

Design of New Anilines with Predicted Values of Their Octanol/Water Partition Coefficients

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Abstract

In our previous work, we established a predictive QSPR (Quantitative Structure-Property Relationship) model for the octanol/water partition coefficient based on ionization energy (IE), electronic energy (E_T), and dipole moment (μ). This model has been shown to be suitable for predicting the properties of new anilines falling within its applicability domain, with a 95% confidence level. The present study, which builds upon that earlier work, aims to expand the dataset for this family of compounds by designing new anilines that fit the model's applicability domain and predicting their octanol/water partition coefficients. In this context, we designed a series of thirty-three (33) new anilines. All these molecules were optimized at the B3LYP/6-311G (d, p) level of theory, and vibrational frequencies were calculated at the same level. The calculated octanol/water partition coefficients for these molecules indicate that they are all lipophilic. The formation reaction for these new compounds proceeds spontaneously, accompanied by heat release and a decrease in disorder.

Keywords

Design, Aniline, QSPR Model, Octanol/Water Partition Coefficient, Standard Thermodynamic Quantity of Formation

1. Introduction

Humanity has made significant progress in numerous fields, such as agriculture, electronics, the pharmaceutical industry, and many other sectors. Chemical products play a vital role in industrial development. In general, the applications of any material depend on its characteristics and properties [1]. Aniline (aminobenzene)

is one of the most important substances used across many industrial sectors. Due to the diversity of its applications, it has attracted the interest of many researchers. It plays a major role in multiple industrial fields, particularly in the manufacture of rubber and engine components. It is a fundamental industrial chemical, with interest in it growing following its use as an intermediate in the synthesis of numerous chemical compounds. Aniline significantly influences everyday products; notably, it is a component of many medicines. A prime example is paracetamol, a widely used drug that represents considerable production value on the market [1]. Aniline is a simple, well-known molecule; its octanol/water partition coefficient has been studied as a reference parameter or intermediate in broader research within toxicology, medicinal chemistry, and materials science (such as polyaniline). Understanding aniline's lipophilicity is essential for predicting its toxicity, its ability to cross biological membranes (such as skin or cell membranes), and its environmental behavior (biodegradation and accumulation in soil). In this context, it is necessary to predict the lipophilicity of its derivatives prior to their synthesis. The general objective of this work is to utilize the QSPR (Quantitative Structure-Property Relationship) model for predicting the octanol/water partition coefficient that was developed in our previous research [2]. In fact, the aim is clearly to design a series of new aniline analogues falling within the model's applicability domain and to predict their octanol/water partition coefficients using the QSPR model developed to expand the database.

2. Material and Methods

2.1. Material

2.1.1. Reference Molecule Structure

The new molecules were designed by substituting hydrogen atoms on the aniline molecule (the reference or parent molecule, sourced from the experimental database) with alkyl groups [2]. The two-dimensional structure of aniline is as follows (Figure 1):

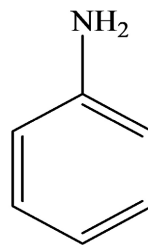


Figure 1. 2D structure of aniline.

2.1.2. Software and Level of Theory Used

GaussView 5.0 [3] software was used to represent the 3D structure and visualize the molecules under study. Subsequently, Gaussian 09 [4] software was used for geometry optimization and frequency calculations at a temperature of 298.15 K and a pressure of 1 atmosphere in the gas phase. The level of theory used to

calculate the various molecular descriptors was B3LYP/6-311G (d, p). The 2D structures were generated using ChemSketch [5].

2.2. Methods

2.2.1. Domain of Applicability of a Model

A QSPR/QSAR (Quantitative Structure-Property Relationship/Quantitative Structure-Activity Relationship) model cannot be considered universal, as it is developed using a limited number of compounds that do not cover the entire chemical space. Consequently, the predicted property or activity of a compound that is chemically dissimilar to the training set cannot automatically be considered reliable [6] [7]. The applicability domain (AD) defines the region within which a compound's properties can be predicted with confidence. The AD thus corresponds to the area of chemical space encompassing the training set compounds and similar compounds located nearby in that same space [8]. Several methods exist for determining the AD of a QSPR/QSAR model; among these is the fragment-based method [8]. This method assesses whether a molecule falls within a model's AD based on the presence of specific fragments. If a new molecule contains novel fragments, it is deemed to lie outside the model's AD. Conversely, if the new molecule presents no novel fragments, it is considered to be within the AD, and the prediction is regarded as reliable. The fragment-based method is employed in this study because it is well-suited to our simple molecules, unlike complex ones.

