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Theoretical Calculation of pka of some Aromatic Ketones compounds by AM1 methods

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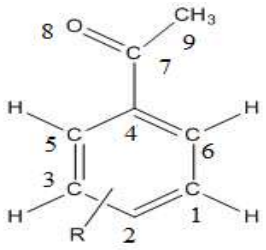
ABSTRACT

In this study of nineteen aromatic ketones compounds, their structure is shown in the figure below. The ionization constants were calculated by a theoretical method through statistical correlation with regression analysis of the values of the practical ionization constants for these compounds with a number of theoretically calculated structural properties of these compounds. The structural properties were calculated using the (AM1) method. The bonds, angles , and charges on the atoms, while the second type included the energy variables, which included the highest occupied molecular orbita (HOMO) the lowest unoccupied molecular orbita (LUMO), hardness (η), the electronic chemical potential (μ) and the general electrophilic index (W) and the total energy. The single and multiple regression analysis was carried out using the Statistical Analysis Program (SPSS). The relationship between the theoretically calculated variables and the practically calculated ionization constants was evaluated through the correlation coefficients R 2, where it ranged from. Through the single regression analysis, it was found that there are a number of variables that have a strong correlation with the values of the practical ionization constants, and the most powerful of those variables was the charge on the oxygen atom number 8 in the carbonyl group. During the triple regression analysis, we obtained the best correlation strength for three theoretically calculated variables with the values of practical ionization constants.

Electronic Structure



General form of the composition of the studied aromatic ketones

C7-O8: represents the length of the bond between a carbon atom number 7 and an oxygen atom number 8.
C7-C4: represents the length of the bond between a carbon number 7 atom and carbon number 4 atom.
C7-C9 : represents the length of the bond between carbon number 7 and carbon number 9.
C9-C7-O8 : represents the angle between carbon 9, carbon 7 and oxygen 8 atoms.
O8 : represents the charge on the oxygen atom number 8.

Keywords: Aromatic Ketones, Pka, Theoretical Calculation, AM1.

Introduction

Ketones Except for matte:

compounds have a non - localized pi electrons system in which single and double bonds exchange, and it contains at least one ring, and it is flat. It is the union of a carbon atom with an oxygen atom linked by a covalent bond, ketones are chemicals secreted by the liver in the human body, where they are secreted as an alternative source for energy production, when the amount of insulin needed to convert glucose into energy (2) is used to test urine in the detection of blood sugar As the presence of ketones is an indication of the presence of disease (3). Ketones are one of the commonly used solvents, from the properties of ketones, ketones of low molecular weight are colorless substances, ketones are characterized by their pleasant smell, the density of ketones less than the density of water.

Ionization constant: The ionization constant, or known in some sources, is used as a dissociation constant to measure the extent of the basic and acidic strength of any chemical compound. Aromatic ketones are highly acidic and can easily lose a proton when there is a base. The values of the ionization constants are different from one compound to another. Induction or resonance effect. As the driving groups reduce the acidity value, thus increasing the value of PKa , NH_2 such as NR_2, NHR , OR , OH , and other groups, while the withdrawing groups work to increase the acidity value and thus The value of PKa decreases like NO_2, CN , F , CL , BR , COOR , COR , CHO , COCL ,NH_2 COO

The is also known PKa is the ratio between the concentrations of dissociated or ionized substances from the base or acid To the concentration of the non-ionized substance[4] , the ionization constants are considered to be of importance in the field of pharmaceutical sciences, and from the study of drugs, it was found that 62.9 of the drugs are capable of ionization, and from the results of previous studies, it was found that 75% of these drugs are weak bases, and 20% are weak acids. The remaining percentage is non-ionizable, such as alcohols and others [5].

Methods for setting the ionization constant:

There are several methods for determining the values of the ionization constants for aromatic ketones and organic compounds, including theoretical and practical methods.

1-Practical methods:

These methods are based on practical experiments in the laboratory through which the measurement of Ionization constant and from them .

Or not- connection method, Secondly- spectrophotometer,

Third - electrochemical methods.

Fourthly- Thermal Methods, Fifthly –the method of jihadi tasheeh .

2-Theoretical methods:

Due to the progress made in the field of computer and software, many researchers have used computer programs to find many chemical calculations, including calculating the PKa values for many basic and acidic organic compounds. A study of hydrogen bonds and their impac[6] . Where the scientist Liptak and his group have found the values of the ionization constant for the compensated phenolic compounds through the standard free energy according to the following equation [7].

