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The Use of the Density Threshold Value as a Shape Descriptor on the Toxicity of Benzene Derivatives

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ABSTRACT

The Quantitative Structure Activity Relationship (QSAR) method, based on the three-dimensional (3D) shapes of formal molecular bodies and computed molecular descriptors, was used to calculate the octanol-water partition coefficient (logKow) of benzene derivatives to indicate their toxicity. The aim of this study is to use electron density threshold values as descriptors in predicting toxicology of benzene derivatives. Through Density Domain Analysis (DDA), a shape fragment database of benzene derivatives was constructed. Electron density threshold values were generated from molecular isodensity counter surfaces (MIDCO) of benzene molecules that were calculated at the ab initio HF/6-31G* level. Multiple linear regression analyses were performed, and two successful QSAR models were obtained. The analysis of variance (ANOVA) ratio for regression (F) and the significance of F (Fs) values was also used to evaluate the predictive power of the established QSAR models. The results indicate that the electron density threshold value, "a", gives a specific description of the 3D shape of electron density clouds. These models were further analyzed by three 3D shape features as one local and two global descriptors based on the electron density threshold "a" value. The global and local properties of benzene derivatives were found to exhibit similar toxicity behaviors.

Keywords: QSAR; octanol-water partition coefficient; electron density threshold value, topological descriptors; benzene derivatives.

INTRODUCTION

Toxicity is a key parameter in studies of the environmental fate of organic chemicals. According to several studies (Karelson, 1996; Inel and Işeri, 1997; Warne et al. 1990), the toxic effect of chemicals is successfully indicated by K_{ow}. In this research, benzene derivatives (which are known to be toxic chemicals) were selected as model compounds to estimate the toxicity by QSAR methods (Basak et al., 2000; Roy and Ghosh, 2004). The developed method is proposed as an alternative to conventional toxicity estimation methods. An important tool in the topological method of making chemical predictions is the generation of indices. The indices are derived from algorithms or procedures for converting the topological structure of a molecule into a single characteristic number. Molecular connectivity indices developed by Kier and Hall (1986) were also used in QSAR studies quite successfully as significant descriptors. In addition, atomic charges, molecular orbital energies, and many other quantum chemical descriptors have been used to determine the octanol-water partition coefficient (Karelson, 1996; Basak et al., 2000; Roy and Ghosh, 2004).

In this study, new types of descriptors were used to calculate the toxicity of benzene derivatives. These descriptors were generated by using the Density Domain Approach method. Recently, the DDA method for modeling molecular fragment shape variation indices was used by Paul G. Mezey (2012). The topological shape invariants and corresponding families of nuclear arrangements can be characterized topologically and algebraically for shape analysis (Mezey, 1992). Theoretical studies (Mezey, 2012; Mezey, 1993)

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investigating the topological techniques of molecular electron density shape analysis can be found in the literature.

However, the application of the DDA method in toxicological studies has not been used in QSAR analysis. The density domain approach describes the relative contributions of various regions of space to the chemical bonding of molecular fragments by considering the pattern of their stepwise interconnection as the electron density threshold value "a" is varied. Chemical bonding is attributed to a whole region of space occupied by the electronic charge cloud (Mezey, 1996). It was shown that the Holographic Electron Density Theorem (Mezey, 1999) provides a link between the local and global properties of molecules. This theorem states that the local electron density determines the complete electron density; thus, it determines all of the properties of any single molecule. The electron density itself carries all of the information concerning the static properties of the molecule; therefore, the local electron density establishes the differences in toxicological activities (Mezey, 2009). One of the aims of this research is to prove that the global and local properties of benzene derivatives show similar toxic behaviors. The focus was placed on the chemically important local regions, such as the formal functional groups and combinations of the functional groups, of benzene derivatives.

A shape fragment database of benzene derivatives was generated using the density threshold values as the 3D molecular shape property. This database and the DDA method were used to generate detailed electron density shape values. Next, the density values were compared with physical data on benzene derivatives to correlate the physical, chemical and toxicological properties. In addition, a topological matrix was developed as a specific descriptor. This topological matrix was constructed by using the electron density threshold value "a" for each molecule, as explained in the next section. This study achieved interesting correlations between the shape descriptors and the experimentally observed molecular properties. Similarly, the observed correlations can be used as risk predictors for suspected environmental contaminants or newly synthesized drug molecules.

METHODOLOGY

In this study, a set of chemicals composed of 62 substituted benzene derivatives was used. The selected derivatives had six different substituent groups: fluoro-, chloro-, nitro-, alkyl-, hydroxyl- and amino- substituents. Forty descriptors were considered in four categories: topological, quantum chemical, semi-empirical and graph theoretical. The topological descriptors are the density threshold values of the carbon atoms in the benzene ring, denoted as a_{C1}, a_{C2}, a_{C3}, a_{C4}, a_{C5}, a_{C6}, a_{total}, and a_{last}.

