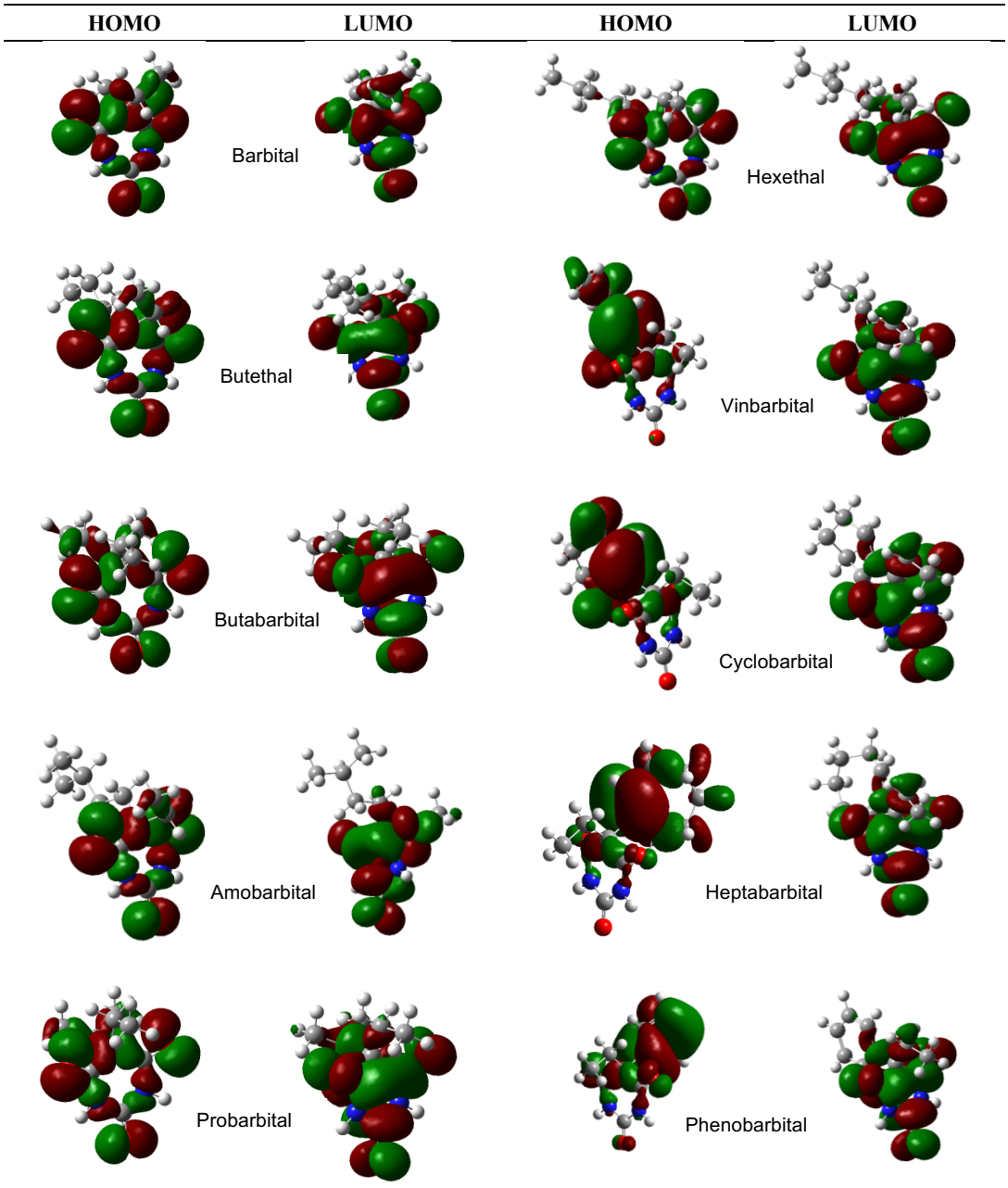


Figure 4: Frontier molecular orbital diagrams of studied barbiturates

It is pretty much practical to use computational methods including solvent models to determine the hydrophilic and lipophilic properties of drug candidates and to get an insight about correlations between computed descriptors and partition coefficients. Some studies reported the correlations between $\log P_{ow}$ and theoretically calculated descriptors such as EHOMO, ELUMO, molecular polarizability (α), molecular volume (V_m), Electrophilicity index (ω) in order to analyze the relationship between physicochemical properties and molecular structure [47-49]. It is mentioned in these publications that the value of logP is inversely proportional to EHOMO and