2.2.2. QSPR Model Used to Predict the Octanol/Water Partition Coefficient of New Anilines

The QSPR model used for the design of the new anilines derivatives was developed in our previous work [2]. The equation for this model is presented below, along with some statistical and validation parameters:

$$\text{Log } P_{\text{theo}} = 5.4544 - 1.8954 IE - 0.0105 E_T + 0.3945 \mu \quad (1)$$

with the ionization energy (IE) expressed in electron-volts (eV), the electronic energy (E_T) expressed in expressed in atomic units (a.u.) or Hartrees (Ha), and the dipole moment (μ) expressed in Debyes (D).

$$\begin{aligned} n &= 17; R = 0.9747; R^2 = 0.9501; R_{\text{adjusted}}^2 = 0.9348; s = 0.2000; F = 82.5446; \\ \alpha &= 95\%; Q_{\text{LOO}}^2 = 0.9149; \overline{r_m^2(\text{LOO})} = 0.6651; \Delta r_m^2(\text{LOO}) = 0.0000; \\ R_{\text{ext}}^2 &= 0.9637; Q_{\text{ext}}^2 = 0.9825; \overline{r_m^2(\text{test})} = 0.9013; \Delta r_m^2(\text{test}) = 0.0787 \end{aligned}$$

2.2.3. Standard Thermodynamic Quantities of Formation

Quantum chemical calculations and the use of experimental data in the form of reference thermodynamic tables [9] allow for the determination of the standard values of the enthalpy of formation ($\Delta_f H^0$), entropy of formation ($\Delta_f S^0$), and Gibbs free energy of formation ($\Delta_f G^0$) for the molecular system at 298.15 K and 1 atm pressure in the gas phase. The enthalpy of formation of a molecular system is calculated using the relationship proposed by J. W. Ochterski [10]:

$$\Delta_f H^0(M, 298 \text{ K}) = \Delta_f H^0(M, 0 \text{ K}) + (H_M^o(298 \text{ K}) - H_M^o(0 \text{ K})) - \sum_{\text{Atoms}} (H_X^o(298 \text{ K}) - H_X^o(0 \text{ K})) \quad (2)$$

where the last two terms of this relation are referred to as the enthalpic correction (or increment) for the molecule and the atoms, respectively. For elemental substances, this corresponds to the heat involved in heating the atoms from 0 K to 298 K. These values are obtained experimentally relative to the standard state of the elements. As for the term $\Delta_f H^0(M, 0 \text{ K})$, it is determined using the following relation:

$$\Delta_f H^0(M, 0 \text{ K}) = \sum_{\text{Atoms}} x \Delta_f H^0(X, 0 \text{ K}) - \sum D_0(M) \quad (3)$$

x defines the number of atoms of species X in molecule M .

$\Delta_f H^0(X, 0 \text{ K})$ is an experimental value corresponding to the heat of formation of atom X at 0 K. The final term, $\sum D_0(M)$, corresponds to the atomization energy of molecule M . This energy arises from the decomposition of one mole of the molecule into its constituent atoms. The calculation of $\sum D_0(M)$ is performed using the electronic energies (ϵ) of the constituent atoms and the molecule, as well as the internal energy at 0 K known as the Zero-Point Energy (ZPE) of the latter, according to the relation below:

$$\sum D_0(M) = \sum_{\text{Atoms}} x \epsilon_0(X) - [\epsilon_0(M) + \epsilon_{\text{ZPE}}(M)] \quad (4)$$

The entropy of formation at 298 K, $\Delta_f S^0(298 \text{ K})$, is determined using atomic entropy values ($S^0(X, 298 \text{ K})$) from the JANAF Thermochemical Tables [9] and the molecular entropy obtained via quantum mechanical calculation. The relationship proposed by J. W. Ochterski [10] for determining the entropy of formation of a molecular system is:

$$\Delta_f S^0(298 \text{ K}) = S^0(M, 298 \text{ K}) - \sum x S^0(X, 298 \text{ K}) \quad (5)$$

where $S^0(M, 298 \text{ K}) = \frac{H_{\text{corr}} - G_{\text{corr}}}{T}$ is the standard absolute entropy.