The quantum chemical descriptors are the energy level of the highest occupied molecular orbital (HOMO); energy level of the lowest unoccupied molecular orbital (LUMO); hardness; atomic charges; Mulliken charges; natural atomic charges; $charge_{total}$ as the summation of the atomic, Mulliken, and natural atomic charges; dipole moment; molecular weight; entropy (ΔS); enthalpy; free energy; total energy; heat capacity at a constant volume; bond dissociation energy; bond distance; stretching vibrations between the carbon (labeled as C_1) atom and the functional group; angle between the two carbon atoms and the neighboring functional group (C_3 - C_1 – X); and the angle between the two carbon atoms and the functional group (C_4 - C_1 – X). The schematic representation of the carbon atoms and the functional groups of benzene derivatives are shown in Figure 1. The semi-empirical descriptors are the solvent accessible surface area, the heat of formation (water), the heat of formation (vacuum), and the difference between the calculated heat of formation with water and under vacuum. The graph theoretical descriptors include the zeroth-order (atomic) valence connectivity index, first-order (bond) valence connectivity index (Chi1V), second-order (path) valence connectivity index, zeroth-order (atomic) molecular connectivity index, first-order (bond) molecular connectivity index, second-order (path) molecular connectivity index, shape index order 1, shape index order 2, and shape index order 3. These descriptors were used to find a correlation with the experimental toxicity data (Hansch, 1995) involving $\log K_{ow}$ for the selected compounds. Ab-initio quality molecular isodensity contour surfaces were obtained using the MacSpartan Pro molecular modeling program (2000).

The sequences of topologically different sets of density domains of the benzene derivatives were computed via the Hartree Fock (HF) molecular orbital calculation with the 6-31G* basis set. Based on the density domain approach, the topologically distinct families of density domains of isodensity surfaces were constructed for benzene derivatives using the above basis set. The density threshold value "a_i" was analyzed according to the connection point of the functional group to the neighboring carbon atom of the benzene ring. The three representative density threshold values were selected for the QSAR analysis. One of these values is a local parameter, which is the density threshold value between the carbon atom, labeled C_1, and the neighboring functional group (X), as shown in Figure 1. This value was referred to as the density threshold value "a_{C1}". The second value is a global parameter, which is called "the last density threshold value" of the bonding pattern. "The last density value" is an important topological invariant, in which the molecule is bound together as a single body. This value was called the density threshold value "a_{last}". The third value is the sum of the density threshold values between the carbon atoms, C_1, C_2, C_3, C_4, C_5, and C_6 and the neighboring functional groups. This value was called the density threshold value "a_{total}" and is used as a global topological parameter.

The (12 × 12) electron density threshold value matrix was constructed by using the electron density threshold value "a" for a molecule by establishing a 12 by 12 array, as shown in Figure 2. Each entry is the electron density threshold value "a" between the carbon atom of the benzene ring and the neighboring functional group. When bonding occurs between the carbon atoms or between a carbon atom and a functional group, the electron density threshold value between these two atoms is assigned to the entry. When there is no bonding between the atoms, the "a" value is set to zero. The (12 × 12) electron density threshold value matrix for the p-chloroaniline molecule is illustrated in Figure 3. The eigenvalue results of the (12 × 12) electron density threshold value matrix were obtained using the program Maple 7 (2001).

The atomic, Mulliken and natural atomic charges were obtained using the HF molecular orbital calculation with the 6-31G* basis set. The charges of the carbon labeled as C_1 in the benzene ring were used as descriptors. In addition, the summation of the atom, Mulliken and natural atomic charges on C_1 was used as a descriptor and referred to as $charge_{total}$. The HOMO energy and the entropy were determined via the HF molecular orbital calculation with the 6-31G* basis set. The valence connectivity index1 (Chi1V) is the first-order (bond) molecular connectivity index of the chemical sample. The shape index order 1 is a topological index qualifying the shape of the molecule. This index quantifies the number of cycles in the chemical sample. Both indices were calculated using a Computer Aided Chemistry worksystem (CAChe) with the

Mopac (2000) package. The results of the calculated descriptors used in QSAR analysis are tabulated in Table 1.

The multiple linear regression technique was employed in the modeling of the experimental toxicity values by using the project leader of the CAChe molecular modeling program (2000). Forty descriptors were employed, and a linear regression model was obtained by using forward stepwise analysis. The quality of the model was assessed by the regression coefficient (r^2) and the cross-validated regression coefficient (r_{cv}^2). The r_{cv}^2 parameter was used to measure the predictive capacity of the model. The regression analyses were computed by using the Microsoft Excel program, so the regression coefficient (r^2), analysis of variance (ANOVA) ratio for regression (F) and significance of F (F_s) values were also used to evaluate the predictive power of the established QSAR models.

The correlations of the benzene derivatives and subsets of the benzene derivatives were analyzed by changing the three selected 3D shape features. In other words, the threshold values "a_{C1}", "a_{total}", and "a_{last}" were altered, while the other descriptors remained the same. This alteration was performed to determine the relationships among the local and global characteristics and the toxicity of the molecules.

