QUANTUM-CHEMICAL CALCULATION METHODS TO DETERMINE THE IONIZATION CONSTANTS OF N-SUBSTITUTED AMINO ACID DERIVATIVES

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A theoretical study was conducted to determine the ionization constants of N-substituted amino acid derivatives using HF, DFT, and MP2 calculation methods. The extent of compatibility of these methods was determined by discussing the theoretical variables calculated in the three methods mentioned above, the relationship between the calculated physical variables have been found to be theoretical and to determine their nature. These variables were then correlated with the known chemical values of amino acids as pK_a ionization parameters. The results obtained by this relationship were found to be good. This is indicated by the results of the statistical analysis across the correlation coefficient values. The theory that gave the best agreement between the values of the theoretical and the experimental ionization parameters were the MP2 method with good correlation coefficient (0.997) and standard error (0.162). As well as the large overlap between pK_a values calculated theoretically with practical values where the difference (0.008) gives the opportunity to apply these variables in other studies.

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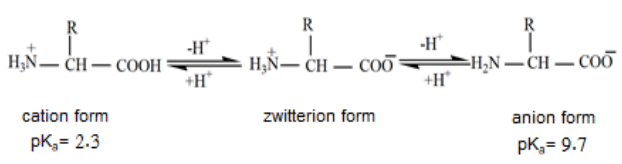
Introduction

Amino acids have a particularly important location in biology as basic building blocks of all proteins and contribute to cellular functions.[1]

The terms dissociation/protonation constants are referred to measure of acidic or alkaline force. The term ionization constant is called in the case of zwitterions.[2] Typically three types of amino acid ionization constants are defined: pK_a refers to the ionization of the carboxyl group, pK_b represents the ionic group ionization constant, and pK_c refers to the side group R, which may contains ionizable groups, and exist in the form of zwitter ions.[3]

Amino acids in a strong basic medium can behave as acids as they lose theirs proton and becomes anion. In the strong acidic medium, they can behave as bases and acquire proton and become positive ion (cation).[4] In neutral solutions, the concentration of zwitterions is very high and this behaviour can be illustrated by Scheme 1.



Scheme 1. Forms of amino acids in media of different acidities.

A list of amino acid derivatives investigated in this study is given in Table 1.

Table 1. Names of amino acids derivatives and their formula.

No.	Compound	Molecular formula
1	N-ethyl glycine	$CH_3CH_2NHCH_2COOH$
2	N-propyl glycine	$CH_3(CH_2)_2NHCH_2COOH$
3	N-n butyl glycine	$CH_3(CH_2)_3NHCH_2COOH$
4	N-isobutyl glycine	$(CH_3)_2CHCH_2NHCH_2COOH$
5	N-phenyl glycine	$PhNHCH_2COOH$
6	N-benzoyl glycine	$PhCONHCH_2COOH$
7	N-methyl alanine	$CH_3NHCH(CH_3)COOH$
8	N-ethyl alanine	$CH_3CH_2NHCH(CH_3)COOH$
9	N-n-propyl alanine	$CH_3(CH_2)_2NHCH(CH_3)COOH$
10	N,N-dimethylglycine	$(CH_3)_2NCH_2COOH$
11	N,N-diethylglycine	$(CH_3CH_2)_2NCH_2COOH$

Computational chemistry

Computational chemistry is one of the branches of physical chemistry along with quantum mechanics and molecular mechanics, whose purpose is to find the most important properties of the chemical compounds and compare them with the experimental values. It is one of the main branches of research used in analysis and diagnostics and support of experimental research.[7] Theoretical chemistry can be presented as a mathematical description of computational chemistry.[8,9] The most important of these variables is the electronic density, which represents the square wave function (), which indicates the possibility of an electron in the vicinity of the nucleus or on any atom in the molecule.[10] Other important variables include van der Waals forces, dipole-dipole, space disruptive energy and energy variables like HOMO and LUMO values. HOMO represents the least energy to remove electrons from the orbital outside the compound to the oxidizing state called ionization potential.