Knowing the enthalpy of formation and the entropy of formation, the standard Gibbs free energy of formation is easily calculated using the relationship:

$$\Delta_f G^0(298 \text{ K}) = \Delta_f H^0(298 \text{ K}) - T \Delta_f S^0(298 \text{ K}) \quad (6)$$

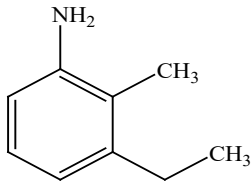
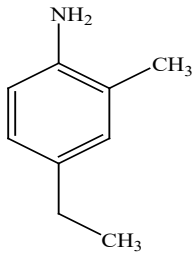
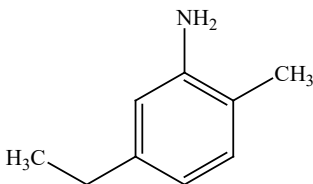
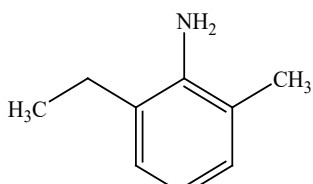
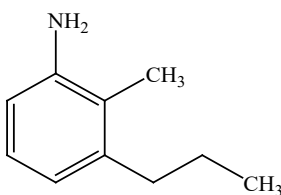
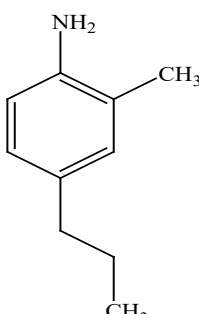
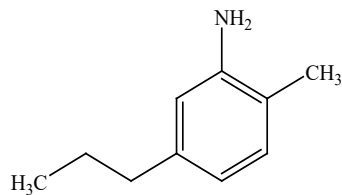
with $T = 298.15 \text{ K}$.

3. Results and Discussion

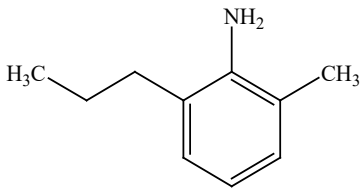
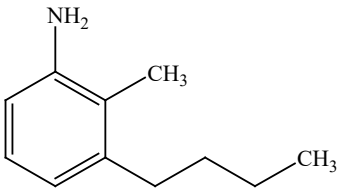
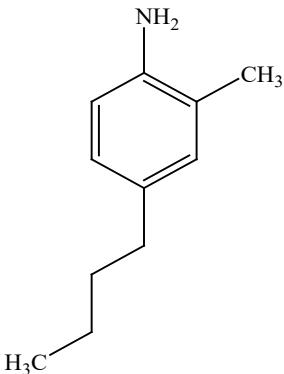
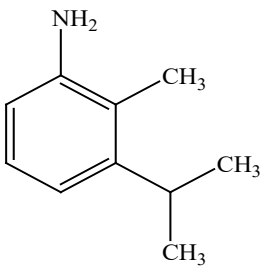
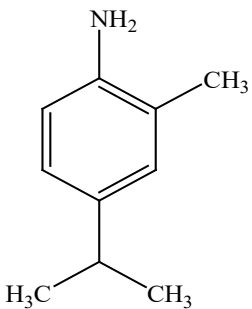
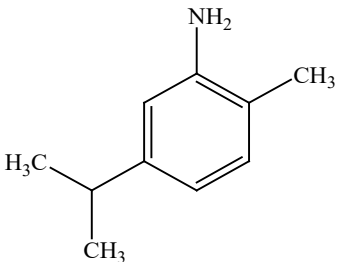
3.1. Design of Novel Aniline-Based Compounds

A series of thirty-three (33) molecules was designed by substituting hydrogen atoms of aniline (the parent molecule) with alkyl groups. The molecules were designated AN- i ($1 \leq i \leq 33$). The developed QSPR model was used to predict the octanol/water partition coefficient for this series. The 2D structures, molecular descriptor values, and theoretical octanol/water partition coefficient values are summarized in **Table 1**.