Density Domain Approach

The Density Domain Approach is a method described by Mezey (1993) that uses the concept of molecular isodensity contours (MIDCO) to describe the full, three-dimensional bonding pattern of molecules. MIDCO G(K,a) of a molecule is defined as $G(K,a) = \{r: q(K,r) = a\}$, where K is the formal nuclear configuration of a molecule and q(r) is the electronic charge density at radius r. The associated density domain DD (K,a) is the collection of all points r where the electron density q(K,r) of molecule M is greater than or equal to the threshold a and is given by $DD(K,a)=\{r: q(K,r)\geq a\}$ (Mezey, 1993).

At a high electronic density threshold value "a", G(K,a) is composed of several disconnected, nearly spherical surfaces. At high-density threshold values, each separate component of G(K,a) encloses one nucleus. As the "a" value decreases, the isodensity contours expand and various parts of the contour surface, G(K,a),become connected. The sequence according to which various parts of G(K,a) become connected provides information on the 3D shape of the molecular electronic charge density, indicating the pattern by which the electron density bonds the molecular fragments together. Some molecular fragments retain a separate closed contour within a wide interval of density threshold values "a"; usually, these fragments have a well-established chemical identity as a "functional group". A gradual decrease of value "a" eventually leads to the interconnection of all parts of G(K,a).

The isodensity contour becomes a single envelope surface, surrounding all of the nuclei of the molecule. For very small isodensity contour values "a", the surface G(K,a) becomes a nearly spherical balloon (Mezey, 1993). In this study, the shape fragment database of benzene derivatives was constructed by analyzing the isodensity contour surfaces of the electron density threshold values of benzene molecules that were calculated at the ab initio HF/6-31G* level.

A Specimen Procedure: Application of the Density Domain Approach in the case of the p-chloroaniline Molecule

Based on the density domain approach, the topologically distinct families of the density domains of molecular isodensity surfaces were constructed for benzene derivatives. The bonding patterns of the benzene derivatives were analyzed by varying the electron density threshold value "a_i" through the range of $0.002 \leq a \leq 0.699$ atomic units. The electron density threshold value "a_i" is the value at which connections and disconnections occur and are characteristics of the given molecular configuration and the electronic state. As an example of benzene derivatives, the density domain analysis of the p-chloroaniline molecule is shown in Figure 4.

The density domains of the carbon atoms appear separately at a threshold value of a_1=0.699 a.u. The density domain of the chlorine atom is the bulkiest, reflecting an accumulation of electronic density due to the largest atomic size of chlorine among these atoms. Because an electronegativity difference exists among the chlorine, nitrogen, carbon and hydrogen atoms, first, the most electronegative one appears. Theoretically, the density domains of hydrogen atoms are expected to be observed at lower density threshold values (Mezey, 1996).

The following topological changes are the sequential appearance of hydrogen atoms H_4, H_3, and H_7 at threshold density values a_2 = 0.343 a.u., a_3 = 0.338 a.u., and a_4=0.328 a.u., respectively. Thus, the bonding between C_4 and C_5 atoms and C_3 and C_6 atoms are observed at values a_5=0.327 a.u. and a_6=0.325 a.u, respectively. The next two patterns of the family are at density threshold values a_8=0.310 a.u. and a_9=0.309 a.u., where bonds form between the C_2 and C_5 atoms and between the C_1 and C_4 atoms, respectively. The following topological changes are the appearances of H_1 and H_5 atoms at a_{10}=0.306 a.u. and a_{11}=0.303 a.u, respectively. The next significant topological changes are the bonding patterns of the C_2 and C_6 carbon atoms and of the C_1 and C_3 atoms at the threshold value of a_{12}=0.302 a.u. and a_{13}=0.301 a.u., respectively; these bonds complete the benzene ring.

The formation of a benzene ring is completed between the 0.325 a.u. and 0.301 a.u. electron density threshold values within the localized density range. Next, the formation and connection of aniline group are completed within the interval from 0.293 a.u. to 0.275 a.u. First, the merger occurs between the density domains of C_1 and N_1 atoms at the threshold value a_{14}=0.293 a.u., and then, the hydrogen H_1 and H_7 atoms connect to the nitrogen atom at the threshold values a_{15}=0.284 a.u. and a_{16}=0.275 a.u., respectively. Thus, the formation of the meta-substituted functional, NH_2, group is completed. The functional group does not have a separate identity because the nitrogen, N_1, an atom of the functional group joins to the carbon, C_1, atom earlier than the merger of hydrogen atoms to the nitrogen. The following pattern is the sequential bonding of the hydrogen density domains, H_5, H_3, H_4, and H_2, to the carbon atoms of the benzene ring at threshold values a_{17}=0.272 a.u., a_{18}=0.268 a.u., a_{19}=0.264 a.u., a_{20}=0.262 a.u., respectively.

