Journal of Engineering Research and Applied Science
Available at www.journaleras.com
Volume 13 (2), December 2024, pp 2637-2642
ISSN 2147-3471 © 2024

Statistical Analysis of Substituent Effects on pKa of Aniline

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Accepted 11 December 2024

Abstract
In this study, the effects of geometric and electronic factors on the pKa values of aniline derivatives were investigated by statistical methods. The effects formed by the binding of different substituents to the phenyl ring were evaluated through the parameters of C-N bond length, CCNH angle, which is the angle between the benzene ring and the NH_2 group, electronegativity and distance group. According to the results obtained from the study; It was determined that C-N bond length and CCNH angle showed the strongest positive effects on pKa. It was observed that electronegative groups had a significant but negative effect on pKa. However, no significant effect was found with the distance group. These results emphasize the importance of geometric and electronic factors in pKa optimization and provide applicable information in chemical design and drug development processes.

Keywords: *Aniline, Gaussian, Statical method, ANOVA*

1. Introduction

Aniline molecule is a molecule that contains aromatic phenyl and $–NH_2$ group in its structure. In general, aniline is a non-planar molecule, as its molecular structure is given in Figure 1. As seen in Figure 1, the NH_2 group is located at an angle of approximately 42 degrees to the phenyl ring. This structure of the aniline molecule is interesting in terms of examining some physicochemical properties of the molecules by binding different functional groups to the ring. The pKa values of the molecules are one of them. It is important to examine the changes in the electronic properties of these groups by binding different substituents to the phenyl ring. The change in the angle between the aromatic ring and the $–NH_2$ group can be studied by microwave, UV, IR and theoretical studies [1-7].

The binding of different substituents to the aniline molecule can cause some changes in the molecular structure. The addition of different groups to the structure is quite interesting because it creates some electronic changes in the molecule. There are many studies on this in the literature. In one of these studies, the effect of the charge change on the nitrogen atom and the pKa change according to the electron-withdrawing and -donor states of the substituted groups attached to the aniline molecule was investigated. In this study, the pKa value of the aniline molecule was determined as approximately 4.58 [8]. In addition, the C-N bond lengths and the change of the CCNH out-of-plane angle according to the substituted groups were also listed. However, the numerical electronegative values of the added groups and the effect of the distance of these groups to the -NH_2 group were not investigated. In this study, the contribution of the aniline group to the pKa value will be statistically investigated according to the C-N bond length, CCNH out-of-plane angle, electronegativity values of the substituents and the position of these groups in the aromatic ring. Among these four parameters, the variable that contributes the most to the pKa change will be determined.

When we look at the studies in the literature on the examination of the changes by adding substituents to the aniline molecule, the electronic effects on aniline depending on whether the added groups are electron withdrawing or releasing have generally been examined with the help of substituent constants developed by Hammett from reactivity studies [9-12]. In addition, another study has examined the effect of these groups on the charges on the nitrogen atom on aniline [8]. Atomic charges, although not real physical properties, have a long history of use as intuitive aids in mechanical studies and therefore seem to be natural

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parameters to be examined. However, a statistical approach has not been reached before within the scope of this study.

Optimized and MEP properties of Aniline

In order to determine the appropriate optimized structure of the aniline molecule, the molecular geometry was revealed using the semiempirical method and pm6 basis set. The frequency calculation of the optimized structure obtained was also performed and it was confirmed that it was optimized in the most appropriate geometry. No negative frequency was encountered in the frequency values of the molecule. The optimized molecular geometry of the aniline molecule is depicted in Figure 2. The bond lengths of the molecule are marked on the picture. As can be seen from Figure 2, the nitrogen atom on the phenyl ring is in the same plane, but the hydrogens attached to the nitrogen are out of plane.