$pKa = \Delta G° / 2.303\ RT$ ……..(2)

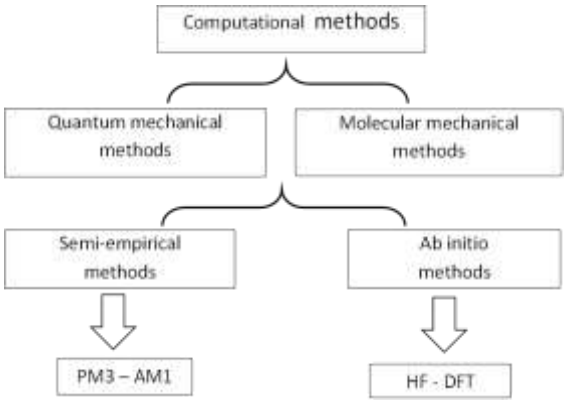
Since:-

ΔG° expresses standard free energy.

R expresses the general constant for gases.

T It expresses the temperature.

Computational chemistry: Computational chemistry is one of the branches of advanced chemistry that aims to calculate the most important chemical properties and compare them with practical results. Through computational chemistry, the most important properties of molecules can be found, such as total energy, atomic charges, frequencies, NMR properties, interaction method, the spatial structure of transition states. IR spectroscopy, RAMAN spectroscopy, dipole moment, thermochemical properties[8] . Where computational chemistry aims to find mathematical equations to solve problems in a quick time and less expensive than those used in practice in the laboratory. Computational chemistry classify It is divided into two main categories, according to the following scheme:



Computational chemistry chart

Molecular Mechanics Methods: This method is one of the fastest and simplest methods, but it does not give accurate results when compared with quantum mechanics, and it is used in compounds with relatively large molecules such as proteins, polymeric solutions, steroids and other complex compounds Molecular mechanics describes the energy of molecules by relying on the classical methods and laws used in this field, where they are used to find the potential energy of compounds, which is expressed by the field energy and used in certain types of atoms[9] .

Quantum mechanics methods:

Quantum mechanics is considered a generalization of classical physics because it can be applied at the atomic and ordinary levels.

The name quantum mechanics is due to the presence of quantum in its construction, which is a physical term used to describe the smallest amount of energy that can be exchanged between particles and is used to refer to a specific amount of energy that is emitted intermittently rather than continuously, and the emergence of this theory was in 1900 when the scientist Max Planck studied the distribution law for black body radiation, and the scientist Schroedinger developed this theory in 1926 [10]. Quantum mechanics is a set of physical phenomena and theories that appeared in the twentieth century, where phenomena were explained at the atomic level and subatomic particles.

Austin Method AM1: Austin Model 1

German scientist Micheal Dewar first developed the Austin AM1 method in 1985 AD. The AM1 method is a developed and updated method for the (MNDO) method, as it is considered a quick method for calculating the energies and compositions of organic compounds [11]

The AM1 method is one of the methods Semi-experimental as it relies on theoretical information on loading experimental data. The AM1 method succeeded in explaining and clarifying many chemical phenomena that were not previously known. This method was developed through the use of variables representing compounds containing the following atoms : H, S, N: (Mg,O,BC,Si,Sn,Ge,Cl,Br.Zn.Al,F) by using one hundred models of compounds such as HgBr . One of the most important information that we obtain in this way is the lengths of bonds of the different molecules, the temperature of formation, the ionization potential and the charges Atoms and electronic density. This method uses atomic orbitals S,P and the central repulsion function[12].

The practical part :

In this study, some physical and energy variables were calculated using semi-experimental and basic calculation methods. These variables include:

1-The values of the atomic charges and was chosen (Mullikan Charge).

2- Evaluate the angles between the atoms.

3-The length of the bonds between atoms.

4-What are the energies of atomic orbitals (HOMO, LUMO).

5-Total energy.

6-Hardness values, chemical electronic potential, spherical electrophilic index, which were calculated based on the values of molecular orbitals (HOMO, LUMO) according to the previously mentioned equations.

The calculations were carried out in the following way Semi-empirical Mehtods (AM1).

Steps for theoretical calculations of the compounds under study:

1- Drawing the molecular formula for the compounds using the Chem. Office program.

2-Make a selection for the particle, by selecting Edit) from which we choose Select All) .