ELUMO because of their roles in formation of hydrogen bond and directly proportional to molecular volume and electrophilicity index. In the light of this information, if we evaluate the relationship between $logP_{ow}$ values and computed descriptors, the ranking should be as follows:

	Straight-chain barbiturates	Branched-chain barbiturates	Cyclic and unsaturated side chain barbiturates
Considering EHOMO	Barb>Bute>Hex	Amo>Pro>Buta	Phen>Vin>Cyclo>Hepta
Considering ELUMO	Hex>Barb>Bute	Buta>Pro>Amo	Phen>Vin>Cyclo>Hepta
Considering Vm	Hex>Bute>Barb	Amo>Buta>Pro	Hepta>Cyclo>Vin>Phen
Considering ω	Hex>Barb>Bute	Buta>Pro>Amo	Phen>Vin>Cyclo>Hepta

Barb: Barbital, Bute: Butethal, Hex: Hexethal, Amo: Amobarbital, Pro: Probarbital, Buta: Butabarbital, Phen: Phenobarbital, Vin: Vinbarbital, Cyclo: Cyclobarbital, Hepta: Heptabarbital

When looking at this ranking, it can be seen that ELUMO, V_m, and ω descriptors give reasonable results rather than EHOMO. The robustness, reliability and validity of the property predictive power of a QSPR model vary depending on the compatibility of computed molecular descriptors.

Many sources of molecular descriptors can be found through quantum chemical calculations. Meanwhile, other lipophilicity descriptors Molecular Lipophilicity Potential (MLP) and Polar Surface Area (PSA) were calculated by using molinspiration cheminformatics software. The maps of MLP were visualized in Molinspiration Galaxy 3D Structure Generator v2018.01 beta [50, 51].

The map of Molecular Lipophilicity Potential defines qualitatively the 3D distribution of lipophilicity of a molecule on molecular surface. Polar surface area is characterized as the surface area ($Å^2$) of O- and N-centered polar fragments and hydrogens bonded to them in a molecule and it is mightily related to hydrogen bonding capacity and polarity. It has been stated that for a molecule to penetrate the brain, the polar surface area must be around 90 $Å^2$ at most [52]. The barbiturates mentioned in this study are structurally similar, they all contain the same number of Hydrogen Binding Donor and Hydrogen Binding Acceptor sites, because of this the calculated PSA values (75.27 $Å^2$) are the same for studied barbiturates. Therefore, the lipophilic character of the substituents attached at the position 5 has a major influence on the $LogP_{ow}$ value.

Figure 5 represents maps of MLP and calculated molecular volume values for ten barbiturate derivatives. When Fig. 5 is examined, it is clearly seen which surfaces of the

barbiturate derivatives are lipophilic and which are hydrophilic. The most lipophilic surfaces are coded by violet and blue, the intermediate lipophilic surfaces are coded by green, and finally the hydrophilic surfaces are coded by orange and red. This situation demonstrated the effect of the structural properties of the substituents on lipid solubility of barbiturates.