LUMO is the least possible energy needed to acquire an electron into the outer orbit and the compound changes to a reduced state called electronic affinity.[11] Some other variables such as hardness (η),[12] electronic chemical potential (μ)[13] and the global electrophilicity index (W)[14] are calculated from these energy variables with the help of following relationships.

$$\eta = 1/2(E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}) \quad (1)$$

$$W = \frac{\mu^2}{2\eta} \quad (2)$$

$$\mu = 1/2(E_{\mathrm{LUMO}} + E_{\mathrm{HOMO}}) \quad (3)$$

Theoretical Calculations

The theoretical calculations have been completed in different ways such as (HF-6.31G (d)), (DFT- (B3LYP / 6.31G (d)) and (MP2-6.31G (d)) and using the (Chem office2015 Gaussian3 program) according to the following steps:

1. The molecular formula was drawn using the program (Chem. Draw)
2. Perform the process of preparing the molecule for calculations using the Clean Up directive
3. The energy reduction process was performed using the MM2 program.
4. The calculations were conducted according to each of the methods mentioned above.
5. Some variables related to the constants to be studied (e.g., charge, van der Waals, HOMO, LUMO) are taken from the program results

The variables that taken from step 4 were processed by SPSS package to obtain the best of these variables about the values to be calculated and the weight of each.

Results and Discussion

Theoretical Calculations

In this study, some of the physical variables of the amino acid derivatives were observed for the effective sites as shown in Figure 1. The finding of the relationship between them and the values of ionization constants by the methods mentioned above.

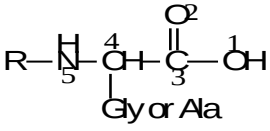


Figure 1. Proposed active sites for amino acid derivatives.

The purpose of selecting these methods is to compare them and to indicate the performance of each method through the accuracy of the calculations and their compatibility with the experimental values of pK_a. The choice of these methods is based on the most common and most widely used in this field of studies and their propensity to yield accurate results observed in the literature.[15-19]

Theoretical calculations of some physical variables of amino acid derivatives

Charge effect

Calculations of the Mulliken charge (which represent the difference between the negative electron density in orbits and the amount of positive protons in the nucleus) were calculated for five atoms at the centre of the interaction of amino acid derivatives using the basic calculation methods (MP2, DFT and HF). The results are given in Tables 2-4.

From the observation of the values of the charges in Tables 2-4 we see that they change in a certain pattern. This change can be explained if we take one of the compounds as an example of this change and explain it in detail and quantitative quantities. Taking into consideration the N-ethyl glycine we find the electron charge is concentrated on the C4-carbon atom because it is close to the amino group associated with the R group, while the electron charge decreases on the C3-atom near the O1 and O2 in the carboxyl group and the increase in the charge on O1, O2 and N5 is clearly observed. As expected, due to the electronegativity of these atoms with the electron abundance on these atoms, especially the presence of free electronic pairs, and reference to other amino acids, the value of the electronic charge on the C4-atom varies with the change in the nature of the group R linked to nitrogen Through its ability to draw and donate, during the observation of the movement of electrons on the atoms in the centre of the interaction can be concluded that the electronic movement, although the aliphatic systems it does not depend on the neighbouring atoms, but beyond it to reach further and this can be demonstrated by the decrease in the electron charge on C3-atom and its increase in the outer O1 and O2 atoms. It is different from what is expected if these groups were isolated. This change includes all methods (MP2, DFT and HF) With differences in charge values following the same pattern for each method.

The theoretical basis for this comparison is the extent of differences in the distribution of charges on atoms at the centre of the reaction (Figure 1). The greatest variation in the distribution of charges on atoms at the centre of the interaction is the sensitivity of the method adopted in this type of application. In order to better explain these differences, charges on O1, O2, C3, C4 and N5 in N-n-butyl glycine, determined by the three methods were plotted (Figure 2). The plots showed that the difference in the values of these charges, calculated by MP2 (1), is the most extensive when compared with the methods of HF (3) and DFT (2). This distinguishes HF and DFT from other methods and qualifies them for wider use and makes the results obtained are more accurate and consistent. This is in line with previous studies[21] in this field on the thiophene and furan derivatives because they gave significant differences between C-3 and oxygen which have high electronegativity.