3-From the instructing Structure we choose the instructing Clean up

4-Carrying out a process of reducing energy by instructing MM2

5-From Calculation we choose GAMESS interface and from it we choose Minimize

Energy Geometry and from it we choose the theoretical method and then we chooseBasiset

6-Statistical analysis was carried out using SPSS software.

Statistical analysis:

was carried out between the selected and calculated variables by means of theoretical methods with PKa values obtained in practice by means of the statistical analysis program SPS and the values of the correlation coefficient R2 were relied upon as a reference for this purpose to know the strength and type of relationship between the physical variables that were calculated HOMO , LUMO , μ, ŋ , W , E , C4 , C7 , C9 , O8 , C7-C9 , C7-O8 , C4-C7 , C9-C7-O8 , C9-C7-C4 , O8-C7-C4 .

Statistics for these variables were carried out with each other and with the values of the ionization constant, by the four methods, each method separately, and by the following steps

1- The physical variables of aromatic ketones compounds, which are undependent ariables, have been entered with the values of the ionization constant, which is a dependent variable.

2-The variables were analyzed through a series of steps in the castration program SPSS with the following steps (Linear + regression + analysis)

3-Then, the values of the correlation coefficient (R2) are obtainedwhere through the values of the correlation coefficient it is known which variables have a significant impact on the values of PKa in the simple regression analysis..

4-Then we conduct the process of multiple regression analysis to find out the strength of the relationship between the dependent functions with each other and the extent of their impact on the values of the ionization constant obtained from the literature.

Table compositions and names of compounds that have been studied Comp.

Comp. Nu.	Nameclature	Structure
1	acetophenone	H
2	1-(*p*-tolyl)ethan-1-one	CH_3
3	1-([1,1'-biphenyl]-4-yl)ethan-1-one	p-Ph
4	1-(4-methoxyphenyl)ethan-1-one	p-OCH_3
5	1-(3-methoxyphenyl)ethan-1-one	m-OCH_3
6	1-(4-(dimethylamino)phenyl)ethan-1-one	p$N(CH3)_2$
7	1-(3-(dimethylamino)phenyl)ethan-1-one	m$N(CH3)_2$
8	1-(4-fluorophenyl)ethan-1-one	pF
9	1-(3-fluorophenyl)ethan-1-one	mF
10	1-(4-chlorophenyl)ethan-1-one	p-Cl
11	1-(3-chlorophenyl)ethan-1-one	m-Cl
12	1-(4-bromophenyl)ethan-1-one	p-Br
13	1-(4-(phenylthio)phenyl)ethan-1-one	pS(Ph)
14	1-(4-(phenylsulfinyl)phenyl)ethan-1-one	p-SO(Ph)
15th	1-(4-(phenylsulfonyl)phenyl)ethan-1-one	p-SO_2(Ph)
16	1-(3-(phenylsulfonyl)phenyl)ethan-1-one	m-SO_2(Ph)
17	4-acetylbenzonitrile	p-CN
18	1-(4-(trifluoromethyl)phenyl)ethan-1-one	p-CF_3
19	1-(3-(trifluoromethyl)phenyl)ethan-1-one	m-CF_3

Results and discussion

1- Theoretical calculation

The aromatic ketone compounds are of importance at the present time for their use in many areas of life, including scientific, medical and industrial. From this principle, our interest increased to a theoretical study to calculate the PKa values of these compounds in order to enhance the practical aspect. In this study, some structural variables were calculated. Which are of importance in our theoretical calculations of the compounds that have been studied and the calculation of PKa values for them. Among these variables are atomic charges, lengths of bonds between atoms, values of angles between atoms as well as calculating energy functions such as the values of atomic orbitals HOMO , LUMO and hardness The ionization constant for all of these compounds was calculated by obtaining the best relationship between the variables with each other and with the ionization constant, taking into consideration the effect of compensating groups pushing or pulling electrons, as well as the effect of induction, resonance and the vacuum effect.