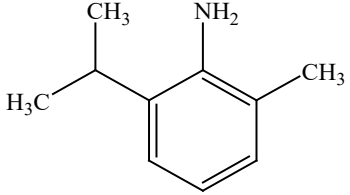
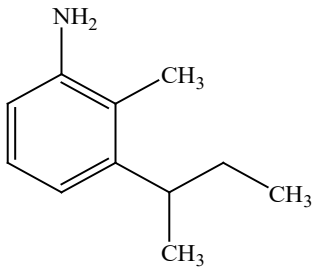
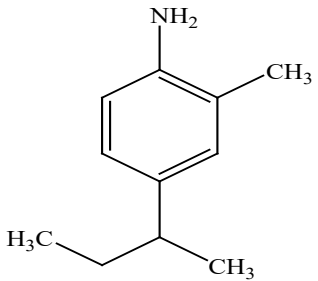
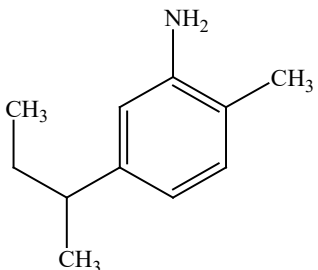
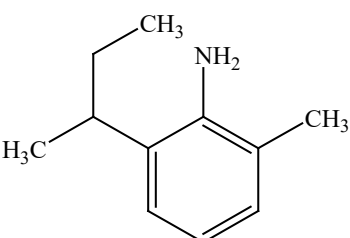
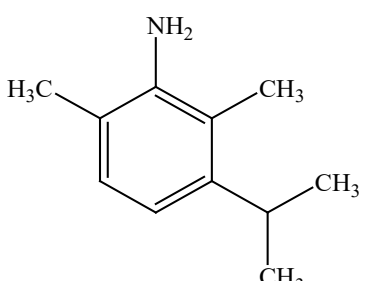
Table 1. 2D structures of the designed molecules, molecular descriptor values, and theoretical octanol/water partition coefficient values obtained using the QSPR model.

Compound	2D structure	<i>IE</i> (eV)	<i>E_T</i> (u.a.)	μ (D)	$\text{Log}P_{\text{theo}}$
AN_1		4.2835	-405.6567	1.6054	2.23
AN_2		4.2141	-405.6598	1.5990	2.36
AN_3		4.2755	-405.6605	1.6079	2.24
AN_4		4.2468	-405.6581	1.8052	2.38
AN_5		4.2763	-444.9792	1.5376	2.63
AN_6		4.2091	-444.9843	1.5732	2.77
AN_7		4.2712	-444.9850	1.5664	2.65

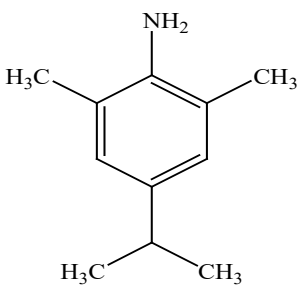
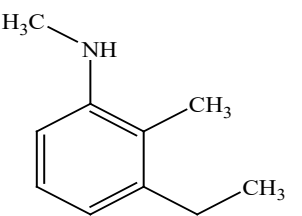
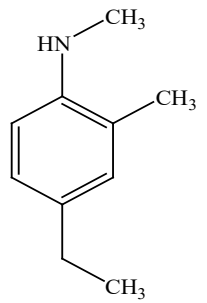
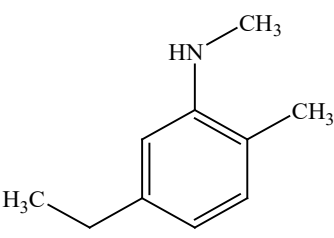
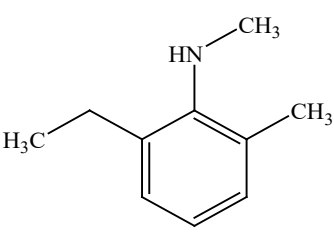
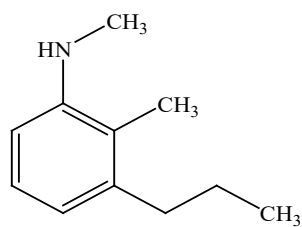
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AN_8		4.2436	-444.9821	1.7273	2.76
AN_9		4.2750	-484.3034	1.5699	3.06
AN_10		4.2059	-484.3084	1.5696	3.19
AN_11		4.2899	-444.9782	1.6359	2.64
AN_12		4.2175	-444.9833	1.6297	2.78
AN_13		4.2663	-444.984	1.6670	2.70