Table 2. The values of physical variables of the amino acid derivatives calculated by MP2 method.

Compound No.	Charge on atom						S.E	Dipole-Dipol	VDW
	O1	O2	C3	C4	N5	H6			
1	-0.7107	-0.5691	0.7720	-0.1985	-0.7010	0.46971	0.1449	0.8626	1.7399
2	-0.7109	-0.5689	0.7713	-0.1973	-0.7103	0.4695	0.2201	0.8928	2.4189
3	-0.7108	-0.5696	0.7733	-0.1983	-0.7120	0.4693	0.2782	0.8578	3.1401
4	-0.7105	-0.5702	0.7741	-0.1968	-0.7150	0.4695	0.3502	0.8518	3.0536
5	-0.7070	-0.5780	0.7685	-0.1961	-0.8011	0.4737	0.2900	3.3964	5.8515
6	-0.7151	-0.5726	0.7823	-0.2177	-0.7879	0.4712	0.4253	-0.603	6.8529
7	-0.7076	-0.5628	0.7761	-0.0433	-0.6840	0.4669	0.2136	1.4979	1.8326
8	-0.7079	-0.5634	0.7746	-0.0345	-0.6975	0.4665	0.2764	1.5301	2.7540
9	-0.7228	-0.5667	0.7826	-0.0545	-0.6914	0.467	0.3338	1.5047	3.4710
10	-0.7160	-0.5633	0.7664	-0.2108	-0.5287	0.4683	0.4398	2.1946	3.3251
11	-0.7174	-0.5644	0.7713	-0.2164	-0.5534	0.4677	0.8671	2.2670	5.0292

O_1, O_2, C3 C4 = Charge on the carbonyl group in Coulomb, N5 Charge on the amine group in Coulomb, Steric S.E = Energy in Kcal mol^{-1}, VDW = Van Der Waals interaction, For names of the compounds see Table 1.

Table 3. The values of physical variables of the amino acid derivatives calculated by DFT method.

Compound No.	Charge on atom						S.E	Dipole-Dipole	VDW
	O1	O2	C3	C4	N5	H6			
1	-0.5738	-0.4576	0.5616	-0.1837	-0.53309	0.4159	0.1449	0.8626	1.7399
2	-0.5779	-0.4550	0.5671	-0.1889	-0.5451	0.4119	0.2201	0.8928	2.4189
3	-0.5781	-0.4539	0.5665	-0.1915	-0.5414	0.4141	0.2782	0.8578	3.1401
4	-0.5779	-0.4542	0.5655	-0.1884	-0.5422	0.4144	0.3502	0.8518	3.0536
5	-0.5620	-0.4576	0.5658	-0.1771	-0.6763	0.4175	0.2900	3.3964	5.8515
6	-0.5681	-0.4601	0.5965	-0.2261	-0.5866	0.4140	0.4253	-0.603	6.8529
7	-0.5709	-0.4605	0.5763	-0.0007	-0.5307	0.4092	0.2136	1.4979	1.8326
8	-0.5712	-0.4611	0.5739	0.0077	-0.5429	0.4089	0.2764	1.5301	2.7540
9	-0.5765	-0.4591	0.5892	-0.0203	-0.5458	0.4085	0.3338	1.5047	3.4710
10	-0.5697	-0.4524	0.5713	-0.1970	-0.3522	0.4103	0.4398	2.1946	3.3251
11	-0.5708	-0.4541	0.5753	-0.2124	-0.3620	0.4096	0.8671	2.2670	5.0292

Table 4. The values of physical variables of the amino acid derivatives calculated by HF method.