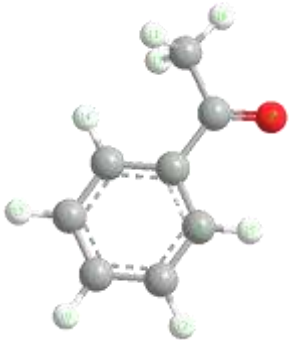
Calculation of some structural variables of aromatic ketones compounds

Table of structural variables of aromatic ketones compounds theoretically calculated AM1 method

	Charge. In (Coulomb)				Bond Length (Angstrom)			Angle in (Degree)		
COMP.	C4	C7	C9	O8	C7-C9	C7-O8	C4-C7	C9-C7-O8	C9-C7-C4	O8-C7-C4
1	-0.1564	0.2668	-0.2661	-0.2977	1.496	1.238	1.479	121.117	117.407	121.475
2	-0.1623	0.2679	-0.2659	-0.2995	1.496	1.239	1.478	121.042	117,429	121.53
3	-0.1556	0.2657	-0.265	-0.2978	1.496	1.238	1.478	121.146	117.273	121.579
4	-0.1864	0.2704	-0.2656	-0.3025	1.497	1.239	1.477	120.786	117.86	121.352
5	-0.1456	0.2662	-0.2659	-0.2931	1.496	1.238	1.48	121.21	117.255	121.434
6	-0.2066	0.2738	-0.2653	-0.3104	1.497	1.24	1.473	120.79	117,535	121.674
7	-0.1196	0.2666	-0.2652	-0.3009	1.496	1.238	1.481	.120,862	117.555	121.583
8	-0.1711	0.2691	-0.2656	-0.2985	1.496	1.239	1.479	120.586	118,422	120.991
9	-0.1301	0.2656	-0.2661	-0.2892	1.496	1.238	1.482	121.281	117.312	121.407
10	-0.1561	0.2671	-0.2664	-0.2939	1.496	1.238	1.48	121.136	117.553	121.31
11	-0.1468	0.2669	-0.2662	-0.291	1.496	1.238	1.481	121.164	117.433	121.403
12	-0.1444	0.2657	-0.2667	-0.2911	1.496	1.237	1.48	121.202	117.37	121.427
13	-0.1286	0.2639	-0.2668	-0.2901	1.496	1.238	1.481	121.135	117.246	121.429
14	-0.121	0.264	-0.2634	-0.2974	1.496	1.241	1.483	119.623	120.137	120.225
15th	-0.0943	0.259	-0.2668	-0.2815	1.494	1.237	1.484	121.452	117.509	121.037
16	-0.1815	0.2691	-0.2663	-0.2939	1.495	1.238	1.48	121.283	117,634	121.08
17	-0.1342	0.2642	-0.2667	-0.2871	1.495	1.238	1.482	121.43	117.377	121.192
18	-0.1268	0.2634	-0.2667	-0.2848	1.495	1.237	1.483	121.378	117,554	121.068
19	-0.1588	0.2663	-0.2666	-0.2859	1.495	1.237	1.481	121.266	117,461	121.273

Some of the structural variables of the aromatic ketones compounds were calculated and compensated with the groups of withdrawing and pushing electrons by the methods used, and among these variables are the atomic charges and the charges were calculated for the following atoms

O8 , C7 , C9 , C4 according to the following formula. Which is a general formula for all compounds used, regardless of the compensated groups



It is known that there are many types of charges Lodin charge, Molican charge, Natural numerical analysis charge, atom charge in the molecule, but the Mullican charge was relied on in this study because this charge is present in all the theories used and research and that these charges can be It is one of the most effective variables in the compounds for calculating the ionization constant PKa by theoretical methods The lengths of the bonds between atoms C7-C9 , C7-O8 , C4-C7 , according to the previous formula, which also has a significant impact on the values of PKa , as well as calculating the values of the angles between the atoms C9-C7-O8 , C9-C7-C4 , O8-C7-C4 .

stereo effects:

The steric effects express the geometric shape that these compounds can take and how their atoms are distributed in the vacuum, which is controlled by different factors. It is caused by these aggregates, and the second effect is all the steric interferences such as the Vander Waals forces, the total energy, the hydrogen bonds, the dipole moment and other other interferences and that the sum of all these interferences, whether combined or opposite to one another, can increase or decrease the stability of the molecule, that Among the most important structural variables that affect the stereo structure of aromatic ketone compounds are the lengths of the bonds between atoms, the angles between atoms, and charges , as well as the energy variables such as HOMO , LUMO , hardness, chemical electron potential, and spherical electrophilic index .