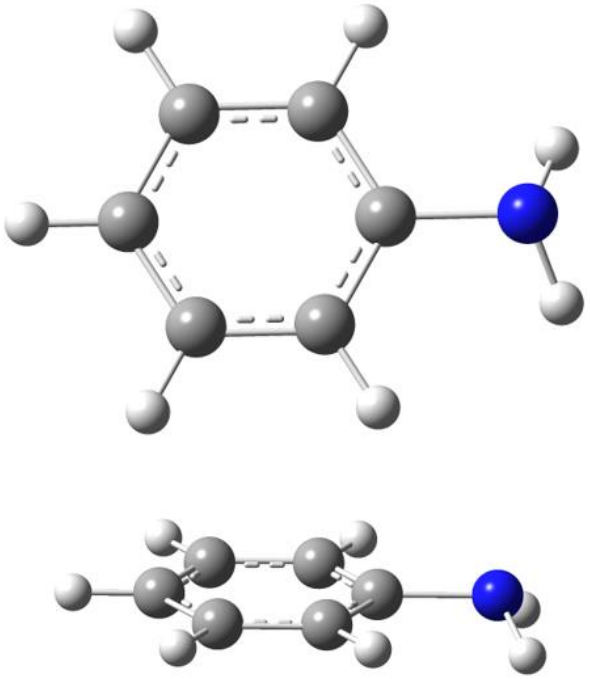

Figure 1. Aniline molecular structure

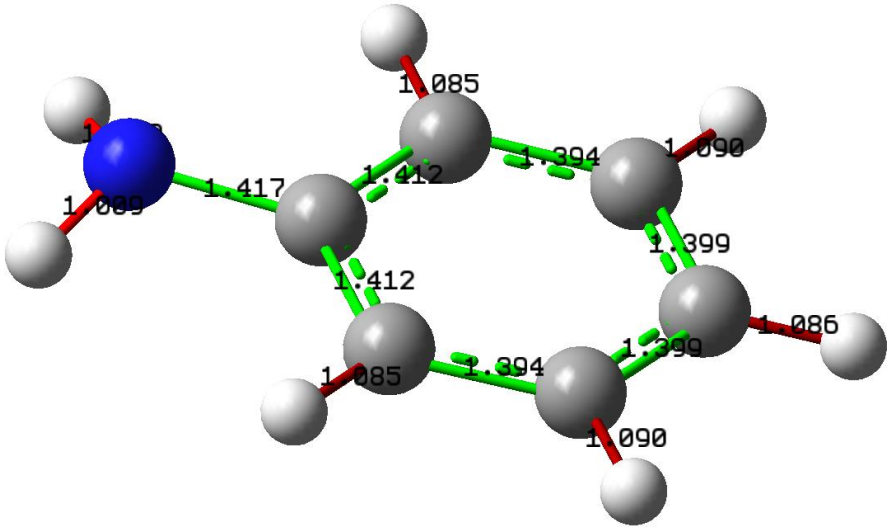

Figure 2. Optimized geometry of aniline

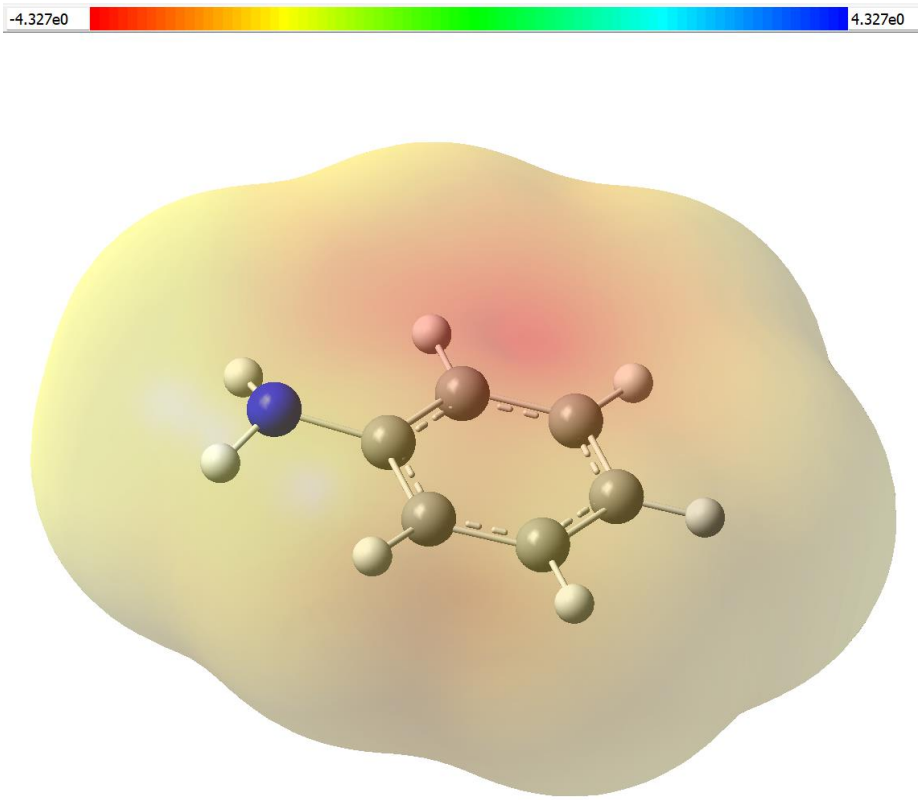

Figure 3. MEP surface of aniline

The reactive behavior of the molecule is visualized with the help of a three-dimensional molecular electrostatic potential (MEP) surface. The MEP surface defines the charge distribution in the molecule. Molecular electrostatic potential (MEP) is used to investigate the chemical reactivity of a molecule, the surfaces of the aniline molecule were calculated and drawn with the same method and basis set used in the optimization as shown in Figure 3. MEP surfaces are represented with different colors, the maximum negative region with the preferred location for electrophilic reactivity is shown in blue, the maximum positive region with the preferred location for nucleophilic reactivity is shown in yellow and the zero potential region is shown in green [13]. According to the results, the MEP map shows that the negative potential regions are on the aromatic ring and nitrogen atom and the positive potential regions are around the hydrogen atoms. The electronic properties on the surface maps also change with the electron-withdrawing and repulsive groups added to the aniline molecule. This situation can also guide the examination of the change in pKa values.

2. Material and Methods

Within the scope of the study, pKa changes of molecules depending on the binding of different substituents to phenyl ring in meta and para positions were investigated. In the study, electronegativity values of different groups, bonding positions on phenyl ring, change of C-N bond length between phenyl and $–NH_2$ group and bond angle between phenyl ring and $–NH_2$ group were determined as input variables and experimental pKa values were taken as output [8]. pKa, C-N bond length and angles between phenyl ring and $–NH_2$ group of 19 molecules were taken from literature. Again, electronegativity values of substituent groups were listed from literature [14]. The last variable, bonding positions, was determined as two for ortho and four for para. All input and output data are listed in Table 1.

Table 1. Some properties and electronefative values for aniline derivatives, with experimental p*Ka*'s.

		inputs				output
		R(C—N) (Å)[8]	θ (deg) [8]	Distance Group	Electronegativity[9]	pKa[8]
1	H	1.396	41.73		2.10	4.58
2	m-amino	1.393	41.34	3	2.63	4.88
3	m-bromo	1.391	40.33	3	2.96	3.51