Compound No.	Charge on atom						S.E	Dipole-Dipole	VDW
	O1	O2	C3	C4	N5	H6			
1	-0.7228	-0.5686	0.7639	-0.1918	-0.6840	0.4754	0.1449	0.8626	1.7399
2	-0.7275	-0.5651	0.7684	-0.1974	-0.6972	0.4712	0.2201	0.8928	2.4189
3	-0.7274	-0.5647	0.7678	-0.1996	-0.6936	0.4734	0.2782	0.8578	3.1401
4	-0.7274	-0.5647	0.7678	-0.1996	-0.6936	0.4734	0.3502	0.8518	3.0536
5	-0.7151	-0.5726	0.7823	-0.2177	-0.7879	0.4712	0.4253	-0.603	6.8529
6	-0.7207	-0.5691	0.7779	-0.0462	-0.6719	0.4685	0.2136	1.4979	1.8326
7	-0.7207	-0.5691	0.7779	-0.0462	-0.6719	0.4685	0.2136	1.4979	1.8326
8	-0.7209	-0.5700	0.7756	-0.0349	-0.6884	0.4682	0.2764	1.5301	2.7540
9	-0.7108	-0.5482	0.7628	-0.0474	-0.6914	0.4651	0.3338	1.5047	3.4710
10	-0.7160	-0.5633	0.7664	-0.2108	-0.5287	0.4683	0.4398	2.1946	3.3251
11	-0.7057	-0.5472	0.7523	-0.2136	-0.5624	0.4661	0.8671	2.2670	5.0292

Table 5. Relation between spatial impedance energy and size of the substituent.

Compounds	**1**	**2**	**3**	**4**	**10**	**11**
R	Et	n-Pr	n-Bu	I-Bu	Me_2	Et_2
S.E	0.145	0.220	0.278	0.350	0.440	0.867

Spatial effect

The purpose of the vacuum arrangement is the geometrical form that amino acids can take and the distribution of atoms in the vacuum controlled by different factors: the first is the disability factor (increasing the particle's energy and decreasing its stability), which works to increases the electrons pushing the atoms of the disabled in the distant direction to alleviate the dissonance caused by these totals.

Table 6. Relation between vacuum impedance and size of the substituent.

Compounds	7	8	9
R	Me	Et	N-Pr
S.E	0.2136	0.2764	0.3338

The second effect is the spatial interference of different types, such as interference of van der Waals and hydrogen bonds. Based on the above, some theoretical variables were selected such as the energy of spatial disability (S.E.) and the power of van der Waals interactions (VDW 1-4). It was calculated as a model to describe the effect of the substituted groups in the reaction centre of the amino acids under study. The values of these variables are listed in Tables 2-4.

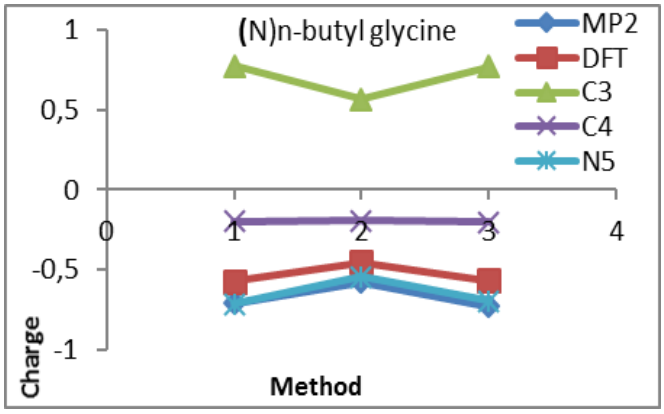


Figure 2. Charge on the reaction centre atoms of the N-butyl glycine compound by the three methods.

Table 7. Energy variables calculated theoretically for amino acid derivatives by MP2.

Compound No.	**HOMO**	**LUMO**	**η**	**μ**	***W***
1	-0.37381	0.18093	0.016766	-0.09644	0.27737
2	-0.37302	0.18137	0.016563	-0.09583	0.27720
3	-0.37263	0.18141	0.016499	-0.09561	0.27702
4	-0.37216	0.18063	0.016590	-0.09577	0.27640
5	-0.28984	0.14216	0.012621	-0.07384	0.21600
6	-0.34576	0.09444	0.035871	-0.12566	0.22010
7	-0.37722	0.17036	0.019536	-0.10343	0.27379
8	-0.37598	0.17301	0.018760	-0.10149	0.27450
9	-0.37866	0.17545	0.018631	-0.10161	0.27706
10	-0.36743	0.17874	0.016297	-0.09435	0.27309
11	-0.36265	0.17999	0.015371	-0.09133	0.27132

Table 8. Energy variables calculated theoretically for amino acid derivatives by DFT.