The accounts the theory l for dual energy:

In this study, we depend on the energy variables, which represent the stability of the different molecules through the interactions and the steric changes. The energy variables that were obtained during the calculations are the energy of the orbitals HOMO, LUMO and the total energy and some other variables that were calculated such as hardness, electrophilic index. spherical, chemical electron potential which Calculated from the energy of orbitals HOMO, LUMO according to equations 6,7,8 that were mentioned in the first chapter, and graphs were made for the values hardness, spherical electrophilic index, chemical electronic potential to clarify which compounds have electrophilic or nucleophilic behavior as well as aromatics for the compounds studied. Whereas, the low values of hardness, electronic chemical potential indicate that the molecule is highly reactive towards nucleophile, while high values of hardness and chemical electronic

potential indicate that the molecule has an electrophilic behavior .

Table values of the energy variables calculated theoretically for the aromatic ketones compounds in the AM1 method

CUMP.	HOMO (ev)	LOMO (ev)	W (ev)	μ (ev)	ŋ (ev)	E (ev)
1	-0.3783	-0.0101	0.104	-0.1942	0.1841	-33538.5845
2	-0.3634	-0.014	0.1019	-0.1887	0.1747	-37133.1326
3	-0.3386	-0.031	0.111	-0.1848	0.1538	-52512.2964
4	-0.3641	-0.0194	0.10666	-0.19175	0.17235	-44511.99791
5	-0.3702	-0.0187	0.10756	-0.19445	0.17575	-44511.9418
6	-0.3088	0.0077	0.07161	-0.15055	0.15825	-45799.8344
7	-0.3057	-0.0043	0.0797	-0.155	0.1507	-45798.2775
8	-0.374	-0.0244	0.1135	-0.1992	0.1748	-44409.1384
9	-0.3713	-0.027	0.11519	-0.19915	0.17215	-44408.7175
10	-0.3677	-0.0314	0.1184	-0.19955	0.16815	-41842.5767
11	-0.3784	-0.0269	0.1193	-0.204	0.1744	-41842.1943
12	-0.3758	-0.0342	0.123	-0.205	0.1708	-41369.5848
13	-0.3167	-0.0282	0.10308	-0.17245	0.14425	-56993.3483
14	-0.2911	-0.0673	0.1434	-0.1792	0.1119	-64370.6898
15th	-0.3913	-0.0727	0.1689	-0.232	0.1593	-71751.5394
16	-0.3962	-0.07	0.1665	-0.2331	0.1631	-71754.3408
17	-0.3835	-0.0486	0.13937	-0.21605	0.16745	-40928.83
18	-0.3892	-0.0428	0.1346	-0.216	0.1732	-69757.6851
19	-0.3922	-0.0255	0.11894	-0.20885	0.18335	-69757.8759

triple stats:

In this method, good and acceptable results were obtained by relying on three of the variables that were calculated with the ionization constant, which is considered a constant.

Table of the values of the correlation coefficient between pKa with the variables calculated by the triple analysis method AM1

Variables	R^2
O8+W+LOMO	0.932
O8+C4-C7+LOMO	0.942
O8+LOMO+μ	0.932
LOMO+O8+ŋ	0.932
W+μ+O8	0.932
LOMO+O8+C9	0.937
O8+C9-C7-C4+C9-C7-O8	0.932
LOMO+O8+C7-O8	0.936
O8+W+C4-C7	0.944
LOMO+O8+C9-C7-C4	0.94
O8+W+C9-C7--O8	0.938
LOMO+O8+E	0.94
HOMO+LOMO+O8	0.932
O8+W+C9-C7-C4	0.939
C4+O8+C4-C7	0.931

Calculate the values of the ionization constants theoretically:

The results of the multiple statistical analysis were used, which we obtained by identifying the important variables in calculating the theoretical PKa values and the difference between them and the practical values taken from the literature and by the methods used. In the PM3 method, the best value of the correlation coefficient was R 2 = 0.941 among the following variables W , C7-C9 , C4-C7 which is the highest value obtained in this way and thus the variables that were used They are the most influential variables on PKa values, where the theoretical PKa values were calculated according to the following equation :

pKa=222.79+(-86.136*O8)+(18.914*W)+(-149.916*C4-C7)

Table 3-22 Calculation of the ionization constant pKa (using the AM1 method)