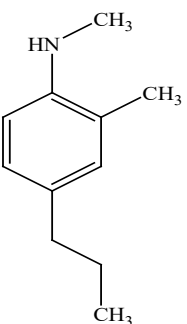
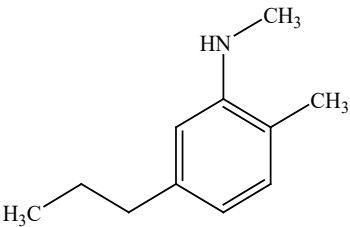
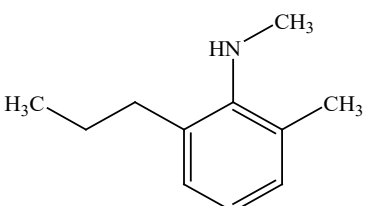
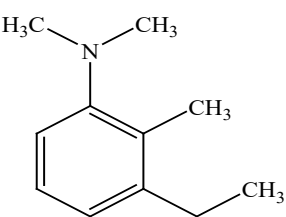
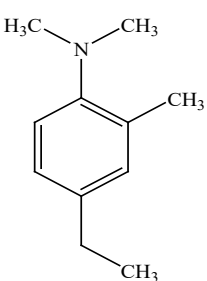
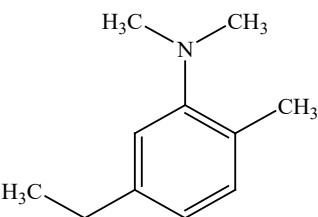
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AN_14		4.2727	-444.9811	1.7300	2.71
AN_15		4.2916	-484.3016	1.6309	3.05
AN_16		4.2228	-484.3071	1.6807	3.20
AN_17		4.2725	-484.3077	1.6608	3.10
AN_18		4.2668	-484.3038	1.6640	3.11
AN_19		4.2120	-484.3052	1.6905	3.22

Continued

AN_20		4.1592	-484.3103	1.6936	3.32
AN_21		4.4802	-444.9665	0.9547	2.01
AN_22		4.3898	-444.9694	0.9662	2.19
AN_23		4.1259	-444.9753	1.7789	3.01
AN_24		4.4622	-444.9658	1.3539	2.20
AN_25		4.1312	-484.2958	1.7410	3.40

Continued

AN_26		4.0690	-484.2992	1.7488	3.52
AN_27		4.1371	-484.2989	1.8597	3.43
AN_28		4.4630	-484.2900	1.2892	2.59
AN_29		4.3107	-484.2742	0.7854	2.68
AN_30		4.3310	-484.2781	0.6134	2.57
AN_31		4.3391	-484.2782	0.4777	2.50

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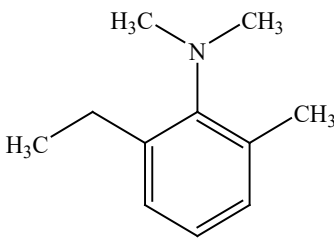
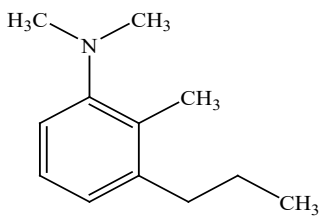
AN_32		4.3665	-484.2750	0.8021	2.58
AN_33		4.3752	-523.5974	0.9235	3.02