4	m-chloro	1.391	40.20	3	3.16	3.34
5	m-cyano	1.391	39.91	3	3.33	2.76
6	m-fluoro	1.389	39.65	3	3.96	3.59
7	m-hydroxy	1.391	40.66	3	3.44	4.17
8	m-methoxy	1.394	41.27	3	2.60	4.20
9	m-methyl	1.395	41.77	3	2.55	4.69
10	m-nitro	1.390	39.64	3	4.19	2.50
11	p-amino	1.407	45.32	4	2.63	6.08
12	p-bromo	1.392	40.70	4	2.96	3.91
13	p-chloro	1.393	41.00	4	3.16	3.98
14	p-cyano	1.381	36.32	4	3.33	1.74
15	p-fluoro	1.400	42.88	4	3.96	4.65
16	p-hydroxy	1.406	44.70	4	3.44	5.50
17	p-methoxy	1.405	44.77	4	2.60	5.29
18	p-methyl	1.399	43.13	4	2.55	5.12
19	p-nitro	1.376	34.22	4	4.19	1.02

Table 2. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,972[a]	,944	,928	,34662
a. Predictors: (Constant), R(C—N) (Å), θ (deg), Distance Group, Electronegativity				

Tablo 3. Analysis of ANOVA

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	28,506	4	7,127	59,317	,000b
	Residual	1,682	14	,120		
	Total	30,188	18			
a. Dependent Variable: pKa						
b. Predictors: (Constant), R(C—N) (Å), θ (deg), Electronegativity, Distance Group						

In this part of the study, the effects of different variables (e.g. C-N bond length, CCNH out-of-plane angle, distance group, electronegativity) on the pKa value of aniline derivatives were investigated statistically. IBM SPSS Statistics 23 program was used for the statistical analyses. Table 2 and Table 3 provide the model summary of the analysis and the results of the ANOVA analysis.

When Table 2 is examined, R^2=0.944 was obtained. This result shows that the model explains 94.4% of the total variance in the pKa value, which is the dependent variable. A high R^2 value shows that the model is an optimized regression model. It also indicates that the correlations and relationships between the variables are well defined, and the model is systematically created. The fact that the model cannot explain 5.6%

of the variance suggests that external factors (such as solvent effects, temperature, size of the substituents) may be effective, and these factors can be considered in future studies.

The values of F=59.317 and p<0.001 obtained because of the ANOVA test given in Table 3 clearly show that the model is statistically reliable and the effects of the independent variables on pKa are significant. This result supports that the model can be used as a powerful analysis tool both theoretically and practically. The development of such models, especially in the fields of chemistry such as pKa estimation and molecular design, will contribute to obtaining more sensitive and reliable results..