O8	-86.136			
W	18.914			
C4-C7	-149.916			
Constant	222.79			
Compound	**O8**	**W**	**C4-C7**	**pKa**
1	-0.2977	0.104	1.479	24.77
2	-0.2995	0.1019	1.478	25.08
3	-0.2978	0.111	1.478	24.77
4	-0.3025	0.10666	1.477	25.4
5	-0.2931	0.10756	1.48	24.13
6	-0.3104	0.07161	1.473	27.35
7	-0.3009	0.0797	1.481	25.18
8	-0.2985	0.1135	1.479	24.63
9	-0.2892	0.11519	1.482	23.35
10	-0.2939	0.1184	1.48	23.99
11	-0.291	0.1193	1.481	23.58
12	-0.2911	0.123	1.48	23.66
13	-0.2901	0.10308	1.481	23.8
14	-0.2974	0.1434	1.483	23.37
15th	-0.2815	0.1689	1.484	21.37
16	-0.2939	0.1665	1.48	23.08
17	-0.2871	0.13937	1.482	22.7
18	-0.2848	0.1346	1.483	22.45
19	-0.2859	0.11894	1.481	23.14

Conclusion

In this study, the dissociation constants for nineteen compounds of the aromatic ketones have been calculated by using theoretical calculation, using two methods of quantum mechanics, One are semi-empirical (AM1)The study included one type of variables first that were the inductive or structural variables which include bond lengths , bond angles and the atom charges , the second type of variables are energy or spatial variables which include higher occupied molecular orbital (HOMO), lower unoccupied molecular orbital (LUMO), hardness (η), electronic chemical potential (μ), global electrophilicty index (W) and total energy. The simple and multiple statistical analysis was carried out through the statistical program (SPSS), the relationship between the theoretically calculated variables of aromatic ketones and practical pKa of them had judged by the values of correlation coefficient R 2 . The most variable effect on the dissociation constant was the charge of oxygen atom in carbonyl group . Through the use of triple regression analysis of pKa with variables the aromatic ketones, with the structure below substitute with different groups (electron withdrawing and donating groups) .

General structure of aromatic ketones in this study

C7-O8: Represents the bond length between carbon atom number 7 and oxygen atom number 8 .

C7-C4 : Represents the bond length between carbon atom number 7 and carbon atom number 4 .

C9-C7 : Represents the bond length between carbon atom number 9 and carbon atom number 7.

C9-C7–O8: Represents the angel between the C9, C7 and O8.

O8 : Represents the charge on oxygen atom number 8.

References

1- Anne Marie Helmenstine (8-3-2017) , " Ketone " Definition , www.thoughyco.com, Retrieved 12-12-2018.Edited.

2- Rachel Nall, RN, BSN, CCRN (5-30-2017), Checking Ketone Levels , www.healthline.com, Retrieved 11-20-2018. Edited.

3-Marvel, CS; sperry; W. M. (1928). "Benzophenone" Organic chemistry. 8:26-doi:10. 15227/Orgsyn. 008-0026.

4- K. M. David and M. n. Ibrahim, (1990) , "The Mechanics of Organic Reactions", Dar Al-Hekma Press, pp. 75-80

5-B.Pilarski,R. Kaliszan, D. wyrzykowski, J. Mlodzianowski and A. Balinska. , (2015), . "General analytical procedure for determination of acidity parameters of weak acids and bases". Journal of analytical methods in Chemsitry, pp, 1-8.

6-Ho, Jm, Coote, ML A universal approach for continuum solvent PKa calculations: Are we there yet? Theor. Chem. Acc. 2010, 125(1-2), 3-21.

7-M. Liptak, K. Gross, p. Seybod, S. Feldgus, and G. Shileds, (2002), "Absplute pka Determination for Substituted phenols" , J. Amer. Chem. soc ., 124, 22. Pp.6421-3427.

8-AR Leach; (1999) "Molecular Modeling Principles and Applications", Addison Wesley Longman.

9-CR Brooks, RE Brucooleri, BD Olafson, DJ States Swaminathan, and M.Karplus; (1985), "Coputer

Graphics in Real-time Docking with Energy Calculation and Minimization" J.Comput. Chem., 6, 5, 432-436.

10-DA McQuarrie; (1983), "Quantum Chemistry", University Science Books.New York

.

11-MJS Dewar, EG Zoebisch EF Healy and JJP stewart; (1985), J.Am. Chem. Soc., 107, 2802.

12-DC Young ;(2001), "Computational Chemistry a Practical Guide for Applying Techniques to Real World Problems", John Wiley & Sons, Inc., New York, 19-29 .