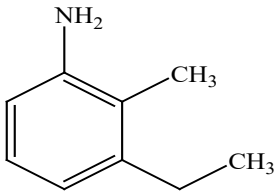
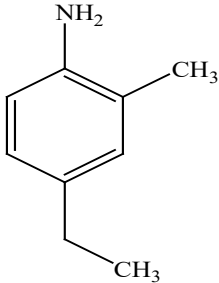
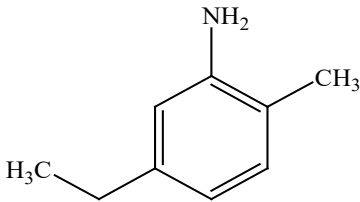
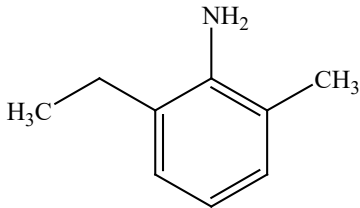
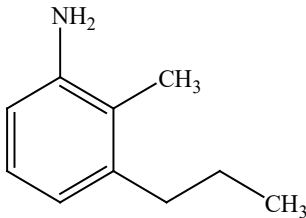
Table 1 shows variations in each determined parameter from one molecule to another. The data indicate that the octanol/water partition coefficient values are all positive, revealing that the designed molecules are lipophilic (hydrophobic). Consequently, these compounds are soluble in fatty substances but insoluble in polar solvents such as water. This lipophilic nature stems from the substitution of hydrogen atoms on the aromatic ring or nitrogen atom with alkyl groups, which are lipophilic moieties. Molecules with a LogP value between 0 and 3 are moderately lipophilic, whereas those with a LogP greater than 3 are highly lipophilic. Furthermore, the hydrophobicity of the molecules increases with the length of the substituent's carbon chain. For instance, a compound with a methyl group ($-\text{CH}_3$) on the ring is less lipophilic than one with an ethyl group ($-\text{C}_2\text{H}_5$); similarly, a compound with an ethyl group is less lipophilic than one with a propyl group ($-\text{C}_3\text{H}_7$). Positional isomers exhibit virtually identical octanol/water partition coefficient values, implying they possess essentially the same degree of hydrophobicity. Generally, for a given total number of carbon atoms, a molecule with a branched alkyl group (e.g., isopropyl) shows a slightly lower lipophilicity parameter than one with a linear chain (e.g., propyl) due to differences in steric hindrance. Overall, the hydrophobicity of the molecules varies with the dipole moment. Indeed, as the dipole moment increases, hydrophobic character increases. Conversely, a decrease in hydrophobic character is observed when the dipole moment decreases. For aniline (the parent molecule), the experimental value of the octanol/water partition coefficient is $0.90 (\pm 0.05)$ [2]. This positive value clearly indicates that aniline is also lipophilic. The lipophilicity of aniline derivatives varies predictably depending on whether the aniline is primary, secondary, or tertiary, as well as on the nature of the substituents attached to the nitrogen atom or the aromatic ring. Overall, lipophilicity increases with the degree of substitution (from primary to tertiary aniline) and with the length or volume of the alkyl

groups. However, ideally, experimental octanol/water partition coefficient values for these new molecules should be obtained.

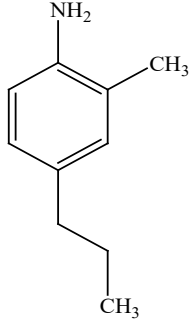
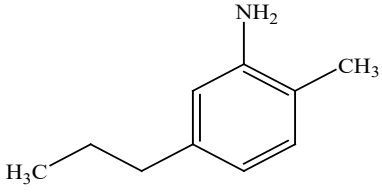
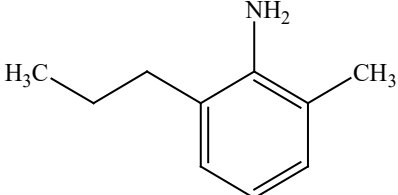
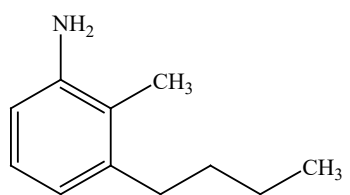
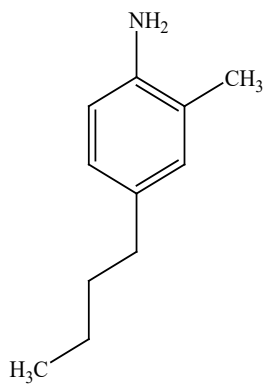
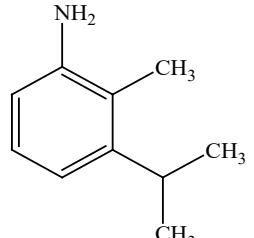
3.2. Standard Thermodynamic Quantities of Formation of the Molecules

The thermodynamic quantities of formation were determined in order to study the thermodynamic stability and characteristics of the formation reactions of the designed molecules.