The last pattern of the family is at the density threshold a_{21}=0.192 a.u., where the chlorine atom, Cl_1, and the carbon atom, C_2, bond. The topological sequence families of the density domains are now complete; this sequence provides a detailed, three-dimensional description of bonding in the p-chloroaniline molecule. Atoms lose their separate contours within a small interval of density values from 0.699 a.u. to 0.192 a.u. The functional groups of p-chloroaniline are amino- and chloro- groups. The electronic properties of these groups affect the bonding pattern of the molecule.

In this case, the three different density threshold values selected as representatives of the local and global parameters are "a_{C1}", "a_{last}" and "a_{total}". The descriptor "a_{C1}" is a_{14}=0.293 a.u., where the first merger occurs between the density domains of C_1 and the neighboring N_1 atoms. The descriptor

"a_{last}" is a_{21}=0.192 a.u., where the molecule is bound together as a single body. The other descriptor "a_{total}" is 1.551 a.u., which was calculated as the summation of the density threshold values between the carbon atoms and the neighboring functional groups. All of the benzene derivatives in the data set were analyzed as explained in the case of the p-chloroaniline molecule.

RESULTS AND DISCUSSION

The electron density threshold value descriptors and the log K_{ow} values show significant statistical correlations in the case of the benzene derivatives considered in this study. The relationships between the threshold values "a_{C1}", "a_{total}" and "a_{last}" and the log K_{ow} value were examined, and two statistically significant correlations were found. These two correlations were named QSAR 1 and QSAR 2.

In the study of QSAR 1, a good correlation to the experimental log K_{ow} was obtained using the threshold value "a_{C1}", valence connectivity index 1, HOMO energy, entropy and $charge_{total}$. For the set of 62 benzene derivatives, the best correlation model provides a regression coefficient with r^2=0.862, $r_{cv}{}^2$=0.836 F=70.88 and F_s=3.37×10^{-23}. In the case of the prediction of the octanol-water partition coefficient, the models that have a_{total} and a_{last} parameters also exhibit very good correlations, as shown in Table 2. These results show that a local shape property is significant in predicting the toxicity as a global shape property. The findings verify the Holographic Electron Density Theorem (Mezey, 1999), which states that within any boundary-less molecular electron density cloud in a nondegenerate ground electronic state, any nonzero volume piece of the electron density cloud contains the complete information about the entire molecule. The results of QSAR 1 analyses show that the charge distribution and the electron density cloud of a molecule are able to describe its toxicity behavior. The presence of π-orbitals on the electron cloud surfaces is significant to the correlations between toxicity properties and the shape features of their electron density features.

In the QSAR 2 study, a significant correlation to the experimental log K_{ow} was obtained using the threshold value "a_{C1}", valence connectivity index 1 and maximum eigenvalues of (12 × 12) density threshold value matrices. The regression analysis establishes a significant relationship between the topological properties and the toxicity data. For the set of 62 benzene derivatives, the best correlation model had regression coefficients of r^2=0.815, $r_{cv}{}^2$=0.800, F=84.96, and F_s=3.31×10^{-21}, as shown in Table 2. In this model, the most important variation is the use of the maximum eigenvalues of the (12 × 12) density threshold value matrices. These matrices were constructed by using the electron density threshold values, which are topological descriptors. The maximum eigenvalue result of the (12x12) matrix is also a topological descriptor. Thus, the eigenvalues of this matrix must also be a direct reflection of the 3D shape of electron density clouds. The correlation of the eigenvalues shows that toxicity trend of the benzene molecules is topology dependent.

The results of two QSAR studies indicate that the electron density threshold value "a" can be further used to describe the toxicity characteristics of the chemical compounds.

CONCLUSIONS

As a result of the QSAR studies in this research, it was found that the electron density threshold value "a" can be used as a specific description of the 3D shape of electron density clouds based on standard ab-initio calculation. Both the local and global properties of benzene derivatives were proved to have significant correlations with toxicity. In other words, the local electron density, fully determines the complete electron density. Therefore, the results of this study are in agreement with the Holographic Electron Density Shape Theorem. The Density Domain Approach can be used as a new computational tool in toxicological risk assessment applications and pharmaceutical drug research.

The relevance of this study helps to reduce the expense and time consumption of predicting the toxicity data of chemical agents. Without performing experiments, the toxicity value of a chemical agent can be predicted via a QSAR study. To evaluate the environmentally safe levels of dangerous chemicals, there is a need for a set of toxicity data, which is often unavailable or inadequate. In this respect, 3D molecular shape features and physicochemical descriptors can be used to develop QSAR models for determining the toxicity of environmental pollutants for better toxicological management.