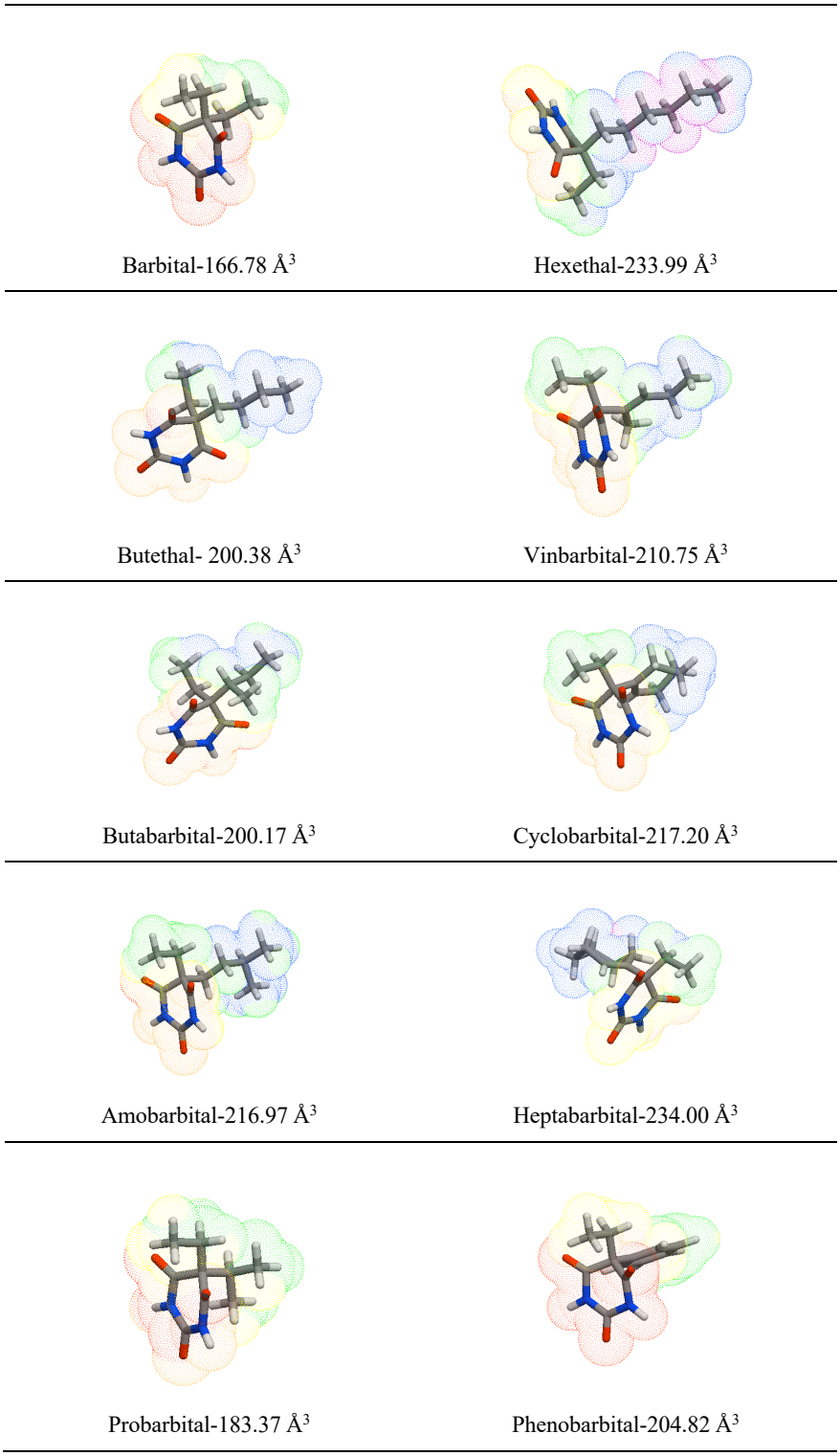


Figure 5: Maps of MLP and calculated molecular volume values for ten barbiturate derivatives

4. Conclusion

Partition coefficient estimations of ten barbituric acid derivatives containing straight, branched, cyclic or unsaturated side chain at C-5 position have been performed by using DFT/B3LYP method and 6-311++G(d,p) basis set. The correlation between the calculated values and the values given in the literature was examined. According to the scatter diagram obtained as a result of the linear correlation study, it was determined that the theoretical method used could predict the partition coefficients of barbiturate derivatives with a ratio of over 50%. Method performance analysis has been conducted by calculating RMSE, MSE, MAD, and MAPE to investigate the compatibility of this method in estimation of $LogP_{ow}$. The error analysis results show that DFT/B3LYP/6-311++G (d, p) method has a predictive capability for mentioned ten barbiturate derivatives. Additionally, HOMO-LUMO evaluation and calculations of quantum chemical descriptors such as Chemical Hardness (η), Softness (s), Electronegativity (χ), Chemical Potential (μ) and Electrophilicity index (ω) have been carried out with the same level of theory for not only gas phase but also water and n-octanol phases. It has been observed that there is no notable change in the energy gap values, which help to characterize chemical reactivity and kinetic stability, when passing from the gas phase to the solvent phase. According to 3D HOMO-LUMO diagrams of studied barbiturates, while the LUMO locations do not change, the HOMO locations change in barbiturates containing cyclic and unsaturated substituents.

Besides, the relationships between $logP_{ow}$ and computed descriptors EHOMO, ELUMO, V_m and ω have been presented. ELUMO, V_m, and ω descriptors gave reasonable results rather than EHOMO. Last, it is clear that the maps of Molecular Lipophilicity Potential (MLP) visualized in Molinspiration Galaxy 3D Structure Generator v2018.01 beta are consistent with the results. According to the MLP map, it was seen that the most lipophilic regions coded with blue and violet colors were more intense in the Hexethal derivative with the highest partition coefficient. Hence, the usage of computational methods may offer an influential strategy in order to derive novel descriptors that may assist to determine lipophilicity in drug design studies.

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