Compound No.	**HOMO**	**LUMO**	**η**	**μ**	***W***
1	-0.22267	0.01021	0.11644	-0.10623	0.048458
2	-0.22282	0.00865	0.11574	-0.10709	0.049541
3	-0.22087	0.00888	0.11488	-0.10600	0.048901
4	-0.22245	0.00800	0.11523	-0.10723	0.04989
5	-0.19883	0.00909	0.10396	-0.09487	0.043287
6	-0.25201	0.04065	0.14633	-0.10568	0.038161
7	-0.22700	0.00195	0.11448	-0.11253	0.055304
8	-0.22559	0.00315	0.11437	-0.11122	0.054078
9	-0.22721	0.00717	0.11719	-0.11002	0.051644
10	-0.22136	0.00670	0.11403	-0.10733	0.050512
11	-0.21764	0.00844	0.11304	-0.10460	0.048395

Table 9. Energy variables calculated theoretically for amino acid derivatives by HF.

Compound No.	HOMO	LUMO	η	μ	*W*
1	-0.37506	0.18243	0.27875	-0.09632	0.01664
2	-0.37589	0.18062	0.27826	-0.09764	0.017129
3	-0.37316	0.18104	0.2771	-0.09606	0.01665
4	-0.37393	0.18032	0.27713	-0.09681	0.016908
5	-0.28984	0.14216	0.216	-0.07384	0.012621
6	-0.34580	0.09443	0.22012	-0.12569	0.035883
7	-0.38089	0.17213	0.27651	-0.10438	0.019701
8	-0.37818	0.17467	0.27643	-0.10176	0.018729
9	-0.37860	0.17586	0.27723	-0.10137	0.018533
10	-0.36743	0.17874	0.27309	-0.09435	0.016297
11	-0.35338	0.19562	0.2745	-0.07888	0.011333

Table 10. Correlation coefficient values for the relationship between the calculated variables of MP2.

Variables	O1	O2	C3	C4	N5	H6	SE	*VDW*	*HOM*	*LUM*	η	μ	*W*
O1	1												
O2	0.240	1											
C3	0.390	0.009	1										
C4	0.055	0.494	0.445	1									
N5	0.428	0.763	0.410	0.059	1								
H6	0.304	0.945	0.233	0.649	0.603	1							
SE	0.522	0.215	0.081	0.325	0.568	0.142	1						
VDW	0.256	0.549	0.175	0.411	0.260	0.570	0.535	1					
HOM	0.264	0.773	0.264	0.353	0.454	0.836	0.081	0.712	1				
LUM	0.003	0.533	0.432	0.183	0.562	0.553	0.058	0.790	0.571	1			
η	0.145	0735	0.101	0.301	0.574	0.782	0.078	0.848	0.883	0.890	1		
μ	0.285	0.238	0.755	0.175	0.134	0.283	0.023	0.109	0.437	0.489	0.037	1	
W	0.214	0.089	0.704	0.011	0.335	0.073	0.037	0.451	0.043	0.794	0.431	0.916	1

Table 11. Multiple regression analysis of the variables used to calculate pK_a values of amino acid derivatives for all methods.

Method &Group	Parameter	*SE*	*R*
MP2	C4,N5, μ	0.162	0.997
DFT	C4,N5,HOM	0.397	0.994
HF	C4,LUM,W	0.471	0.985

An examination of Tables 2-4, revealed that the value of the spatial impedance energy increases with the size of the substituted group (Table 5).

In the substituted alanine, the value of vacuum impedance also increases by increasing the size of the compensated group in the following order (Table 6).

In the N-benzoylglycine compound, the value of vacuum impedance is greater than that of N-phenylglycine due to the presence of the carbonyl group, which makes it more stable.