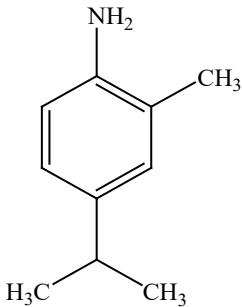
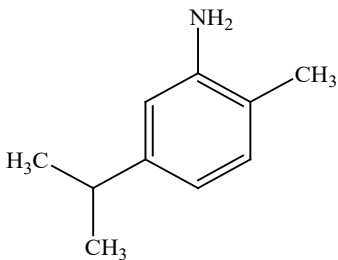
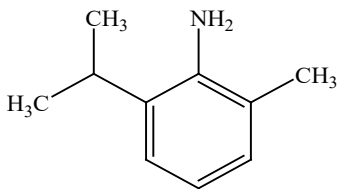
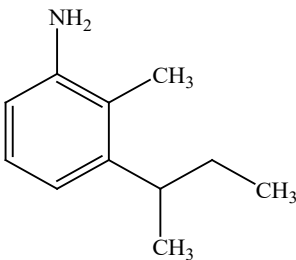
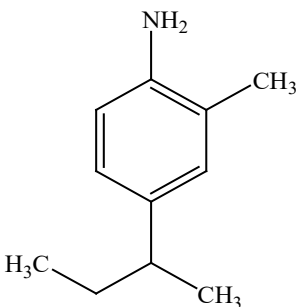
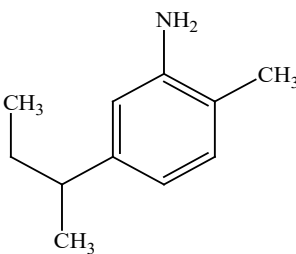
Table 2. Structures of the designed molecules and values of formation quantities (in kcal/mol), except for entropy of formation (in cal/mol.K) ($T = 298.15$ K, $P = 1$ atm, gas phase).

Compound	2D structure	$\Delta_f H_{298}^0$	$\Delta_f S_{298}^0$	$\Delta_f G_{298}^0$
AN_1		-413.8600	-636.6470	-224.0437
AN_2		-415.9772	-634.0562	-226.9334
AN_3		-416.4139	-634.5171	-227.2327
AN_4		-414.7542	-636.9269	-224.8544
AN_5		-456.3109	-720.9608	-241.3565

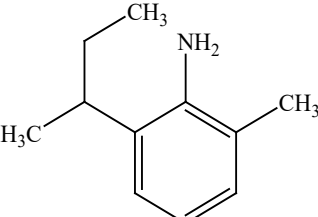
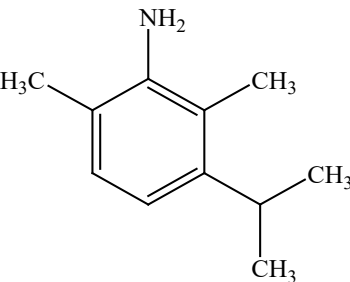
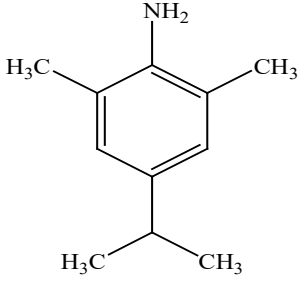
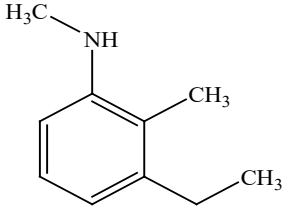
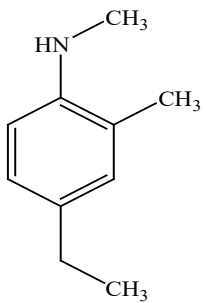
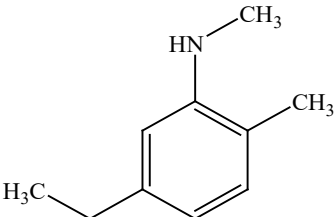
Continued

AN_6		-459.6800 -719.0918 -245.2828
AN_7		-460.1143 -719.6201 -245.5595
AN_8		-458.1244 -722.0426 -242.8474
AN_9		-499.7747 -806.2616 -259.3878
AN_10		-503.0992 -804.3716 -263.2758
AN_11		-455.8792 -721.5816 -240.7396