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Table 1. The results of the calculated descriptors used in the QSAR analyses

Benzene Derivatives	a (C1)	"a" total	"a" last	HOMO (eV)	Charges total	Entropy (cal/mol*K)	Eigenvalue (12x12) max	Chi1V
acetophenone	0,270	1,651	0,224	-9,290	-0,3490	85,625	0,731	2,865
methylphenylether	0,290	1,579	0,245	-8,759	1,3039	82,908	0,714	2,523
benzaldehyde	0,278	1,595	0,252	-9,437	-0,2805	78,251	0,717	2,435
benzene	0,275	1,587	0,250	-8,997	-0,5526	63,168	0,716	2,000
benzoic acid	0,269	1,640	0,262	-9,376	-0,3908	82,740	0,730	2,588
benzylalcohol	0,260	1,557	0,234	-8,919	-0,0367	81,611	0,715	2,580
bromobenzene	0,160	1,481	0,160	-9,052	-0,2605	76,405	0,712	2,893
butylbenzene	0,236	1,525	0,236	-8,653	0,3217	97,872	0,699	3,971
chlorobenzene	0,195	1,487	0,195	-9,108	0,0167	73,581	0,706	2,478
cyanobenzene	0,269	1,589	0,254	-9,656	-0,1110	75,693	0,733	2,384
ethylbenzene	0,251	1,615	0,232	-8,680	0,1370	83,432	0,719	2,971
fluorobenzene	0,242	1,536	0,242	-9,077	1,2208	70,870	0,717	2,100
isopropylbenzene	0,245	1,586	0,231	-8,670	0,0187	83,059	0,712	3,354
nitrobenzene	0,260	1,577	0,253	-9,946	0,1537	80,525	0,720	2,499
n,n-dimethylaniline	0,298	1,328	0,245	-7,993	0,9704	87,628	0,715	3,029
n-propylbenzene	0,254	1,615	0,224	-8,664	0,1758	90,548	0,728	3,471
phenol	0,264	1,608	0,260	-8,831	1,3062	72,231	0,726	2,134
toluene	0,257	1,638	0,251	-8,672	0,3934	73,017	0,732	2,411
m-aminotoluene	0,251	1,625	0,242	-7,795	0,5462	84,468	0,729	2,610
m-chloroaniline	0,300	1,547	0,183	-8,233	1,2110	81,169	0,698	2,677
m-chlorophenol	0,295	1,561	0,200	-8,808	1,4067	80,305	0,726	2,612
m-dichlorobenzene	0,195	1,462	0,258	-9,372	0,0674	80,384	0,703	2,955
m-ethylphenol	0,286	1,629	0,225	-8,318	1,4114	88,755	0,722	3,106
m-hydroxyphenol	0,295	1,670	0,247	-8,392	1,4902	78,757	0,720	2,269
m-hydroxytoluene	0,254	1,606	0,254	-8,309	0,6283	82,311	0,734	2,545
m-methyltoluene	0,254	1,582	0,239	-8,511	0,4550	77,908	0,721	2,821
m-nitroaniline	0,287	1,634	0,258	-8,700	1,1358	88,379	0,734	2,699
m-nitrophenol	0,290	1,670	0,268	-9,333	1,4140	87,293	0,731	2,634
m-nitrotoluene	0,257	1,628	0,242	-9,617	0,3821	92,480	0,728	2,910
o-aminotoluene	0,256	1,641	0,249	-7,795	-0,0167	81,084	0,725	2,616