As for the values of the impact of dipole moment, we noticed that it is also affected by the nature of the substituent found on the amino acids, and increase the size of the substituted and its polarities in a manner consistent with the effects of spatial disability. It is observed that the values of van der Waals interaction are minimum in the N-ethylglycine. This energy increases with an increase in the size of the substituent, which is the result of a type of van der Waals power as a result of interference resulting from spatial disability, and this is consistent with the values of spatial disability.

Similar results are obtained by other methods, MP2 and HF also. Although the values vary, the pattern of change is identical by the remaining methods. This confirms that the above results are in line with known chemical bases.

The values of the energy variables calculated theoretically for amino acid derivatives by three different methods are given in the Tables 7-9. The relationship between each of the variables was found in the MP2 method as a model and for amino acid derivatives. The results of these ratios were included in the Table 10.

The tables showed that there are good relations between some variables vary by proximity and distance from each other in terms of vacuum location and electronic payment, these relations vary in values according to the different method.

Table 12. The theoretical and calculated pKa values and the difference between the amino acids derivatives by the three methods.

Compound No.	MP2			DFT			HF		
	pK_a^*	pK_a^{**}	ΔpK_a	pK_a^*	pK_a^{**}	ΔpK_a	pK_a^*	pK_a^{**}	ΔpK_a
1	2.34	2.3892	-0.0492	2.34	2.3867	-0.0467	2.34	2.298062	0.04193
2	2.35	2.3813	-0.0313	2.35	2.4203	-0.0703	2.35	2.341551	0.00844
3	2.35	2.3798	-0.0298	2.35	2.3513	-0.0013	2.35	2.313705	0.03629
4	2.35	2.3882	-0.0382	2.35	2.4020	-0.0520	2.35	2.327509	0.02249
5	1.83	1.7791	0.0509	1.83	1.7759	0.0541	1.83	1.82977	0.00023
6	3.62	3.5785	0.0415	3.62	3.5652	0.0548	3.62	3.597436	0.02256
7	2.22	2.2426	-0.0226	2.22	2.2077	0.0123	2.22	2.275847	-0.05585
8	2.22	2.1800	0.04	2.22	2.1632	0.0568	2.22	2.185033	0.03496
9	2.21	2.2193	-0.0093	2.21	2.2740	-0.0640	2.21	2.193352	0.01664
10	2.08	2.0613	0.0187	2.08	2.0767	0.0033	2.08	2.290829	-0.21083
11	2.04	2.0096	0.0304	2.04	1.9906	0.0494	2.04	1.948099	0.09190

pK_a^* = Experimental Values, pK_a^{**} = Calculated Values, ΔpK_a = $pK_a^* - pK_a^{**}$

For example, in Table 10 correlation coefficient values were in the MP2 theory between the C3 atom and the chemical voltage is 0.755. Its value is also relatively good with the energy variables represented by VDW and hardness interference on the one hand and chemical and electrolyte on the other i.e. 0.848 and 0.916, respectively.

The following equation represents the model used to calculate pKa values in the MP2

$$pK_a=-2.529+(-2.300*C4)+(-1.670*N5)+(-34.137*\mu)$$

In considering the above table, it can be noted that the correlation coefficient obtained in MP2 theory was high and close to one. This indicates the importance of using these variables in calculating the value of pK_a and comparing them with the values obtained from the literature The standard error (S.E) of the relationship between the values of ionization constants and the theoretically calculated variables in simple analysis was small for the amino acid derivatives in MP2 theory where they were better than the rest of the theories.

Theoretical calculation of pK_a ionization parameters for amino acid derivatives

The results of the statistical analysis were used to determine the important variables used to calculate the ionization parameters in the calculation of the theoretical values and the differences from the experimental values taken from the literature[27-23] and the three methods as shown in Table 12.

It is observed that there is a large congruence between the values of the pKa ionization constants calculated theoretically with the experimental values obtained from the literature for the MP2 method of amino acid derivatives. This is an indication of the accuracy of the variables used to calculate these values. MP2 theory gave the most accurate results in the convergence of values between the constants of theoretical ionization and the constants of ionization obtained from literature and the sequence of theories in terms of preference is DFT<MP2<HF.

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