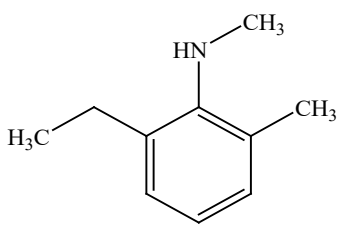
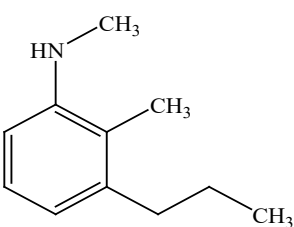
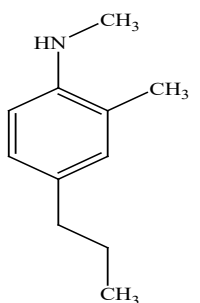
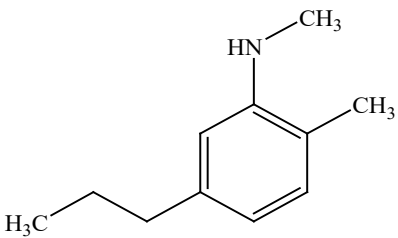
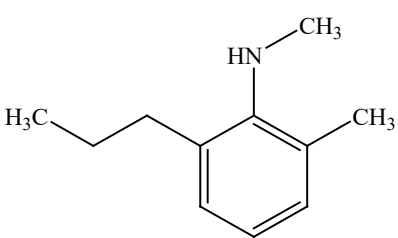
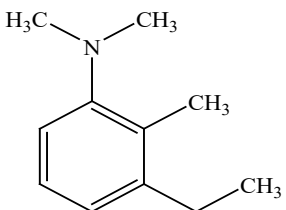
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AN_12		-459.2828 -721.1207 -244.2807
AN_13		-459.7039 -721.2238 -244.6710
AN_14		-457.6833 -723.8799 -241.8585
AN_15		-498.8811 -806.3794 -258.4591
AN_16		-502.5018 -806.2932 -262.1055
AN_17		-502.8689 -806.4426 -262.4281

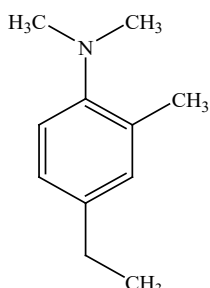
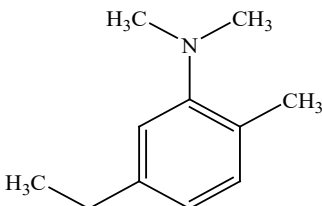
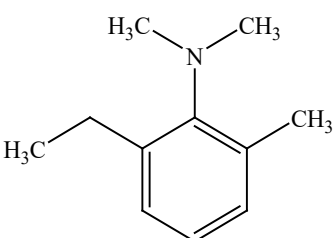
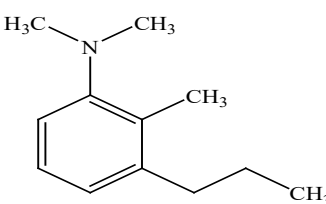
Continued

AN_18		-500.1800 -808.9998 -258.9768
AN_19		-501.4332 -807.5770 -260.6541
AN_20		-504.8186 -806.4573 -264.3733
AN_21		-448.3114 -721.8552 -233.0903
AN_22		-450.3226 -718.7508 -236.0270
AN_23		-454.0613 -720.0831 -239.3685

Continued

AN_24		-447.8835 -720.9376 -232.9359
AN_25		-548.5927 -807.3602 -307.8782
AN_26		-550.8818 -805.4934 -310.7240
AN_27		-550.7118 -805.5270 -310.5439
AN_28		-544.9117 -805.9774 -304.6095
AN_29		-535.7908 -805.9585 -295.4943

Continued

AN_30		-538.3097 -804.5484 -298.4336
AN_31		-538.3668 -803.6223 -298.7668
AN_32		-536.3041 -806.4994 -295.8463
AN_33		-578.7444 -888.6958 -313.7798

Variations in the determined thermodynamic quantities are also observed from one molecule to another. The values for the standard thermodynamic quantities of formation for the new anilines are all negative. Negative values for enthalpy and Gibbs free energy indicate an exothermic reaction and a spontaneous reaction, respectively. A negative entropy value indicates a decrease in disorder. Consequently, the formation of all the new anilines occurs spontaneously, accompanied by heat release and a decrease in disorder, at a temperature of 298.15 K and a pressure of 1 atm in the gas phase (Table 2). The negative value of the Gibbs free energy of formation thus reflects the existence and stability of the newly designed molecules.

4. Conclusion

Regarding this study, which aimed to design new aniline derivatives, a key finding

is that all thirty-three (33) designed molecules exhibit positive octanol/water partition coefficients, indicating that they are lipophilic. Overall, lipophilicity increases with the degree of substitution (from primary to tertiary aniline) and with the length or volume of the alkyl groups. As for the thermodynamic parameters of formation, all values are negative; this indicates that the formation of these new molecules occurs spontaneously, accompanied by heat release and a decrease in disorder. The lipophilicity of the aniline derivatives varies predictably depending on whether the aniline is primary, secondary, or tertiary, as well as on the nature of the substituents attached to the nitrogen atom or the aromatic ring. However, obtaining experimental values would be ideal, as this would allow for the confirmation or refutation of the theoretically determined molecular properties.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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