o-chloroaniline	0,300	1,588	0,190	-8,158	1,0467	80,797	0,714	2,683
o-chlorophenol	0,306	1,609	0,193	-8,759	1,2803	79,892	0,715	2,618
o-dichlorobenzene	0,194	1,468	0,194	-9,314	-0,0621	80,076	0,710	2,961
o-difluorobenzene	0,254	1,588	0,254	-9,296	1,0895	75,091	0,739	2,205
o-ethylphenol	0,281	1,625	0,224	-8,266	1,2395	87,255	0,715	3,112
o-hydroxyphenol	0,277	1,589	0,247	-8,570	0,9056	78,169	0,720	2,275
o-hydroxytoluene	0,260	1,587	0,248	-8,273	-0,1146	81,131	0,732	2,551
o-methyltoluene	0,251	1,558	0,240	-8,522	0,1645	81,980	0,713	2,827
o-nitroaniline	0,303	1,685	0,267	-8,526	1,3276	87,450	0,720	2,705
o-nitrophenol	0,299	1,640	0,249	-9,293	1,4619	85,259	0,724	2,640
o-nitrotoluene	0,243	1,628	0,243	-9,619	0,4548	88,056	0,719	2,916
p-aminotoluene	0,253	1,660	0,240	-7,649	0,2037	85,472	0,733	2,610
p-chloroaniline	0,293	1,551	0,192	-8,059	1,1400	81,429	0,720	2,677
p-chlorophenol	0,267	1,553	0,194	-8,953	1,2736	79,084	0,725	2,612
p-dichlorobenzene	0,196	1,530	0,196	-9,203	-0,0128	79,029	0,713	2,955
p-ethylphenol	0,263	1,595	0,238	-8,534	1,2461	87,703	0,728	3,106
p-hydroxyphenol	0,269	1,659	0,269	-8,681	1,1297	74,976	0,738	2,269
p-hydroxytoluene	0,248	1,632	0,248	-8,533	0,2146	83,089	0,734	2,545
p-methyltoluene	0,256	1,627	0,249	-8,394	0,3063	86,399	0,732	2,821
p-nitroaniline	0,301	1,663	0,261	-8,813	1,2860	87,462	0,730	2,699
p-nitrophenol	0,271	1,625	0,248	-9,959	1,3937	85,882	0,737	2,634
p-nitrotoluene	0,257	1,651	0,256	-9,804	0,4907	93,136	0,741	2,910
1,2,3-trichlorobenzene	0,201	1,399	0,201	-9,587	0,2716	86,500	0,694	3,445
1,2,4-trichlorobenzene	0,209	1,438	0,204	-9,427	-0,0527	88,250	0,697	3,439
1,2,4-trifluorobenzene	0,286	1,638	0,245	-9,431	0,9788	80,584	0,737	2,305
1,2,3,4-tetrachlorobenzene	0,205	1,411	0,205	-9,592	-0,0669	92,914	0,706	3,928
1,2,3,5-tetrachlorobenzene	0,209	1,392	0,197	-9,678	-0,0338	93,272	0,706	3,922
1,2,4,5-tetrachlorobenzene	0,205	1,363	0,195	-9,566	-0,0592	91,976	0,696	3,922
pentachlorobenzene	0,204	1,292	0,203	-9,745	-0,0367	99,315	0,685	4,412
pentafluorobenzene	0,271	1,652	0,266	-9,987	1,1917	87,781	0,736	2,522
hexachlorobenzene	0,205	1,274	0,205	-9,912	-0,0991	101,737	0,693	4,902
hexafluorobenzene	0,270	1,393	0,269	-10,359	0,8196	88,625	0,738	2,634

Table 2. Statistical results and the equations of the QSAR study

	n	*r^2*	*r_{cv}^2*	*F*	*F_s*	*Equations*
QSAR 1 with a_{C1}	62	0.862	0.836	70.88	$3.37\text{x}10^{-23}$	$\log K_{ow} = -6.698\ a_{C1} + 2.090$ Chi1V $- 0.280$ HOMO $- 0.061\Delta S + 0.174$ charge$_{total} + 0.771$
QSAR 1 with a_{total}	62	0.848	0.823	63.56	$4.69\text{x}10^{-22}$	$\log K_{ow} = -\ 0.618\ a_{total} + 2.280$ Chi1V $- 0.329$ HOMO $- 0.072\Delta S + 0.032$ charge$_{total} + 0.096$
QSAR 1with a_{last}	62	0.847	0.819	62.84	$6.15\text{x}10^{-22}$	$\log K_{ow} = 0.262\ a_{last} + 2.432$ Chi1V $- 0.356$ HOMO $- 0.080\Delta S + 0.041$ charge$_{total} - 1.015$
QSAR 2 with a_{C1}	62	0.815	0.800	84.96	$3.3\text{x}10^{-21}$	$\log K_{ow} = -10.11\ a_{C1} + 1.26$ Chi1V $- 7.61$ Eigenvalues max(12x12) $+ 7.00$
QSAR 2 with a_{total}	62	0.776	0.752	67.03	$7.66\text{x}10^{-19}$	$\log K_{ow} = -\ 2.88\ a_{total} + 1.28$ Chi1V $- 4.69$ Eigenvalues max(12x12) $+ 6.75$
QSAR 2 1with a_{last}	62	0.752	0.745	58.58	$1.49\text{x}10^{-17}$	$\log K_{ow} = -\ 2.54\ a_{last} + 1.45$ Chi1V $- 12.43$ Eigenvalues max(12x12) $+ 7.92$