Table 4. Correlation Analysis

		pKa	R(C—N) (Å)	θ (deg)	Distance Group	Electronegativity
pKa	Pearson Correlation	1	,930**	,956**	,127	-,600**
	Sig. (2-tailed)		,000	,000	,604	,007
R(C—N) (Å)	Pearson Correlation	,930**	1	,991**	,222	-,463*
	Sig. (2-tailed)	,000		,000	,361	,046
θ (deg)	Pearson Correlation	,956**	,991**	1	,153	-,509*
	Sig. (2-tailed)	,000	,000		,533	,026
Distance Group	Pearson Correlation	,127	,222	,153	1	,092
	Sig. (2-tailed)	,604	,361	,533		,707
Electronegativity	Pearson Correlation	-,600**	-,463*	-,509*	,092	1
	Sig. (2-tailed)	,007	,046	,026	,707	
**. Correlation is significant at the 0.01 level (2-tailed).						
*. Correlation is significant at the 0.05 level (2-tailed).						

When the correlation analysis in Table 4 is examined; there is a strong positive relationship between pKa and CCNH angle calculated as r=0.956 and at 0.01 significance level. This finding shows that CCNH angle has a critical effect on steric and electronic properties of the molecule. Larger CCNH angles can increase the proton accepting capacity of nitrogen atom by changing the geometric structure of the molecule. These results reveal that pKa value is extremely sensitive not only to electronic properties of the molecule but also to geometric structures. It is understood that nitrogen atom can exhibit stronger basic properties especially in molecules with large CCNH angles. This situation emphasizes that CCNH angle should be considered as a critical optimization parameter in molecular design processes. Especially in drug design and chemical synthesis processes, correlating steric and electronic properties of the molecule with such angle values can enable the development of more effective molecules.

There is a strong positive correlation between pKa and R(C—N) at the 0.01 significance level (r = 0.930**). The strong positive correlation between C-N bond length and pKa suggests that increasing the bond length increases basicity. The molecular geometry may contribute to the pKa value by affecting how the electron density is distributed around the nitrogen atom.

It was determined that there is a significant and negative relationship between pKa and electronegativity at the 0.01 level (r = -0.600**). This finding clearly shows the significant effect of electronegative groups on the basic properties of aniline derivatives. Electron-withdrawing groups (groups with high electronegativity values) significantly reduce the electron density on the nitrogen atom by changing the electronic distribution in the molecule. This weakens the proton accepting capacity of the nitrogen atom, causing a decrease in the pKa value.

No significant relationship was found between distance group and pKa (r=0.127, p>0.05p>0.05). This result shows that distance group has no significant effect on pKa and is a less important parameter compared to other variables.

4. Conclusion

In this study, the effects of geometric and electronic factors on the pKa values of aniline derivatives were investigated in detail. The results obtained show that the changes on pKa do not depend on a single factor, but that multiple factors such as the geometric structure of the molecule, electron density and bonding positions should be evaluated together.

The strong positive effects of C-N bond length and CCNH angle on pKa are the most striking findings of the study. Longer C-N bond lengths and larger CCNH angles increased the proton binding capacity of the nitrogen atom and increased the pKa value. This shows that the geometric arrangement of the molecule directly changes the electron density and steric effects on nitrogen. This effect of geometric parameters on molecular basicity is an important factor to be considered in drug design and chemical synthesis processes. However, the generalizability of this relationship should be confirmed by studies conducted on larger sets of molecules.

The negative relationship between electronegativity and pKa shows the direct effect of substituents on the basic behavior of the nitrogen atom. Strong electron-withdrawing groups, especially nitro ($-NO_2$), decreased the electron density on nitrogen and decreased the pKa. These findings are consistent with Hammett constants and the literature, supporting the basicity-weakening effects of electron-withdrawing groups. However, a more detailed examination of the effects of electron-donating groups may provide an understanding of the differences between weak and strong donors.

This study analyzed the factors affecting the pKa values of aniline derivatives in detail and identified the basic parameters that have significant effects on pKa. It has been seen that considering geometric and electronic effects together is of critical importance in the prediction and optimization of molecular properties. Such models can contribute to the development of more effective and targeted solutions in areas such as chemistry and drug design.

However, studies with a wider set of molecules and additional parameters can increase the generalizability of this model. In addition, the inclusion of other electronic and geometric properties such as polarity, dipole moment and molecular orbital energies in the model can provide a more comprehensive analysis.

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