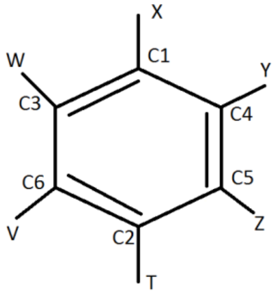


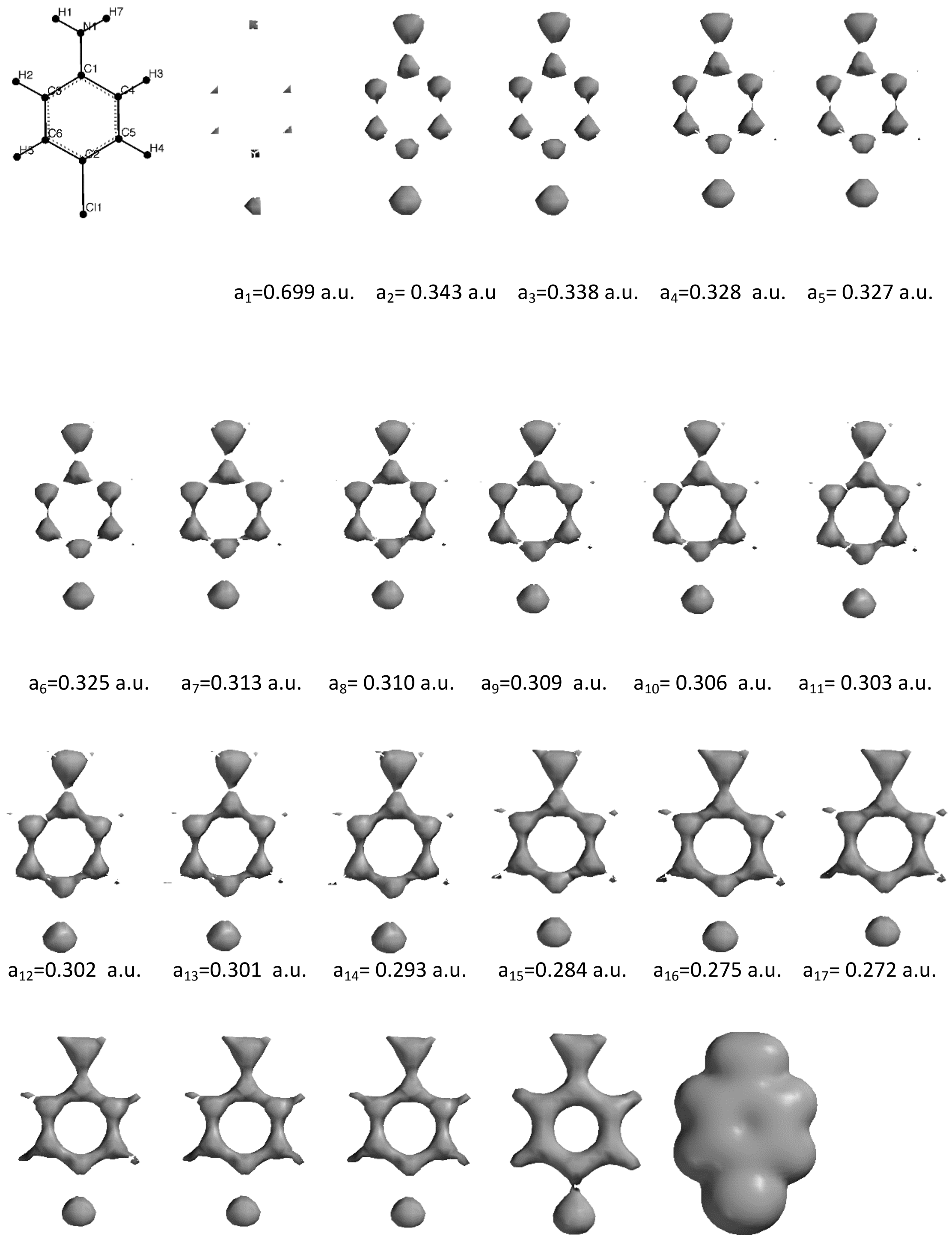
Figure 1. The schematic representation of benzene derivatives; the letters T, V, W, X, Y, and Z represent the functional groups

$$\begin{pmatrix}
a_{C1\text{-}C1} & a_{C2\text{-}C1} & a_{C3\text{-}C1} & a_{C4\text{-}C1} & a_{C5\text{-}C1} & a_{C6\text{-}C1} & a_{X\text{-}C1} & a_{W\text{-}C1} & a_{Y\text{-}C1} & a_{Z\text{-}C1} & a_{V\text{-}C1} & a_{T\text{-}C1} \\
a_{C1\text{-}C2} & a_{C2\text{-}C2} & a_{C3\text{-}C2} & a_{C4\text{-}C2} & a_{C5\text{-}C2} & a_{C6\text{-}C2} & a_{X\text{-}C2} & a_{W\text{-}C2} & a_{Y\text{-}C2} & a_{Z\text{-}C2} & a_{V\text{-}C2} & a_{T\text{-}C2} \\
a_{C1\text{-}C3} & a_{C2\text{-}C3} & a_{C3\text{-}C3} & a_{C4\text{-}C3} & a_{C5\text{-}C3} & a_{C6\text{-}C3} & a_{X\text{-}C3} & a_{W\text{-}C3} & a_{Y\text{-}C3} & a_{Z\text{-}C3} & a_{V\text{-}C3} & a_{T\text{-}C3} \\
a_{C1\text{-}C4} & a_{C2\text{-}C4} & a_{C3\text{-}C4} & a_{C4\text{-}C4} & a_{C5\text{-}C4} & a_{C6\text{-}C4} & a_{X\text{-}C4} & a_{W\text{-}C4} & a_{Y\text{-}C4} & a_{Z\text{-}C4} & a_{V\text{-}C4} & a_{T\text{-}C4} \\
a_{C1\text{-}C5} & a_{C2\text{-}C5} & a_{C3\text{-}C5} & a_{C4\text{-}C5} & a_{C5\text{-}C5} & a_{C6\text{-}C5} & a_{X\text{-}C5} & a_{W\text{-}C5} & a_{Y\text{-}C5} & a_{Z\text{-}C5} & a_{V\text{-}C5} & a_{T\text{-}C5} \\
a_{C1\text{-}C6} & a_{C2\text{-}C6} & a_{C3\text{-}C6} & a_{C4\text{-}C6} & a_{C5\text{-}C6} & a_{C6\text{-}C6} & a_{X\text{-}C8} & a_{W\text{-}C8} & a_{Y\text{-}C8} & a_{Z\text{-}C8} & a_{V\text{-}C8} & a_{T\text{-}C8} \\
a_{C1\text{-}X} & a_{C2\text{-}X} & a_{C3\text{-}X} & a_{C4\text{-}X} & a_{C5\text{-}X} & a_{C6\text{-}X} & a_{X\text{-}X} & a_{W\text{-}X} & a_{Y\text{-}X} & a_{Z\text{-}X} & a_{V\text{-}X} & a_{T\text{-}X} \\
a_{C1\text{-}W} & a_{C2\text{-}W} & a_{C3\text{-}W} & a_{C4\text{-}W} & a_{C5\text{-}W} & a_{C6\text{-}W} & a_{X\text{-}W} & a_{W\text{-}W} & a_{Y\text{-}W} & a_{Z\text{-}W} & a_{V\text{-}W} & a_{T\text{-}W} \\
a_{C1\text{-}Y} & a_{C2\text{-}Y} & a_{C3\text{-}Y} & a_{C4\text{-}Y} & a_{C5\text{-}Y} & a_{C6\text{-}Y} & a_{X\text{-}Y} & a_{W\text{-}Y} & a_{Y\text{-}Y} & a_{Z\text{-}Y} & a_{V\text{-}Y} & a_{T\text{-}Y} \\
a_{C1\text{-}Z} & a_{C2\text{-}Z} & a_{C3\text{-}Z} & a_{C4\text{-}Z} & a_{C5\text{-}Z} & a_{C6\text{-}Z} & a_{X\text{-}Z} & a_{W\text{-}Z} & a_{Y\text{-}Z} & a_{Z\text{-}Z} & a_{V\text{-}Z} & a_{T\text{-}Z} \\
a_{C1\text{-}V} & a_{C2\text{-}V} & a_{C3\text{-}V} & a_{C4\text{-}V} & a_{C5\text{-}V} & a_{C6\text{-}V} & a_{X\text{-}V} & a_{W\text{-}V} & a_{Y\text{-}V} & a_{Z\text{-}V} & a_{V\text{-}V} & a_{T\text{-}V} \\
a_{C1\text{-}T} & a_{C2\text{-}T} & a_{C3\text{-}T} & a_{C4\text{-}T} & a_{C5\text{-}T} & a_{C6\text{-}T} & a_{X\text{-}T} & a_{W\text{-}T} & a_{Y\text{-}T} & a_{Z\text{-}T} & a_{V\text{-}T} & a_{T\text{-}T}
\end{pmatrix}$$

Figure 2. The general representation of the (12 × 12) electron density threshold value matrix

$$\begin{pmatrix}
0 & 0 & .301 & .309 & 0 & 0 & .293 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & .310 & .302 & 0 & 0 & 0 & 0 & 0 & .192 \\
.301 & 0 & 0 & 0 & 0 & .325 & 0 & .262 & 0 & 0 & 0 & 0 \\
.309 & 0 & 0 & 0 & .327 & 0 & 0 & 0 & .268 & 0 & 0 & 0 \\
0 & .310 & 0 & .327 & 0 & 0 & 0 & 0 & 0 & .264 & 0 & 0 \\
0 & .302 & .325 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & .272 & 0 \\
.293 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & .262 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & .268 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & .264 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & .272 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & .192 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix},$$

Figure 3. The (12 × 12) electron density threshold value matrix for the p-chloroaniline molecule



a_1=0.699 a.u. a_2= 0.343 a.u a_3=0.338 a.u. a_4=0.328 a.u. a_5= 0.327 a.u.

a_6=0.325 a.u. a_7=0.313 a.u. a_8= 0.310 a.u. a_9=0.309 a.u. a_{10}= 0.306 a.u. a_{11}= 0.303 a.u.

a_{12}=0.302 a.u. a_{13}=0.301 a.u. a_{14}= 0.293 a.u. a_{15}=0.284 a.u. a_{16}=0.275 a.u. a_{17}= 0.272 a.u.

a_{18}=0.268 a.u. a_{19}= 0.264 a.u. a_{20}= 0.262 a.u. a_{21}=0.192 a.u. a_{22}=0.002 a.u.

Figure 4. The isodensity contour surfaces (MIDCOs) of the electron density values of the p-chloroaniline molecule calculated at the ab initio HF/ 6-31G* level